An Overview of Botulinum Toxins: Past, Present, and Future

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KEYWORDS

• Botulinum • Neurotoxin • Dysport • Botox • Cosmetic

Botulinum toxin (BTX) has revolutionized the field of cosmetic medicine. With more than 11 million injections since 2002,[1] its administration is by far the most common cosmetic procedure being performed in the United States. This achievement is truly impressive for what may be the most toxic chemical on earth. Based on the estimated inhalational lethal dose, a single gram of BTX is capable of killing 1 million people.[2] Fortunately, a vial of BTX for cosmetic use contains about a 200 million-fold smaller quantity of active neurotoxin. The rapid ascent in popularity of BTX with both clinicians and patients can be attributed to its remarkable efficacy; predictable and reproducible results; excellent safety record; and the relative ease, comfort, and speed of administration. Over the past 9 years since its Food and Drug Administration (FDA) approval for the treatment of glabellar lines, physicians have explored myriad applications for BTX not only for the treatment of the aging face and neck but also for a long list of neuromuscular and glandular disorders, muscle contouring, and various pain syndromes. In keeping with the theme of this issue, this review focuses predominantly on aesthetic uses of BTX. The pharmacodynamics, clinical properties, and safety profiles of the 2 BTX products FDA approved for cosmetic use, onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport), are also explored in detail.

STRUCTURE AND MECHANISM OF ACTION

Botulinum toxin is produced by various species of gram-positive, spore-forming bacilli of the genus, *Clostridium*, but chiefly from strains of *C botulinum*. Seven serotypes of BTX have been identified to date, which are labeled alphabetically, A to G. Many of these possess additional subtypes; for example, there are 4 described distinct subtypes of serotype A toxins.[3] All of the serotypes have a similar chemical structure and, except subtype C_2, are neurotoxins. Each botulinum toxin is initially synthesized as a continuous 150-kDa gene product. Biologic activity requires posttranslational proteolysis, or nicking, which clips the BTX polypeptide into 2 separate moieties of 100 kDa and 50 kDa in size. This process results in a heavy chain and light chain that remain covalently bound by a single disulfide bridge.[4] In human tissue, the heavy chain is recognized by receptors on presynaptic nerve terminals and the active di-chain neurotoxin is endocytosed. Upon acidification of the endosome, the heavy chain forms a channel in the endosomal membrane and the disulfide bond

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between the chains is reduced.[5] The liberated light chain translocates to the cytosol where its zinc-dependent protease domain cleaves a member of the soluble NSF attachment protein receptor (SNARE) complex. The loss of any of these proteins abrogates exocytosis of presynaptic acetylcholine-rich vesicles, thereby eliminating signal conduction in afflicted cholinergic neurons. The various serotypes have specific molecular targets: SNAP-25 for toxins A and E; VAMP/synaptobrevin for B, D, F, G; and both SNAP-25 and syntaxin for C.[6]

Botulinum toxin serotype A (BTX-A), the serotype in both onabotulinumtoxinA (Botox/Vistabel; Allergan, Inc) and abobotulinumtoxinA (Dysport), naturally exists as a complex with a surrounding coat of catalytically inactive, protective proteins, known collectively as neurotoxin- associated proteins (NAPs). NAPs, including 4 distinct hemagglutinin proteins and a nontoxic nonhemagglutinin protein, are synthesized by the clostridial bacterium and shield the neurotoxin from potential destruction by gastric acidity. Clostridial cultures yield 3 sizes of progenitor complexes: 300 kDa, 500 kDa, and 900 kDa.[7] Allergan asserts their proprietary purification method for onabotulinumtoxinA (OnaA) isolates the 900-kDa complex exclusively.[8] It has been suggested that the column chromatography purification method used to isolate abobotulinumtoxinA (AboA) results in a heterogeneous mixture of the 3 progenitor complexes, with the smaller complexes conferring more rapid diffusion in tissues.[9] These claims have been disputed by Ipsen[10] and admittedly the authors were unable to identify any convincing studies that establish a direct correlation between tissue diffusion properties and complex size.

Pharmacologic activity of BTX-A requires dissociation of the progenitor complex and release of the active BTX-A 150-kDa monomer. This process does occur at physiologic pH but the kinetics of the dissociation are not fully clarified. Some have suggested that dissociation is nearly immediate.[11] A recent study conducted by Merz Pharmaceuticals (manufacturers of one of the new naked neurotoxin agents discussed later) reported that the 150-kDa toxin was released from both OnaA and AboA in less than 1 minute at neutral pH.[12] The investigators suggested that dissociation may occur in the vial even before injection. The relative kinetics of dissociation versus diffusion have implications for the safety profiles of the various formulations of BTX-A in current or future clinical use and, therefore, these remain contentious issues for their respective manufacturers.

In addition to the well-characterized effects previously detailed, a growing body of evidence indicates that BTX-A targets some noncholinergic neurons. Inhibition of neurotransmitters, such as substance P, glutamate, and calcitonin gene-related peptide, has been demonstrated, supplying the mechanistic underpinning for the use of BTX-A in the treatment of chronic pain,[13] one of its most exciting new nonaesthetic applications. It is hoped that future research in this area will establish novel therapeutic indications for BTX-A.

HISTORY

Botulism, derived from the Latin *botulus* meaning sausage, was first described in the 1820s when several cases occurred in Germany associated with the ingestion of improperly preserved smoked sausage. The bacterial etiology was discovered in 1895 and the toxin itself was isolated in the 1940s. In the 1970s, Dr Alan Scott pioneered research on the clinical utility of BTX, treating strabismus in a primate model. He eventually graduated to humans and published the first sizable therapeutic trial in 20 patients with strabismus in 1981.[14] Over the ensuing decade, Dr Scott established or inspired numerous ophthalmologic applications, including blepharospasm, nystagmus, entropion, and hemifacial spasm. In 1989, BTX received its first FDA approval for blepharospasm and nystagmus.

In 1987, a serendipitous observation by a patient of Jean Carruthers, MD, an ophthalmologist, spawned the cosmetic use of BTX. The patient, who was receiving BTX-A for blepharospasm, noted a softening of her frown lines. Dr Carruthers happened to be married to a dermatologist, Alistair Carruthers, MD, so the couple was uniquely positioned to initiate clinical research on the use of BTX in rhytid reduction. They published their first clinical study of BTX for glabellar lines in 1992.[15] Sixteen of 17 patients who completed follow-up had a clear benefit with no major adverse events. It would take another decade to achieve FDA approval for this limited indication. In 2004, approval for treatment of primary axillary hyperhidrosis was granted. All other dermatologic usage of BTX remains off-label despite the general comfort most injectors have enjoyed for many years in using BTX for dynamic wrinkling in multiple areas of the face.

BOTULINUM TOXINS IN CLINICAL USE

Currently, 4 botulinum toxin products have FDA approval in the United States. Three contain serotype A complexes: OnaA (Botox), AboA (Dysport), and incobotulinumtoxinA (Xeomin). There is also 1 serotype B injectable: rimabotulinumtoxinB (Myobloc). RimabotulinumtoxinB (RimB) is only

approved for treatment of cervical dystonia. It has been employed for other conditions of muscular spasticity but has been rarely used for cosmetic purposes. A recent randomized, placebo-controlled trial demonstrated that RimB is effective for the treatment of glabellar lines with patient satisfaction and adverse event profiles comparable to BTX-A products.[16] However, in this study, the benefit persisted for only 8 weeks with the highest doses tested, and, at 12 weeks, muscular activity in almost all patients had returned to baseline. Furthermore, because of the mild acidity of reconstituted RimB (pH = 5.6), injections may not be tolerated as well as BTX-A. The speed of onset, though, may be shorter (2–3 days) than with BTX-A (3–7 days).[17,18] Because of its shorter duration of action, its role in cosmetics will remain limited to unusual and specific situations where rapid onset is critical or when tachyphylaxis to a BTX-A product has developed. In the latter scenario, RimB has proven effective.[19]

AboA (Dysport) was first licensed for medical usage in Europe in 1990. Clinical studies for aesthetic indications were first performed in Europe in 2002 and 2003, followed by US FDA studies in 2009. FDA approval for treatment of glabellar frown lines occurred in May 2009. **Table 1** summarizes the differences between the two formulations of BTX-A. Although variations in progenitor complex size as previously described may exist and the excipients differ, it must be stressed that the *active ingredient is thought to be identical and as such the clinical properties* of the two agents are largely similar. Purported variations in clinical behavior are likely to be subtle when controlled for volume, toxin concentration, and injection technique.

