CME/CE Monograph

EARN CME/CE CREDITS

ABOUT FACE

Navigating Neuromodulators and Injection Techniques for Optimal Results

Visit http://tinyurl.com/AboutFaceDT for online testing and instant CME/CE certificate.

RELEASE DATE: JUNE 1, 2019 **EXPIRATION DATE:** JUNE 30, 2020

FACULTY

Steve G. Yoelin, MD *(Chair)*

Joel L. Cohen, MD

Dee Anna Glaser, MD

Joely Kaufman, MD

Ava Shamban, MD

This continuing medical education activity is jointly provided by Amedco and MedEdicus LLC.

This continuing medical education activity is supported through an unrestricted educational grant from Galderma Laboratories, LP.

AMEDCO MedEdicus LLC

Distributed via DermatologyTimes

ACTIVITY DESCRIPTION

This activity provides a review of the properties and aesthetic uses of currently available neuromodulators, or botulinum neurotoxin type A products, through a review of the literature, real-world cases, and expert clinical perspectives. The desired results of this activity are for health care practitioners to improve their ability to provide neuromodulators appropriately to their patients for optimal patient outcomes.

TARGET AUDIENCE

This educational activity is intended for health care practitioners, including physicians, physician assistants, nurse practitioners, and nurses, with an interest in facial aesthetics.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Explain the conversion ratio needed for individual neuromodulators
- Use appropriate reconstitution procedures for the different neuromodulators
- Explain how to switch between neuromodulators to achieve optimal clinical outcomes
- Employ appropriate strategies for the management of complications to improve patient satisfaction
- Describe the anatomy of the face and neck that is relevant to ensure safe and effective treatment outcomes
- Illustrate the most appropriate injection strategies for a variety of patients treated with neuromodulators

SATISFACTORY COMPLETION

Learners must pass a post-test and complete an evaluation form online by going to **http://tinyurl.com/AboutFaceDT.** Upon passing, you will receive your certificate of completion immediately. You must score 70% or higher to receive credit for this activity, and may take the test up to 2 times. You must participate in the entire activity as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

JOINT ACCREDITATION STATEMENT

In support of improving patient care, this activity has been planned and implemented by Amedco and MedEdicus LLC. Amedco is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

CREDIT DESIGNATION STATEMENT

Amedco designates this enduring activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™ for physicians and 1.5 contact hours for nurses. Learners should claim only the credit commensurate with the extent of their participation in the activity.

GRANTOR STATEMENT

This continuing medical education activity is supported through an unrestricted educational grant from Galderma Laboratories, LP.

DISCLOSURE OF CONFLICTS OF INTEREST

The following table of disclosure information is provided to learners and contains the relevant financial relationships that each individual in a position to control the content disclosed to Amedco. All of these relationships were treated as a conflict of interest, and have been resolved. (C7 SCS 6.1, 6.2, and 6.5)

All individuals in a position to control the content of CME/CE are listed. If their name is not listed below, they disclosed that they had no relevant financial relationships.