The most important difference between OnaA and AboA is in the activity units employed by their respective manufacturers: Botox units (bU) for OnaA and Speywood units (sU) for AboA. Both define 1 unit as the quantity necessary to kill 50% of mice (LD_{50}) with an intraperitoneal injection. Because of differences in the experimental design of their murine assays, however, the units are not equivalent. The Dysport assay is undeniably more sensitive (ie, less toxin is required to kill a mouse when toxin of any formulation is tested in this assay vs the Botox assay).[20] Indeed, in a small study it was shown that, when tested in the Dysport assay, the LD_{50} of Botox is achieved with 0.32 bU (68% less product than that required for LD_{50} in the Botox assay).[20] Therefore, a Speywood unit corresponds to a smaller quantity of active toxin than does a Botox unit. The exact potency ratio between a Speywood unit and

Table 1
Overview of product composition for the FDA-approved Botulinum toxin serotype A agents

Product	OnaA (Botox)	AboA (Dysport)	IncA (Xeomin)
Manufacturer	Ipsen (Europe) Medicis (USA)	Allergan	Merz Pharmaceuticals
Units per vial	100 bU	300 sU (for cosmetic use)	50 or 100 units
Active ingredient (molecular weight)	Botulinum toxin serotype A complex (900 kDa)	Botulinum toxin serotype A complex (500–900 kDa)[a]	Uncomplexed Botulinum toxin serotype A (150 kDa)
Total toxin protein per vial (active toxin + NAPs[b])	5 ng	2.61 ng	0.6 ng (in 100 units)
Excipients	Human serum Albumin 500 μg NaCl 0.9 mg	Human serum Albumin 125 μg Lactose 2.5 mg	Human serum Albumin 1 mg Sucrose 4.7 mg
Bacterial source	*Clostridium botulinum*, Hall strain[c]	*Clostridium botulinum*, Hall strain[c]	*Clostridium botulinum*, Hall strain[c]
Storage conditions	2–8°C	2–8°C	Up to 25°C
Purification process	Dialysis and acid precipitation then vacuum dried	Column chromatography then freeze dried (lyophilized)	Column chromatography then freeze dried (lyophilized)

IncobotulinumtoxinA is only approved for therapeutic use.
[a] Molecular weight of AboA is not firmly established –See discussion in text.
[b] Neurotoxin-associated proteins.
[c] There are numerous Hall strains and the manufacturers do not necessarily use identical bacteria.
Data from Refs.[54,57–61]

a Botox unit remains an open question. Because, in any competitive marketplace, product interchangeability is not a desirable attribute, the BTX-A manufacturers have predictably emphasized the uniqueness of their formulations and have discouraged the use of any unit conversion factors. Nevertheless, practitioners have sought to define a conversion factor to guide the novice injector when transitioning from one toxin to the other for a given application.

Numerous in vivo and in vitro studies have attempted to define this conversion factor with conflicting results. For a comprehensive review of this literature, please refer to the recently published review by Karsai and Raulin.[21] Only a brief summary of the pertinent human studies follows. A 2004 meta-analysis, using Cochrane Review methodology, identified 4 high-quality comparative clinical studies all examining neurologic indications, 2 employed a 1:4 (OnaA/AboA) dose ratio, 1employed a 1:3 ratio, and the last used 1:3 and 1:4 in separate arms.[22] This analysis concluded that a 1:4 ratio was too high and a 1:3 ratio approached bioequivalence, although the included studies suggested that an even lower ratio might be more appropriate. An independently funded, double-blind study of Dysport versus Botox for the treatment of glabellar lines found a longer duration of action as assessed by electromyographic studies with Dysport used at a 1:3 ratio. This finding led the investigators to conclude the bioequivalent ratio was less than 1:3.[23] Lowe and colleagues[24] examined the relative effects of a 1:2.5 dose ratio on glabellar lines assessed by blinded investigator rating and found greater longevity with Botox. Therefore, although the preponderance of current evidence supports a dose ratio of no more than 1:3, a more precise definition awaits additional controlled, head-to-head comparisons with ideally objective measurements of muscle activity. The investigators recommend a conversion factor of 1:2.5, which has become the most commonly quoted unit dose ratio among experienced injectors. The multiple studies that underpinned the FDA-approved dosages for glabellar lines (50 sU of Dysport and 20 bU of Botox) demonstrated comparable efficacy with the two BTX-A products, further supporting the 1:2.5 ratio as a starting point for cosmetic applications.

The perception that an increased capacity for a toxin to diffuse from the site of injection translates into increased side effects has encouraged a lively debate among the manufacturers of the BTX-A products. The question of diffusion has mostly been investigated in humans by measuring anhidrotic haloes after injecting equal volumes of each agent into the forehead. Some comparative studies of Botox and Dysport have demonstrated that anhidrotic haloes are significantly larger for Dysport.[9,25] The only double-blind randomized study used a Botox/Dysport unit ratio of 1:3, and one could argue that the increased anhidrotic haloes observed in this study with Dysport is a consequence of not using equipotent dosages. In other words, diffusion is primarily driven by concentration gradients, and it would be expected that a higher injected concentration of neurotoxin would result in greater diffusion. In an unblinded study, Trindade De Almeida and colleagues[25] examined 3 different dose ratios: 1:2.5, 1:3, and 1:4. They found significantly increased anhidrotic haloes with all dose ratios (the mean absolute increase in area of the anhidrotic halo was 1.2 cm^2 with the lowest Dysport dose). These results were challenged by a similarly designed comparative trial conducted by Hexsel and colleagues,[26] which found no significant difference in the field of anhidrosis using only the more widely accepted equipotent dose ratio of 1:2.5. Hexsel and colleagues[26] reported taking great care to standardize injection technique, which would certainly influence results. Of note, the first two studies described were sponsored by Allergan and the third by Ipsen. A definitive answer to this question will await an impartial, double-blind study comparing truly equipotent injections of neurotoxins.

In conclusion, it must be emphasized that subtle differences in the properties of the BTX-A formulations may exist. Extant data on product composition, diffusion properties, and relative clinical potencies remains inconclusive. Indeed, the number and types of NAPs probably differ between BTX-A products. NAPs have known biologic relevance in the pathogenesis of food-borne botulism.[27] One recent study demonstrated that a hemagglutinin protein binds E-cadherin to facilitate passage of toxin through epithelial tight junctions within the alimentary canal.[28] This finding raises the unexplored and previously discounted possibility that NAPs could have other specific biologic functions, some that might impinge on the neuromuscular activity of injected BTX-A. Until we possess a better understanding of these various issues, the injector is advised to think and treat independently with each BTX-A product, as one learns a foreign language, and avoid converting for usage.

Botulinum Toxins on the Horizon

Other BTX-A preparations now under consideration for aesthetic usage include 2 additional injectables (incobotulinumtoxinA [IncA; Xeomin] and PurTox) and a topical BTX-A (RT001). PurTox

and IncA are both naked neurotoxins (ie, pure formulations of the 150-kDa active-di-chain). They are in phase III trials. Recently published results from a phase III comparative trial of 24 units of either IncA or OnaA in the treatment of glabellar lines exhibited nearly identical response rates and a similar incidence of adverse effects.[29] IncA is already approved in Germany for cosmetic use and was approved in the United States for therapeutic use (blepharospasm and cervical dystonia) on July 30, 2010. Both IncA and PurTox will likely be approved for cosmetic use in the United States within 5 years. The absence of NAPs might theoretically decrease the immunogenicity of the agent (see later discussion of neutralizing antibodies). Of course, the smaller molecular weight has also raised the specter of an increased capacity for tissue diffusion.

RT001 is a particularly exciting new product as it affords an entirely different method of administration. RT001 is a topical gel formulated with the 150-kDa toxin and a proprietary peptide that facilitates transcutaneous delivery. In a recently published placebo-controlled trial, investigators applied RT001 under occlusion to the lateral canthal rhytids for 30 minutes and repeated this at 4 weeks. At 8 weeks, 94.7% exhibited at least a 1-point improvement on a 5-point lateral canthal rhytid scale and 50% experienced a 2-point improvement (vs 0% of placebo).[30] Depth of penetration likely limits its utility to superficial muscles, such as the lateral orbicularis oculi. Because of its potential for frequent painless administration and usage in areas in which injectables pose significant risks (eg, lower eyelids and lateral lips), RT001 may occupy a unique cosmetic niche in the future.

RECONSTITUTION, SUPPLIES, AND STORAGE

The package inserts of Botox and Dysport both advise reconstitution in 2.5 mL of unpreserved saline (1.5 mL is also a listed alternative for Dysport). A randomized, double-blind study has shown that there is less pain and equal efficacy with preserved saline, which is possibly secondary to the anesthetic properties of the benzyl alcohol that is added as a bacteriostatic agent.[31] A 2004 consensus conference of opinion leaders on the cosmetic use of Botox reported that most injectors use a preserved diluent. This consensus conference also reported that a wide range of dilution volumes is in common usage.[32] The field of effect of an injected toxin is dependent both on diffusion (as previously discussed) and spread, a physical parameter that describes the forced dispersion of the toxin as a consequence of injection pressure and volume. Thus, the field of effect increases proportionately with the volume injected assuming other variables are held constant. This consideration is important when precise localization of effect is desired, such as at the inferior orbital rim, and has led many injectors to favor a more concentrated toxin solution. Certainly, smaller volumes are prudent for inexperienced injectors. Also, in theory, larger volumes could decrease efficacy. The albumin that is included in the BTX-A vials (present at 25,000-fold excess relative to the toxin; see **Table 1**) coat potential nonspecific protein binding sites on glassware and plastics used for storage and injection. As the albumin becomes more dilute, the extent of blocking decreases, which creates the potential for loss of toxin caused by adherence to the vial or syringe. The diluent volume at which this phenomenon might become germane is undefined but may be substantial. A recent study demonstrated that dilutions of 10 units/mL to 100 units/mL produced indistinguishable results in the treatment of glabellar rhytids.[33]

The authors reconstitute OnaA in 1 mL of preserved saline and AboA in 3 mL, which yields a concentration of 1 unit per 0.01 mL for both agents (**Table 2**). Thus, each gradation on an insulin syringe corresponds to 1 unit. This approach affords an added safety measure and reduces the potential for error when support staff are instructed to draw up a specified quantity of BTX.

The manufacturers of both BTX-A products recommend usage within 4 hours of reconstitution. However, there is no loss of efficacy after up to 6 weeks of storage of reconstituted OnaA at 4°C.[34] Although it is advised to slowly and carefully add diluent to the vial to avoid bubbles, a comparison of an agitated, foamy solution of BTX-A to an unagitated solution failed to reveal significant differences in response or duration of effect.[35]

Table 2
Dilution table for OnaA (100-unit vial) and AboA (300-unit vial)

Diluent Volume (mL)	OnaA Units (bU) per 0.1 mL	AboA Units (sU) per 0.1 mL
1.0	**10.0**	30.0
1.5	6.7	20.0
2.0	5.0	15.0
2.5	4.0	12.0
3.0	3.3	**10.0**
4.0	2.5	7.5
5.0	2.0	6.0

Authors' preferred concentrations are in bold.

The authors prefer to inject using an insulin syringe with a 31-gauge needle. These syringes have no dead space between the syringe barrel and needle, minimizing waste. They have easily visualized gradations, which correspond 1:1 with units of BTX-A when reconstituted as previously described. Finally, the ultrafine needle is well tolerated by patients.

ONSET AND DURATION OF ACTION

Clinically detectable rhytid reduction occurs 3 to 7 days after injection, although the onset of action of OnaA has not been formally studied. In contrast, the self-reported onset of action of AboA was specifically investigated in its 4 phase III FDA trials. Patients were asked to maintain diaries during the initial 7 days following injection. The patients' self-reported median onset of action ranged from 2 to 4 days with 13.4% to 32.5% responding in the first 24 hours. (Schlessinger J, Kane M, Monheit GD. Time-to-onset of response of abobotulinumtoxinA in the treatment of glabellar lines: a subset analysis of phase 3 clinical trials of a new botulinum toxin type A. Submitted for publication.) Some have proposed, therefore, that AboA has a more rapid clinical efficacy than OnaA but head-to-head comparative analyses of this endpoint do not exist. Furthermore, the mechanistic rationale for speedier onset is unclear. With both agents, maximum benefit may not occur for 2 weeks after injection.

The longevity of the BTX-A response is variable and depends on dose (which determines the extent of denervation) and patient characteristics, such as age and baseline muscle strength. The duration of effect usually falls within a range of 3 to 5 months. There is some evidence that patients experience longer responses with repeated injections. This finding may be caused by slower neural regeneration but may also be a consequence of a conditioned behavioral change in facial expressiveness (ie, the prolonged inability to frown leads to diminished frowning even when muscle strength returns).

PRESENT USES

General Principles

1. Dose must be tailored to the individual patient, taking into account idiosyncratic anatomy, individual muscle size, tone and strength, baseline asymmetries, and perhaps most importantly, desired outcome.
2. A thorough knowledge of the anatomy in an area of injection is required to optimize efficacy and safety.
3. Neurotoxin monotherapy is most gratifying for patients with predominantly dynamic wrinkling or small facial asymmetries or ptoses. Patients with enhanced resting muscle tone that report looking angry or sad all of the time are also good candidates. Permanently etched lines, which usually represent wrinkling from photodamage or volume loss, generally require combined approaches with other modalities for satisfactory results.

TREATMENT OF THE UPPER FACE

Glabellar Lines

Injection of the glabella is the original and by far most common cosmetic usage of BTX-A. Numerous randomized, placebo-controlled trials have demonstrated the efficacy of both AboA and OnaA for this indication.

Anatomy

The glabellar complex depresses the medial brow and consists of the paired corrugator supercilii, which flank the central procerus muscle. Each corrugator originates medially on the frontal bone at the glabella just lateral to its junction with the nasal bone (this bony juncture is referred to as the nasion and underlies the anatomic concavity at the nasal root). The muscle fibers travel superolaterally to insert on the skin of the forehead just superior to the midpupillary eyebrow. As such, the corrugators adduct and depress the medial brow and produce the *vertical glabellar lines*. Laterally, the corrugators decussate with the medial portion of the orbicularis oculi, which also contributes to the glabellar complex.

The procerus originates from the fascia overlying the nasal bones and fans out superiorly to insert broadly in the skin of the lower central forehead. Contraction produces the *horizontal frown lines* at the nasal root.

Injection

Patients are requested to frown maximally. Muscle size and strength can be qualitatively categorized as a mild, moderate, or severe frown (**Fig. 1**) and the dose adjusted accordingly. Also, it is important to compensate for asymmetry in corrugator strength, which is common, with differential BTX dosing. Occasionally, patients present with a broad procerus or even 2 apparent procerus bellies, a bifid procerus. In these patients, we typically divide the procerus dose into 2 injections into each belly.

The standard 5-injection point approach is appropriate for most patients with 2 injections in each corrugator and 1 injection in the procerus as diagrammed in **Fig. 2**. The procerus and medial corrugators are injected deeply and directly into

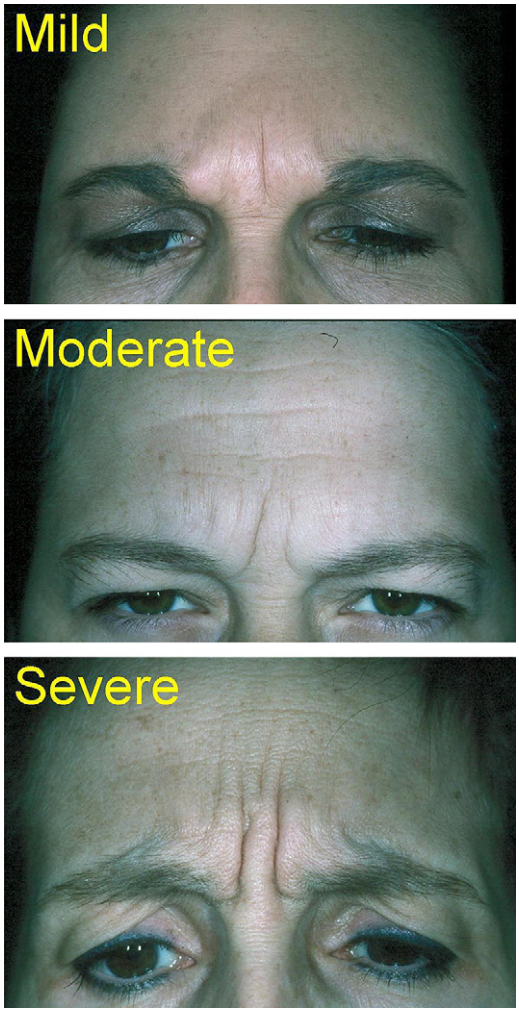

Fig. 1. Frown severity.