NAME	COMPANY	ROLE
Joel L. Cohen	Allergan; Biopelle, Inc; Evolus, Inc; Galderma Laboratories, LP; Lutronic; Merz, Inc; Revance Therapeutics, Inc; Sciton, Inc; SENTÉ Inc; Sonoma Pharmaceuticals, Inc; and Swiss-American CDMO, LLC	Consultant
	Galderma Laboratories, LP; and Sciton, Inc	Speaker
	Athenex, Inc; Biofrontera AG; BioMimetix Pharmaceutical, Inc; Biopelle, Inc; Brickell Biotech, Inc; Croma-Pharma GmbH; Dyve Biosciences; Endo Pharmaceuticals Inc; Evolus, Inc; Ferndale Healthcare, Inc; Galderma Laboratories, LP; Lutronic; Merz, Inc; and Revance Therapeutics, Inc	Contracted Research
Dee Anna Glaser	Dermira, Inc; Galderma Laboratories, LP; and OrthoDerm	Speaker
	Allergan; Atacama Therapeutics, Inc; Brickell Biotech, Inc; Dermira, Inc; Galderma Laboratories, LP; and Revance Therapeutics, Inc	Contracted Research
Joely Kaufman	Allergan; Croma-Pharma GmbH; Cutera; Endo Pharmaceuticals Inc; Evolus, Inc; Galderma Laboratories, LP; Merz, Inc; and Revance Therapeutics, Inc	Contracted Research
	Allergan; and Galderma Laboratories, LP	Speaker
Ava Shamban	Allergan; Galderma Laboratories, Inc; and Merz, Inc	Consultant
	Allergan; Brickell Biotech, Inc; Endo Pharmaceuticals Inc; Galderma Laboratories, Inc; Merz, Inc; Revance Therapeutics, Inc; Sienna Biopharmaceuticals; and Teoxane	Contracted Research
Steve G. Yoelin	Allergan; and Evolus, Inc	Consultant
	Allergan	Speaker
	Allergan; Merz, Inc; and Revance Therapeutics, Inc	Contracted Research

DISCLOSURE OF UNLABELED USE

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Amedco; MedEdicus LLC; Galderma Laboratories, LP; or *Dermatology Times.*

FACULTY

Steve G. Yoelin, MD *(Chair)*
Ophthalmologist
Steve Yoelin, MD, Medical Associates
Newport Beach, California

Joel L. Cohen, MD
Director, AboutSkin Dermatology and DermSurgery
Greenwood Village and Lone Tree, Colorado
Associate Clinical Professor
University of California, Irvine
Irvine, California

Dee Anna Glaser, MD
Professor and Interim Chair
Department of Dermatology
Professor of Internal Medicine and Otolaryngology
Saint Louis University School of Medicine
St Louis, Missouri

Joely Kaufman, MD
Director
Skin Associates of South Florida
Associate Professor of Dermatology
University of Miami Miller School of Medicine
Coral Gables, Florida

Ava Shamban, MD
Assistant Clinical Professor of Dermatology
Geffen School of Medicine
University of California, Los Angeles
Owner and Director
Ava MD
Los Angeles, California

ABOUT FACE

Navigating Neuromodulators and Injection Techniques for Optimal Results

Introduction

Achieving successful outcomes and patient satisfaction with botulinum neurotoxin type A (BTXA) injection requires that clinicians understand the properties of the individual products, along with their similarities and differences, and be knowledgeable about relevant anatomy, reconstitution, dosing, and proper injection technique. Multiple BTXA products are commercially available for cosmetic use, but each product has unique characteristics, and the marketed products are not interchangeable. This review addresses the aforementioned topics through an evaluation of relevant literature, experts' clinical perspectives, and case narratives.

Manufacturing and Composition

Since 2010, practitioners in the United States have had access to 3 commercially available BTXA products with cosmetic indications: abobotulinumtoxinA (aboBTXA), incobotulinumtoxinA (incoBTXA), and onabotulinumtoxinA (onaBTXA) **(Table 1)**.[1-3] A fourth product, prabotulinumtoxinA-xvfs (praBTXA), was approved by the US Food and Drug Administration in February 2019.[4] AboBTXA, incoBTXA, onaBTXA, and praBTXA all contain BTXA produced from fermentation of *Clostridium botulinum* type A strain, but they are produced using different manufacturing processes and vary from each other compositionally **(Table 1)**.[1-3,5-7] (Note: At the time this CME/CE activity was developed, praBTXA was not commercially available. Because of a lack of practical experience with praBTXA, it is not discussed in detail in this activity.)

Clostridium botulinum type A produces a protein complex that contains a core neurotoxin protein, BTXA (~150 kDa), bound to ≥ 1 nontoxic accessory proteins (NAPs). The NAPs are removed during the purification process for incoBTXA. With the other products, the NAPs dissociate from the core neurotoxin in the vial upon reconstitution when the protein complex is exposed to the physiologic pH of normal saline.[8]

Potency for BTXA products is expressed in units and determined for each product with the manufacturer's proprietary assay method and reference standard.[5,9] Therefore, potency units are product specific and not interchangeable among BTXA products.

Conversion Ratios

Preclinical and clinical studies have been conducted to determine conversion ratios among products that can be used as a guide for selecting doses that will result in similar efficacy and safety and for comparing relative treatment cost. The studies produced varying results that can be explained by their methodological inconsistencies, including differences in anatomic sites of injection, BTXA doses, and end points to determine treatment efficacy. Several reviews of available study data, however, suggest that the conversion ratio ranges between 2:1 and 3:1 for aboBTXA:onaBTXA and is 1:1 for incoBTXA:onaBTXA.[9-11] It is important to reiterate that there is no universally accepted conversion ratio among products; the topic remains open to discussion.

Experts' Clinical Perspectives

Dr Yoelin: What conversion ratios for aboBTXA:onaBTXA and incoBTXA:onaBTXA do you use in your practice?
Dr Glaser: I find that the ratio needed to achieve similar results in terms of peak effect and durability with aboBTXA:onaBTXA varies among different anatomic sites. Therefore, a ratio of between 2.5:1 and 3:1 gives a good starting point, but it is not absolute. For incoBTXA:onaBTXA, I generally use a ratio higher than 1:1, typically between 1.2:1 and 1.5:1. I teach residents that converting from one toxin to another is like learning a foreign language in the sense

Table 1. BTXA Products With Cosmetic Indications

	OnaBTXA[1,5]	AboBTXA[2,6]	IncoBTXA[3,5]	PraBTXA[7]
Year of FDA approval	2002*	2009	2010	2019
Active substance (molecular weight)	BTXA with NAPs (900 kDa)	BTXA with NAPs (500-900 kDa)	BTXA without NAPs (150 kDa)	BTXA with NAPs (900 kDa)
Excipients	Human serum albumin, sodium chloride	Human serum albumin, lactose	Human serum albumin, sucrose	Human serum albumin, sodium chloride
Purification method	Crystallization	Chromatography	Chromatography	Not available
Finishing method	Vacuum dried	Freeze dried	Lyophilized	Vacuum dried
Potency testing method	Cell based	Animal based (LD_{50} assay)	Cell based	Animal based (LD_{50} assay)
Units per vial	50 or 100	300 or 500	50 or 100	100
Approved indications for cosmetic use†	Temporary improvement in the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate-to-severe lateral canthal lines associated with orbicularis oculi activity, and moderate-to-severe forehead lines associated with frontalis muscle activity	Temporary improvement in the appearance of moderate-to-severe glabellar lines associated with procerus and corrugator muscle activity in adults aged < 65 years	Temporary improvement in the appearance of moderate-to-severe glabellar lines with corrugator and/or procerus muscle activity	Temporary improvement in the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients

Abbreviations: aboBTXA, abobotulinumtoxinA; BTXA, botulinum neurotoxin type A; FDA, US Food and Drug Administration; incoBTXA, incobotulinumtoxinA; LD_{50}, median lethal dose; NAP, nontoxic accessory protein; onaBTXA, onabotulinumtoxinA; praBTXA, prabotulinumtoxinA-xvfs.

* Year of approval for cosmetic use

† AboBTXA, incoBTXA, and onaBTXA have both cosmetic and medical indications.

that once you become fluent in the foreign language, you no longer convert every foreign word back into English.

Dr Kaufman: I use a conversion ratio of 3:1 for aboBTXA:onaBTXA and 1.5:1 for incoBTXA:onaBTXA. With these ratios, I feel I can get similar results, including duration, with any of the available neuromodulators.

Dr Shamban: When trying to achieve similar results with different toxins, I consider duration of effect to be the important end point. With this in mind, I use a ratio of 3:1 for aboBTXA:onaBTXA and 1.5:1 for incoBTXA:onaBTXA.

Dr Cohen: I, also, use a ratio of 3:1 for aboBTXA:onaBTXA.