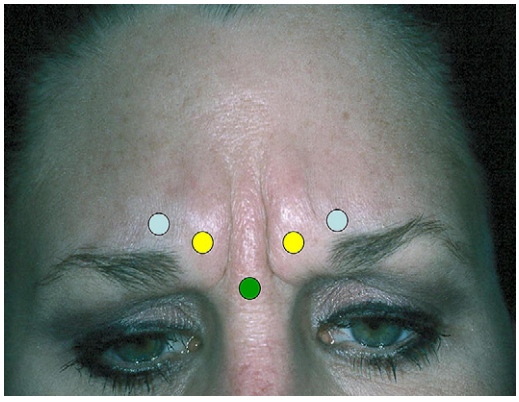

Fig. 2. Injection sites for glabellar line treatment: Blue dots indicate the corrugator insertion/orbicularis oculi fibers, yellow dots indicate the corrugator bodies, and the green dot indicates the procerus.

the bodies of the muscles, which are easily identified at maximal frown in most patients. The lateral corrugator is injected slightly more superficially where it inserts into the dermis and medial to the midpupillary line. These lateral injections also target fibers of the orbicularis oculi. All injections should be 1.0 cm (approximately 1 fingerbreadth) above the orbital rim to limit the risk of eyelid ptosis from the spread of toxin to the levator palpebrae muscle.

The total dose of OnaA should be 20 bU and the total dose of AboA should be 50 sU in women with moderate frown, divided evenly among the 5 injections. As always, doses must be adjusted for the strength of individual muscles and the patients' desired outcome. A dose-ranging study exhibited improved results with men who received 40 bU in the glabella versus 20 bU. Higher doses did not result in more adverse events and no cases of ptosis were reported in this small study.[36] The authors do use a higher dose of toxin in men and may add 2 additional injection points at the midpupillary line in those with bulky corrugators. However, the authors almost never exceed a total dose of 40 bU in any patients.

In the initial clinical trials with AboA, men did not have as robust a response to the 50 sU dose as did women, presumably because of increased muscle mass. This finding inspired a further study that varied the AboA dose with corrugator/procerus volume. Men with mild frown (small muscle mass) received 60 sU, moderate 70 sU, and severe 80 sU. Correlating the dose with muscle mass raised the response rate of men to that of women and increased the longevity of response in all patients.[37]

Forehead Lines

Although an off-label usage, BTX-A provides excellent smoothing of forehead rhytids and is generally a gratifying procedure for patients when performed properly. However, the more severe forms of forehead wrinkles cannot be corrected by BTX-A denervation alone and may need soft-tissue augmentation. This need can be determined by the degree of wrinkling and the affect of BTX in reducing the wrinkle. Moderate to severe dynamic wrinkles at rest and at maximal frown usually indicate filling material or even surgical intervention may be needed for full forehead and brow correction. Perhaps more so than any other region of the face, the placement and dosage of toxin can be highly customized, and optimal results are achieved when factors, such as forehead height and width, muscular strength,

symmetry, and baseline brow position, are all incorporated into a treatment plan.

Anatomy

Contraction of the frontalis muscle produces horizontal forehead lines. This muscle is a paired muscle that originates in the galea aponeurotica inferior to the coronal suture essentially at the frontal hairline. Its fibers run vertically and insert in the subcutis and deep dermis of the eyebrow at the superciliary arch (the bony projection of the frontal bone superior to the orbital rim). The frontalis is frequently absent at the midline, although this is variable. The frontalis is the only significant brow elevator. Its inferiormost portion is critical for opposing brow depression by the orbicularis oculi at rest.

Injection

The goal for the treatment of forehead wrinkles is to soften the undesirable lines without causing brow ptosis or eliminating all expressiveness on the upper face. A conservative approach is preferred, informing patients preoperatively that more than 1 treatment may be needed to reach the desired level of wrinkle reduction while avoiding undesirable side effects. Patients are asked to forcefully raise their eyebrows and the strength of the frontalis is assessed. Any discrepancy in brow position at baseline and at maximal contraction is noted and brought to the attention of the patients. A compensatory downward dose adjustment should be made on the side with the lower eyebrow. In the average brow, 2 to 4 bU or 5 to 10 sU are injected in 4 to 6 sites at least 2.5 to 3.0 cm above the orbital rim. Administration more inferiorly greatly increases the risk of brow ptosis. In toxin naïve patients, the authors almost always begin at the lower end of that dosage range. A common strategy is to place the line of injection parallel and inferior to a deep furrow crossing the middle to upper third of the forehead (**Fig. 3**). For high foreheads (typically men) or those with many fine wrinkles, the same total dose may be divided into 2 lines of injection across the forehead separated by 1 cm. A lateral arch to the eyebrow is characteristic of the female brow pattern. This arch can be accentuated in female patients by placing less toxin lateral to the midpupillary line or raising this injection point 1 cm relative to the midforehead and central forehead injections. The authors commonly use a *V*-shaped configuration for injections in women (**Fig. 4**). Although often desirable in women, this should be avoided in male patients. This approach can also produce an excessively arched brow (the mephisto sign or Dr Spock look) that will require correction with a small dose of additional toxin 1 to 2 cm superior to the apex of the arch.

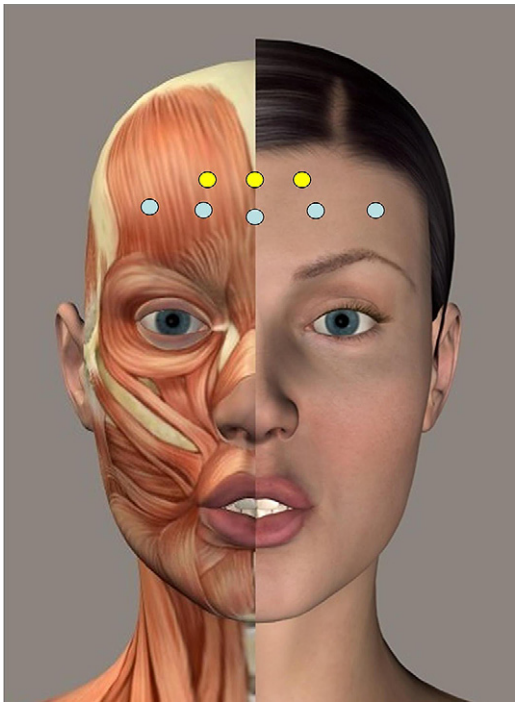

Fig. 3. Standard forehead line treatment: a typical approach is 4 to 6 injection points across middle of forehead (yellow dots indicate optional injection points in high foreheads). Lateral injection points determine degree of eyebrow movement. Keep injections at least 2.5 to 3.0 cm above brow to avoid brow ptosis and loss of expressivity. (*Adapted from* de Maio M, Rzany B. Botulinum toxin in aesthetic medicine. Berlin: Springer-Verlag; 2007; with permission.)

Unless no significant glabellar lines are present, the authors commonly inject the glabella

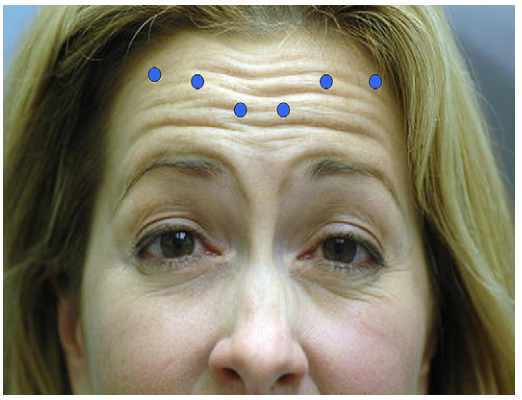

Fig. 4. Forehead line treatment in women. Variation favored by authors to accentuate the lateral arching of the feminine brow pattern.

simultaneously whenever treating forehead wrinkles. This practice generally produces better overall aesthetic results and the concomitant paralysis of the brow depressors reduces the incidence of brow ptosis.

Lateral Eyebrow Lift

The paresis of muscles of facial expression not only smoothes dynamic wrinkles but can also influence the resting position of various facial elements. This property has been successfully exploited to lift the eyebrow, correcting mild brow ptosis, restoring a youthful brow arch, and giving the eye a more open appearance. The eyebrow position is determined by the balance of the resting tone of the brow elevator (the frontalis) and depressors (glabellar complex and orbicularis oculi). Unilateral injection into the medial brow depressors, as occurs with treatment of glabellar lines, elevates the medial and central brow modestly (<1 mm). Glabellar complex treatment alone has also been shown to lift the lateral brow by as much or more than the medial brow.[38] This unexpected result was postulated to stem from inadvertent paralysis of the inferomedial portions of the frontalis with a consequent increased tone in the lateral frontalis.

The vertical fibers of the lateral orbicularis oculi function to depress the lateral brow. BTX-A injected into these fibers can produce a significant lateral brow elevation, as much as 4.88 mm in one study, although a 2-mm elevation is more likely.[39] For this chemical brow lift, the authors typically inject 5 units of OnaA or 10 units of AboA intradermally at the lateral tail of the eyebrow 5 to 7 mm superolateral to the orbital rim (**Fig. 5**A). If performed in isolation, an additional injection into each corrugator body is typically added to complete the chemical brow lift. More commonly, the lateral brow lift injection is done in tandem with other upper face treatments, especially injection of the glabellar complex and forehead. In combination with medial and central frontalis denervation, which tends to lower the medial brow, a pleasingly arched female pattern eyebrow can be shaped (**Fig. 5**B).

Crow's Feet

Lateral periorbital wrinkling is one of the earliest signs of aging. Hyperkinetic lateral canthal lines are effectively treated with neurotoxin. In older patients, static wrinkling caused by photodamage becomes more prominent and is less responsive to BTX alone. It is important to manage expectations in these patients as they may need a resurfacing procedure in addition to toxin to achieve the desired wrinkle reduction.

Anatomy

The orbicularis oculi is the sphincter of the eye. It is divided into 3 parts: orbital, palpebral, and lacrimal. All 3 work in concert during forced closure of the eye. The orbital portion runs circumferentially around the orbital rim and is the primary portion targeted by BTX-A in the treatment of crow's feet (CF).

Injection

CF are typically treated with 3 equal injections of 2 to 4 bU or 5 to 10 sU evenly spaced along an arc lying at least 1 cm external to the orbital rim to avoid diffusion to the palpebral portion of the orbicularis oculi or to the levator palpebrae muscle (**Fig. 6**A, B). The middle injection is placed in line with the lateral canthus. Injections flanking this point at 8 to 10 mm are then placed, but their exact

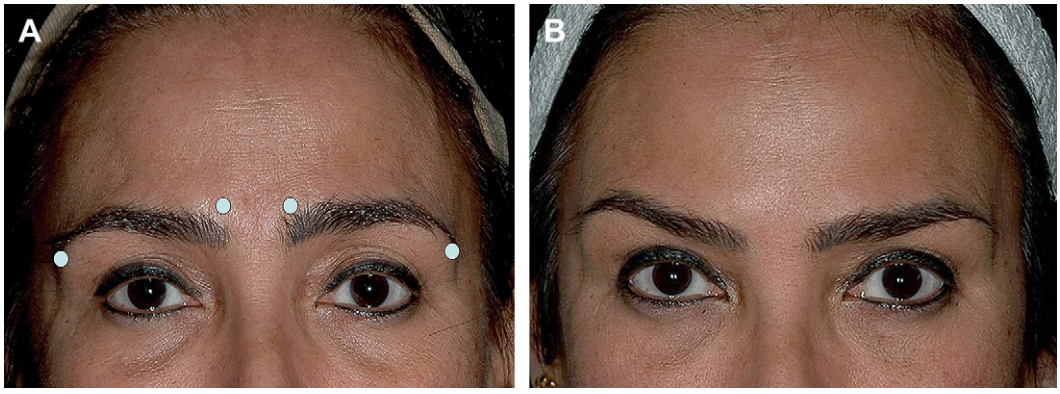

Fig. 5. The chemical brow lift. (*A*) Injection sites for a chemical brow lift if performed alone are shown (5–10 sU or 3–5 bU per injection site). This patient had a male pattern eyebrow without perceptible arching. She received AboA treatment to the lateral tail of each eyebrow (10 sU per side), into the corrugators bodies (total 20 sU), and to the frontalis (20 sU). (*B*) Posttreatment at 33 days reveals an elevated and laterally arched feminine brow.

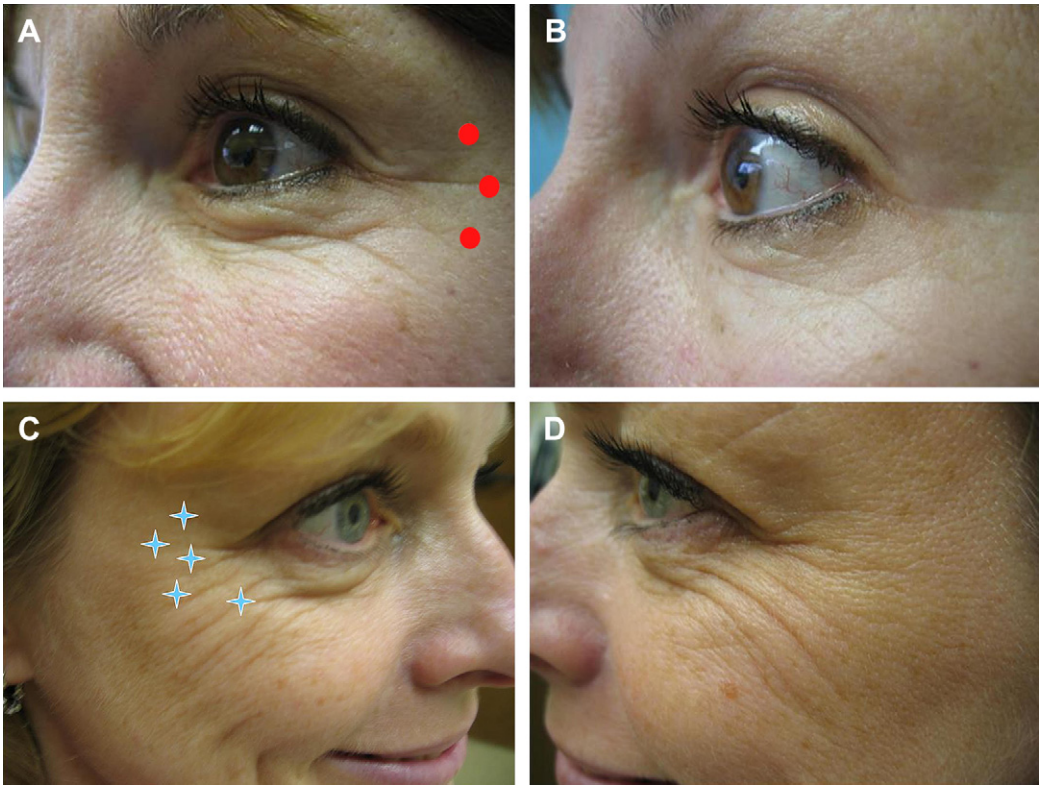

Fig. 6. Crow's feet injection. The standard 3-point CF injection is depicted in (*A*); the patient received 5 bU at each point and had an excellent response (*B*). (*C*) A variation that employs the same total dose (20–30 sU or 10–15 bU per side) but divided into 5 smaller injections for broad and wide canthal lines. (*D*) It is common for CF to have a significant inferior extension as in the pictured patient. It is imperative not to chase CF beyond the zygoma or one risks denervation of the zygomaticus muscles.

positioning depends on the width of the individual's canthal lines (**Fig. 6**C). The highest CF injection is inferior to the lateral eyebrow tail injection previously described for a chemical brow lift. The authors commonly lower this superior CF injection slightly when a CF treatment and a chemical brow lift are performed concomitantly. The skin of the temple is thin with little subcutis and the orbicularis oculi is located more superficially then most facial muscles. Injections, therefore, should be intradermal, producing a visible bleb.