Dr Yoelin: I use the same 3:1 ratio for aboBTXA:onaBTXA. Another area of interest is how quickly the desired effects from these products can be achieved. Patients often want to see results quickly.

Do you think any of the toxins have a faster onset of action?

Dr Cohen: Results of at least 1 controlled split-face study showed a faster onset of action with aboBTXA than with onaBTXA,[12] and patient diary data from clinical trials are consistent with my clinical impression that aboBTXA might have a slightly faster onset than does onaBTXA, but this probably does not have real clinical relevance.

Dr Kaufman: Data from the aboBTXA study I conducted with Dr Cohen suggested that increasing the volume of diluent for reconstitution results in a faster onset.[13]

Dr Shamban: A recent study reported that onset of BTXA action for treatment of forehead and glabellar lines can be accelerated by 24 hours if patients perform postinjection facial exercises.[14]

Reconstitution

Directions for reconstitution found in both the prescribing information for the BTXA products and in manufacturers' guides list different volumes of diluent that result in different final concentrations. **Table 2** provides a simplified listing of reconstitution methods that result in a final volume of 0.1 mL for each BTXA.[1-3,7] The chosen diluent volume can vary, depending on such factors as site of injection, treatment goals, and patient-specific characteristics. Practitioners might have personalized approaches derived from their clinical experience.

Table 2. Simplified BTXA Reconstitution Methods

	Units per Vial	Diluent, mL	Dose per 0.1 mL, U
OnaBTXA[1]	100	2.5	4
AboBTXA[2]	300	3.0	10
IncoBTXA*[3]	100	2.5	4
PraBTXA[7]	100	2.5	4

Abbreviations: aboBTXA, abobotulinumtoxinA; BTXA, botulinum neurotoxin type A; incoBTXA, incobotulinumtoxinA; onaBTXA, onabotulinumtoxinA; praBTXA, prabotulinumtoxinA-xvfs.

* After adding diluent, incoBTXA must be swirled and inverted.

Experts' Clinical Perspectives

Dr Yoelin: I typically use 2 mL of bacteriostatic saline to reconstitute the 100-U vials of onaBTXA and incoBTXA and the 300-U vial of aboBTXA. This technique retains a 3:1 ratio of aboBTXA:onaBTXA and therefore makes it easy for me to do a dose conversion between toxins because I like to think about the volume injected at each site rather than the units dispensed. I believe that this strategy simplifies the injection process for someone who is a novice, intermediate, or advanced injector. In addition, I use the same reconstitution volume regardless of the intended site of injection because I believe it is helpful to reduce as many variables as possible when treating with BTXA.

What diluent volumes do you use for reconstituting vials of 300 U of aboBTXA and 100 U of incoBTXA and onaBTXA?

Dr Cohen: I also use the same diluent volume whether I am reconstituting the 100-U vial of onaBTXA or the 300-U vial of aboBTXA because it makes the dose conversion of aboBTXA to onaBTXA mathematically easy. For most areas, I use a 1-mL dilution for the 300-U vial of aboBTXa and the 100-U vial of onaBTXA.

During my fellowship, Alastair Carruthers, MD, once stated that when treating glabellar lines, dilution is done for the convenience of the injector, whereas dose determines efficacy for the patient. Results of studies I have done are consistent with this idea. In a recent study

evaluating aboBTXA, which Dr Kaufman and I conducted, efficacy, durability, and adverse events were similar when the 300-U vial was reconstituted with either 1.5 or 2.5 mL to administer a total dose of 50 U.[13] In an earlier study in which I was involved with Alastair Carruthers, MD, and Jean Carruthers, MD, during my fellowship, we found no difference in efficacy comparing treatments performed using onaBTXA reconstituted with 1, 3, 5, or 10 mL.[15]

Dr Kaufman: For injectors who are just starting out with BTXA injections, I recommend against using the 1-mL dilution for onaBTXA. The reason is 2-fold: (1) working with the more concentrated solution makes it more difficult to achieve the desired dose precision; and (2) there is more waste if any of the preparation is lost accidentally.