The authors also commonly treat lower eyelid wrinkles with a series of 3 to 4 evenly spaced low dose, infraorbital injections of 0.5 to 1.0 bU or 1 to 2 sU (**Fig. 7**), usually injected in conjunction with and in the same manner as the CF injections. These multiple, low-dose intradermal injections can produce a notable smoothing of wrinkles with an excellent safety profile. The zygoma is a critical landmark for CF treatment. BTX should never be placed inferior to the zygoma (**Fig. 6**D), and any injections medial to the zygoma must be placed at or above the orbital rim. Violation of this rule can lead to unintended paresis of the zygomaticus major or minor muscles resulting in an ipsilateral mouth droop and a dissatisfied patient.

An additional injection of 1 bU or 2 sU can be judiciously placed in the lower lid at the midpupillary line 2 mm below the tarsal plate (**Fig. 8**). This injection will flatten the bulging muscle and create an image of an open eye. Overaggressive treatment may, though, create an unwanted ectropion.

TREATMENT OF THE MID AND LOWER FACE

As experience with BTX-A increases, many practitioners have ventured beyond the traditional applications of BTX-A in the upper face. Although not as extensively chronicled, BTX-A has definite utility in the rejuvenation of the mid and lower face but, in most patients, is best employed as adjuvant therapy with soft-tissue fillers or resurfacing procedures. The latter point has been highlighted in a recent prospective study. Ninety patients were randomized to receive (1) OnaA to the lips, depressor anguli oris (DAO), and mentalis muscles; (2) hyaluronic acid filler (Juvederm Ultra

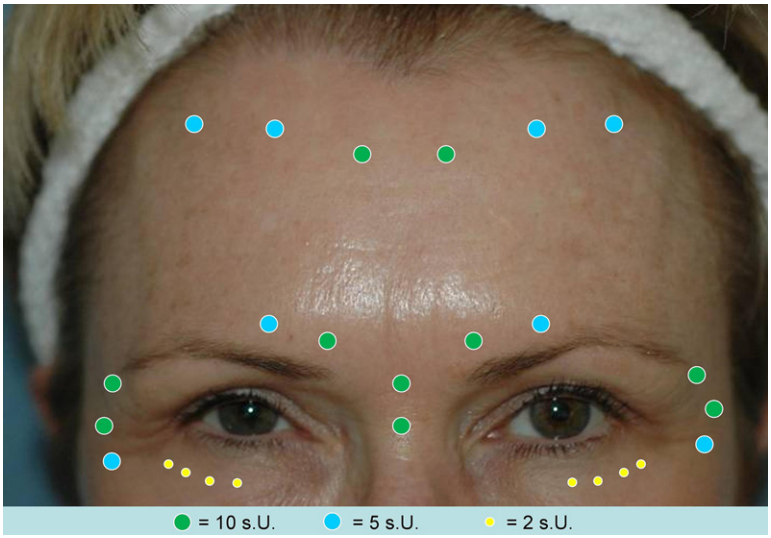

Fig. 7. Treatment of infraorbital wrinkles. A series of 3 to 4 *low dose, superficial* injections can effectively and safely smooth infraorbital rhytids (*yellow dots*). Injection must be at or superior to the orbital rim to avoid inadvertent paresis of mouth elevators and at or lateral to the midpupillary line to prevent epiphora (watering eye). The patient pictured had a complete upper face treatment: chemical brow lift, forehead, glabella, and CF. The picture illustrates the kind of tailored dosing strategy that produces optimal results with neurotoxins. The CF injections were reduced to 2 because of her narrow lateral canthal lines and orbit. A total standard dose of 50 sU was injected into the glabella but the dose was concentrated in her broad, well-developed procerus with less toxin administered laterally.

or Ultra Plus) to the lips, oral commissures, marionette lines, and chin; or (3) combined treatment with both. Multiple objective outcome measures were assessed, as was patient satisfaction. The group receiving both OnaA and dermal filler performed significantly better in all endpoints. Notably, the toxin-only group demonstrated the least efficacy.[40]

Bunny Lines

Multiple dynamic wrinkles on the upper nasal dorsum are common and can even be accentuated in BTX recipients as frowning patients compensate for glabellar paralysis.

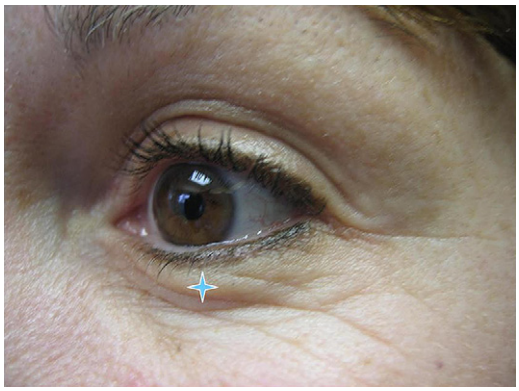

Fig. 8. Location of lower palpebral injection: a tiny dose of toxin into the lower eyelid can create a more youthful, open eye (2 sU or 0.5–1.0 bU).

Anatomy

The nasalis muscle has 2 portions. The alar portion dilates the nares and possesses minimal functional or cosmetic relevance. Nasoglabellar lines are a consequence of contraction of the transverse portion of the nasalis. The nasalis covers the nasal sidewalls, originating on the maxillary bones bilaterally and travelling medially to insert on a thin aponeurosis overlying the nasal bridge.

Injection

A single injection can be aimed at the point of maximal nasalis contraction (ie, the center of an imaginary circle encompassing the bunny lines). This point is usually one-third the way up the nasal sidewall and about 1 cm superior to the alar groove (**Fig. 9**). A dose of 2 to 4 bU or 5 to 10 sU per side is adequate for most patients.

Lips

Vertical perioral rhytids are a consummate feature of the aging face and can be bothersome, especially to female patients. Frequent puckering and pursing of the lips and activities, such as cigarette smoking, can contribute to the development of dynamic wrinkling in this area. However, perioral lines commonly possess a multifactorial etiology, including

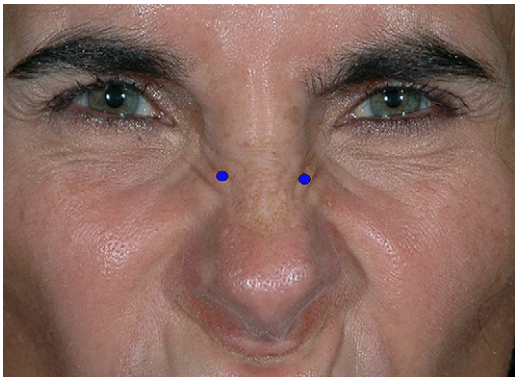

Fig. 9. Bunny line injection points: 10 sU or 5 bU units per point intradermally into nasal sidewall.

photoaging and chronologic aging, and, as such, benefit from a combined modality approach.

Anatomy

The elegant choreography of musculature that enables the diverse functionality of the human mouth (speech, music, mastication, and expression) is complex and a full discussion is beyond the scope of this review. Perioral BTX targets the central portion of the orbicularis oris, a wide, thin muscular band encircling the lips. The orbicularis oris controls closure and protrusion of the mouth.

Injection

For the upper cutaneous lip, 1 or 2 injections of 0.5 bU or 1.0 sU are placed on each side of the philtrum along the vermilion border (**Fig. 10**). BTX should never be placed where unintended paresis of the lateral lip elevators could occur. Therefore, the injections should be medial to a vertical line dropped from the lateral edge of the ala to the vermilion. The lower lip is treated similarly with 1 injection (0.5 bU or 1.0 sU) along the lower vermilion border either in line with the upper vermilion injection (if 1 injection) or bisecting the upper vermilion injections (if 2 injections).

The authors rarely, if ever, employ BTX alone to address perioral rhytids but do find it a useful complement to hyaluronic acid fillers in patients with a significant component of dynamic wrinkling.

Drooping Oral Commissures

Loss of dermal and subcutaneous volume in the lower face and resorption of the mandibular body occur inexorably with age. These processes frequently culminate in the formation of prominent melomental folds or marionette lines and an accompanying inferior displacement and downturn of the corners of the mouth. Adequate correction of this problem requires volume replacement, but a small, precise dose of BTX to the DAO muscles can provide a modest lift to the oral commissures, remedying an inverted smile.

Anatomy

The DAO is a triangular muscle with a broad base along the mandibular body beginning anterior to the masseter and extending to and a little beyond

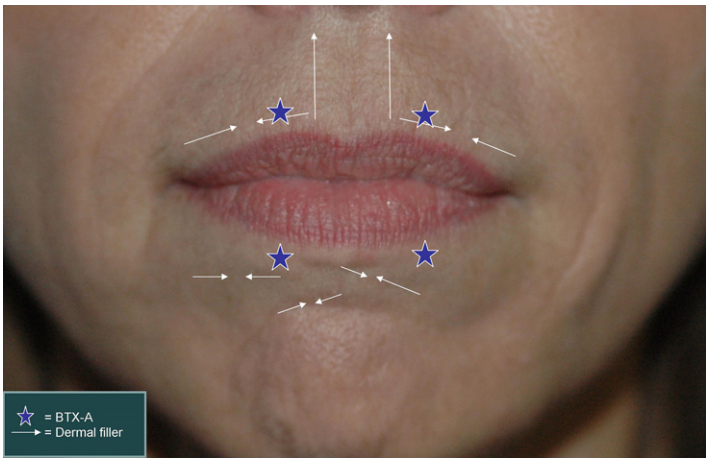

Fig. 10. Treatment of perioral rhytids: superficial perioral rhytids can be ameliorated with 1 to 2 microdoses of toxin per side (0.5 bU or 1.0 sU) placed near the upper vermilion border between the philtral crest and an imaginary vertical line dropped from the lateral edge of the ala (*blue stars*). These microdoses are coupled with a single injection per side at the lower vermilion border, if indicated. In approaching perioral rhytids, the authors usually combine toxin with dermal fillers. The pictured patient received hyaluronic acid filler along both philtral crests along the entire upper vermilion border (excluding the philtrum) and focally for depressions in the lower cutaneous lip (*white arrows*).

the oral commissure. It inserts at the oral commissure where its fibers interdigitate with the orbicularis oris and risorius muscles and contribute to the modiolus complex. As its name implies, DAO contraction generates an inferolateral pull on the corner of the mouth.

Injection

The DAO can be identified by instructing patients to clench their teeth, which facilitates palpation of the anterior border of the masseter. The DAO is then injected with 5 bU or 10 sU at a point 1 cm anterior to the masseter a few millimeters above the inferior border of the body of the mandible (**Fig. 11**A). Contraction of the DAO can usually be palpated at this location by directing patients to forcefully downturn the corners of their mouth. When treating DAOs, precise localization of toxin is critical. If BTX is injected at a point too high or too medial, then weakening of the orbicularis oris or depressor labii inferioris (**Fig. 11**B), respectively, could ensue with accompanying asymmetric smile, lip protrusion, and oral sphincteric incompetence. To avoid these untoward effects, BTX must never be placed close to the oral commissure.

Dimpled Chin and Mental Crease

Occasionally individuals will present with puckering and dimpling of their chin when they voluntarily or involuntarily contract their mentalis muscle. In others, a hyperkinetic mentalis produces a deep mental crease that is a source of self-consciousness. Although not common, these complaints can be ameliorated with partial denervation of the mentalis.

Anatomy

The mentalis is a paired muscle that originates low in the incisive fossa on the midline anterior surface of the mandible and inserts in the integument on either side of the frenulum of the lower lip. Contraction protrudes the lower lip but can also create a corrugated appearance to the chin.

Injection

Bilateral, symmetric 5 bU or 10 sU injections are made 2 mm above the inferior border of the body of the mandible about 5 mm lateral to midline (**Fig. 12**). Some injectors prefer a single midline injection (**Fig. 12**). Instructing patients to raise their lower lip to their nose will accentuate the mentalis and aid in localization of toxin. The depth of injection does not appear to be critical.

Platysmal Bands

Although the progress in nonsurgical rejuvenation of the face over the past decade has been nothing short of sensational, the same, unfortunately, cannot be said of the aging neck, which still poses a conundrum to the cosmetic surgeon. Attempts to eliminate horizontal neck creases with BTX have been discouraging. Despite overall frustration, neurotoxins have a clear role in the treatment of one bothersome component of the senescent neck, platysmal bands. As we age, there is an invariable loss of elasticity and soft-tissue support

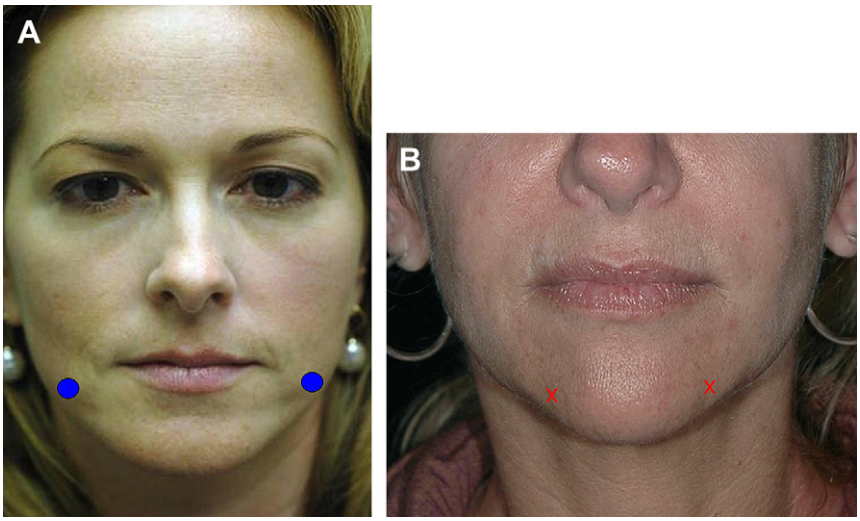

Fig. 11. Depressor anguli oris injection points: (*A*) The DAO is injected approximately 1 cm medial to the lateral edge of the masseter. Although the DAO is actually centered somewhat medial to this point, the injection targets its lateral fibers and is adequate to lift the oral commissure. (*B*) Injection too far medially (*red Xs*) risks paresis of the depressor labii inferioris and an asymmetric smile.

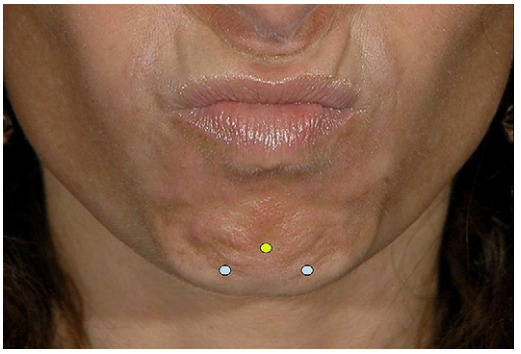

Fig. 12. Dimpled chin injection points: the mentalis is treated with 2 symmetric injections as shown (*blue dots*). A variation is single midline injection at a higher point (*yellow dot*) nearer the center of the body of the mentalis.

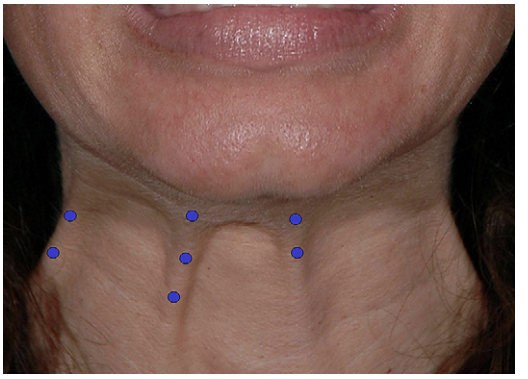

Fig. 13. Platysmal bands injection points: platysmal bands are treated with a series of 2 to 5 injections (2–4 bU or 5–10 sU each) spaced 2 cm apart along the length of the band. The total dose per band should be kept less than 50 sU or 25 bU. Pinching the band before injection can be helpful. Avoid deep injections in the neck.

of the neck. The resultant thinning and flaccidity of the neck skin makes platysmal contraction more prominent. This factor combined with an age-related separation and clumping of anterior fibers of the platysma generates readily apparent, tense, muscular cords vertically in the neck known as platysmal bands.