I generally use 2.0 mL for onaBTXA and aboBTXA, and approximately 1.5 or 1.6 mL for incoBTXA. As exceptions, I double the diluent volume when I am doing superficial intradermal injections for rosacea or when doing a Nefertiti lift to use in the very superficial aspect of the platysma because it wraps around the jawline. When I place the toxin superficially—for example, during Microtox procedures—I prefer to inject tiny amounts of neuromodulator, as low as 1 U per site. The goal is to treat the superficial, extremely thin muscle fibers without affecting the underlying deeper muscles. Other uses for hyperdiluted toxin could be for treating larger areas, in which the desire is to achieve even distribution of drug without reaching the end point of complete muscle paralysis. I love this approach for difficult-to-treat large foreheads, where complete paralysis might look unnatural or lead to flattened and lowered eyebrows.

Dr Shamban: I generally use 2.5 mL for onaBTXA, 3.0 mL for aboBTXA, and 2.0 mL for incoBTXA. I like a more concentrated solution when treating the glabella in order to avoid spread into the frontalis and a splayed brow appearance. For glabellar treatments, I use just 1 mL to dilute 300 U of aboBTXA or the 100-U vials of the other products.

Dr Glaser: I typically use 2.0 mL for onaBTXA and incoBTXA and 3.0 mL for aboBTXA. I increase the amount of diluent I use when I am treating the platysma, or sometimes for the forehead, because I believe that increasing the injection volume for a given dose leads to a greater spread, or field of effect.

My advice to novice injectors is to start by choosing 1 diluent volume for all treatments and staying with it to develop expertise and understand the results. Then, they can think about tweaking the approach by experimenting with different volumes according to body location and anatomy to see what works in their hands.

Field of Effect

Movement of neurotoxin away from the site of injection has relevance for efficacy and safety of BTXA injection, and it is discussed in the literature in various terms, such as spread, diffusion, and migration. Although these terms are sometimes used interchangeably, they are different by definition.[16] **Spread** refers to rapid physical movement of toxin from the injection site and depends on injection-related variables, whereas **diffusion** is the slow kinetic dispersion beyond the original injection site (the toxin's movement to receptors). **Migration** pertains to other mechanisms of movement, such as distal effects far from the injection point or retrograde axonal transport.

From a practical perspective, the overall area affected by injection of the neurotoxin—that is, the **field of effect**—is the issue of interest, regardless of the mechanism. Factors that might influence the field of effect include injection characteristics (eg, volume, speed, angle, depth, pressure, and needle gauge), dose and concentration of the neurotoxin, injection site, and postinjection massage/manipulation.[17,18]

Whether or not the field of effect differs among BTXA products is controversial. There are inconsistent findings from comparative studies that investigated this question, and cross-study comparisons are hampered by a lack of standardized terminology and methodology differences among studies, including differences in treatment sites, outcome measures, conversion ratios, doses, and injection volumes. Despite differences in their molecular weight due to the presence or absence of NAPs, aboBTXA, incoBTXA, and onaBTXA would be expected to have the same field of effect, given that NAPs are thought to dissociate from the core neurotoxin upon reconstitution. Consistent with this concept, an animal study found diffusion to adjacent muscles was similar for the 3 BTXA products and was limited overall.[19]

A small pilot study evaluating patients being treated for forehead hyperhidrosis reported that aboBTXA was associated with a greater field of anhidrotic effect than was onaBTXA.[20] Hexsel and colleagues conducted a series of comparative studies evaluating the field of effect following forehead injections of aboBTXA and onaBTXA using different conversion ratios and concluded that any differences between the products reflect the dose dependency of diffusion.[21-23] A review of these and other studies also supports the notion that dose is the determining factor in the field of effect.[24]

Experts' Clinical Perspectives

Dr Yoelin: From your experience, are there differences in field of effect with the various BTXA products?

Dr Kaufman: I think there is no difference in spread or diffusion among the 3 BTXA products when all other injection parameters are constant. If using a 3:1 conversion ratio for aboBTXA:onaBTXA, however, I might be giving a slightly higher dose of aboBTXA vs onaBTXA, and this might result in a slightly larger field of effect for aboBTXA.