Anatomy

The platysma is a broad sheet of muscle that originates from the superficial fascia of the upper chest, clavicular, and parasternal regions. It envelops the anterior and lateral neck except for a thin strip devoid of fibers at the midline. The platysma crosses the mandible and then blends into the superficial muscular aponeurotic system encasing the muscles of facial expression of the lower face.

Injection

Two to 4 bU or 5 to 10 sU are injected into each platysmal band superficially beginning near the jawline and progressing caudally at 2-cm intervals (**Fig. 13**). Typically 2 to 5 injections and a total of 12 to 25 bU per band are required. To limit the total dose, no more than 3 or 4 bands are treated in one session. Excessive doses of BTX in the neck can produce hoarseness and dysphagia from denervation of laryngeal musculature.

COMPLICATIONS

The overall safety record of BTX is exceptional. A recent meta-analysis of placebo-controlled trials with OnaA for either lateral canthal or glabellar rhytids found only 3 adverse events (AEs) were more common than placebo among 1170 subjects: eyelid sensory disorder (2.4%), which includes subjective symptoms of tightness and heaviness; eyelid edema (1.1%), and eyelid ptosis (1.8%).[41]

Adverse sequelae of BTX administration can be divided into 2 major categories: product-related complications and technical complications. Importantly, all AEs to date have been ephemeral in nature and, to the authors' knowledge, no credible long-term complications have even been proposed, much less established.

Product-Related Complications

Considering the protracted list of side effects with most modern pharmaceuticals and the prodigious number of patients exposed to BTX, the number and frequency of true drug reactions to BTX is remarkably low. The injection of a foreign protein might be expected to trigger immunologic phenomena, but these are exceedingly rare. Type I immediate hypersensitivity reactions characterized by urticaria or anaphylaxis are listed as possible AEs on the package insert for OnaA. However, a literature search for these and other allergic complications revealed only one reported case of anaphylaxis.[42] This case was a fatal AE occurring in response to an unapproved BTX-lidocaine amalgam.[43] No cases of urticaria were found. There were only a handful of reports of cutaneous eruptions or potential hypersensitivity reactions that could be reasonably attributed to BTX-A or an associated excipient.[44–48] A 2005 comprehensive review of FDA AE reporting revealed 47 cases of unspecified "nonserious rash" and 13 "serious" cases of "allergic reactions/rash" out of millions of exposures, with 85% of the latter serious reactions following noncosmetic usage.[49]

Similarly, BTX does not appear to provoke significant cell-mediated immunity with few, if

any, well-established reactions consistent with a delayed type hypersensitivity. There has been one report of postinjection nodules diagnosed as sarcoidosis[50] and one report of a fixed drug eruption elicited by the lactose included with AboA.[48] Three of the documented BTX-related eruptions previously mentioned had a morbilliform character comparable to a classic drug exanthem[45,47] (although 2 of these did not recur on rechallenge). BTX, in sufficient doses and durations, will, however, engender significant humoral immunity, including neutralizing antibodies. These antibodies have been reported in patients treated for cervical dystonia who receive repetitive treatments, each typically well in excess of 100 bU.[51,52] Despite intensive investigations by the manufacturers and others, neutralizing antibodies have not been discovered in patients treated for cosmetic purposes except for one patient after receiving 240 bU (4 injections of 60 bU) for masseter hypertrophy.[53,54]

Complications Related to Technique

Untoward sequelae that can occur at any site from BTX includes bruising, edema, erythema, pain, and transient numbness. These complaints are common to all percutaneous injections. Headache (usually mild) can develop, especially with treatments of the upper face, but in the aforementioned meta-analysis the incidence of headache in the BTX and placebo arms was not statistically different (10.6% vs 9.5%).[41] Alam and colleagues[55] described a rare, idiosyncratic severe headache reaction that can last up to 1 month, and patients should be counseled of this improbable outcome.

The second major group of technical complications is dose-dependent direct pharmacologic effects and involves either overtreatment of a targeted muscle (eg, brow ptosis from forehead paralysis) or unintentional paresis of adjacent musculature (eg, blepharoptosis following glabellar complex treatment). Most of these potential sequelae have been discussed in the relevant sections previously mentioned and are all avoidable with appropriate consideration of placement and dose. Much has been made of the different diffusion characteristics of current and future BTX-A products and how this may impinge on the relative safety of the agents. It is important, however, to temper this theoretical debate with the reality of published clinical experience. Per

Table 3
BTX-A dosages for common cosmetic applications

Indications	Total Usual Dose	Number of Injections	Dose Range
Glabella	50 sU 20 bU	5 (7 in some men)	40–80 sU 15–40 bU
Forehead	40–50 sU[a] 15–20 bU[a]	4–6	20–70 sU 10–30 bU
Crow's feet	60 sU 30 bU	3 per side	30–60 sU 18–30 bU
Lateral eyebrow lift	20 sU 10 bU	1 per side	10–20 sU 6–10 bU
Lower eyelid wrinkles	8–12 sU[b] 4–6 bU[b]	3–4 per side[b]	6–14 sU[b] 3–8 bU[b]
Bunny lines	20 sU 10 bU	2	10–20 sU 6–10 bU
Perioral wrinkles	4–6 sU 2–3 bU	4–6	4–6 sU 2–3 bU
Drooping oral commissure (DAOs)	20 sU 10 bU	2	10–20 sU 6–10 bU
Dimpled chin (mentalis)	20 sU 10 bU	2	10–20 sU 6–10 bU
Platysmal bands	20–35 sU 10–15 bU (per band)	2–5 per band (maximum 4 bands per treatment)	15–50 sU 12–25 bU (per band)

Total dose and dose range assume bilateral treatment, unless otherwise indicated.
[a] The authors almost always begin with a lower dose in new patients (20–30 sU or 10–12 bU).
[b] Does not include the optional extra injection 1 to 2 mm inferior to eyelid margin described in the text.

their respective package inserts, the incidence of lid ptosis accompanying the treatment of glabellar lines with 20 bU of OnaA was 3% compared with 2% with 50 sU of AboA. A review of the overall experience at one center administering AboA to 500 patients for facial rhytids in multiple anatomic locations was recently published. Dr Hevia used a consistent 1:2.67 unit dose ratio (OnaA/AboA) and a concentration of 133 sU/mL. There was a 0.6% overall incidence of ptosis (2 cases of lid ptosis and 1 case of brow ptosis) and no other significant AEs.[56] To the authors' knowledge, at recommended dosages and volumes, evidence of detectable differences attributable to less precise localization of one agent versus another in actual clinical practice does not yet exist. This fact should offer reassurance to the injector when administering either of the currently FDA-approved agents. See **Table 3** for a summary of Botox dose ranges for the most typical cosmetic applications.

SUMMARY

The advent of BTX-A in the 1990s effectively launched the modern era of nonsurgical aesthetic medicine. Many of the components of the senescent face, which previously required surgical intervention, are now readily addressed with neurotoxin. Its wide acceptance paved the way for the adoption of numerous other injectables, which are now commonplace in the cosmetic surgeon's office.

The two BTX-A products currently approved in the United States for cosmetic use share the same active ingredient and largely similar clinical properties. Because of the absence of unit equivalency and unbiased comparative trials, injectors should not consider the agents interchangeable. OnaA and AboA are best conceptualized as unique pharmaceuticals until more data is available.

BTX-A in monotherapy can be used to correct dynamic wrinkling of the upper face with an outstanding safety profile. BTX-A in the lower face is best thought of as a complement to soft-tissue fillers and resurfacing procedures but still plays an important role. In all areas, administration of BTX-A must be individualized based on patients' gender, muscle mass, and baseline symmetry. The patients' desired outcome is also an essential component in designing a treatment plan. Most patients and physicians target a natural look that softens wrinkles while maintaining some facial expressivity. The frozen look, so common when practitioners were first acclimating to BTX, should be a relic of the past. Similarly, in all applications optimal results and patient satisfaction may necessitate combining multiple aesthetic modalities.

The upcoming approval of two additional BTX-A injectables alongside a topical formulation will offer the aesthetic surgeon a diverse armamentarium to denervate facial musculature. Insight into how these new products behave differently from those currently available must await further investigations and more clinical experience. If nothing else, the infusion of healthy price competition among these agents should only serve to make neurotoxins accessible to more of our patients.

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