Dr Cohen: A study reporting similar outcomes with aboBTXA treatment of crow's feet, whether the dose was injected into 1 or 3 sites, might also be interpreted as evidence for spread with aboBTXA.[25] If dose and other potential variables are controlled, I do not think there is any theoretical basis or real evidence to support the idea that there might be field-of-effect differences among the BTXA products. Having said that, however, aboBTXA is my preferred product if I am treating patients who have a large fan-shaped arch of lateral canthal rhytides (in which the patients' crow's feet are extensive, often extending from the lateral orbital rim to the temple hair line, such as in endurance athletes who train and squint for long periods of time) because in my hands, it works better than the other toxins in that setting. I do not know if it is a dose-related phenomenon explained by the conversion ratio I am using or a product-related field-of-effect difference.

Immunogenicity

Because they are foreign proteins, both the 150-kDa neurotoxin and the NAPs can stimulate antibody formation.[26] Antibodies to the neurotoxin that block its binding to neuronal cells might "neutralize" the neurotoxin's activity. Antibodies to the NAPs, however, do not affect neurotoxin activity.[27]

According to the literature, factors associated with the development of neutralizing BTXA antibodies include use of higher doses and a shorter interval between injections (< 2 months).[26] Compared with therapeutic indications, such as for the treatment of dystonia, cosmetic BTXA treatments use low doses, and reported rates of development of neutralizing antibodies in patients treated for cosmetic applications with any of the BTXA products are low or absent (0% to 0.28%).[28,29]

Furthermore, the development of neutralizing antibodies to BTXA does not absolutely result in lack of response, and patients might become nonresponders to BTXA injections without evidence of developing antibodies to BTXA.[28,30] Loss of benefit in the latter situation might be explained by muscle adaptation, inadequate dosing, improper administration technique, and unrealistic patient expectations.[24]

Experts' Clinical Perspectives

Dr Cohen: Anecdotally, I have heard of patients who became nonresponders after developing antibodies, but subsequently became responsive again after some period of time. I have several patients whom I treat for hyperhidrosis or a cosmetic indication (or both) using a shorter interinjection interval; in my experience, they do not seem to have any higher risk of becoming nonresponders. I think this immunogenicity risk significantly declined since onaBTXA had its protein load dramatically decreased in 1996.

Dr Glaser: It is likewise my experience using BTXA for cosmetic treatments that shortening the injection interval does not lead to a decrease in or loss of response.

ABOUT Case: Treatment of Female Glabella

From the Files of Steve G. Yoelin, MD

A 23-year-old woman presented to reduce the appearance of glabellar rhytides. She was treated with incoBTXA. The 100-U vial of incoBTXA was reconstituted with 2.0 mL of bacteriostatic saline. Using a 33G 0.5-in syringe, a total dose of 30 U was injected across 7 sites as follows: 5 U into each medial corrugator, 5 U into each lateral corrugator, and 5 U into the procerus ***(Figure 1A)****. In addition, 2.5 U was injected into the orbicularis oculi at each lateral brow to enhance brow lifting* ***(Figure 1B)****.*

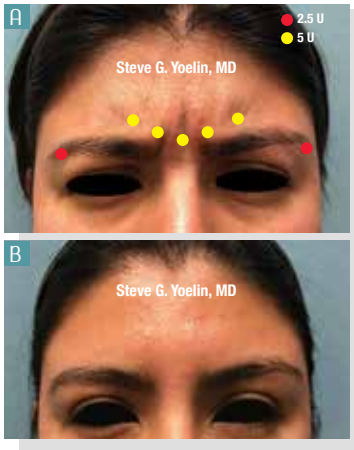

Figure 1. Glabellar rhytides were treated with 30 U of incobotulinumtoxinA as shown (A). A total dose of 30 U would be administered if onabotulinumtoxinA was used. A total dose of 90 U would be administered if abobotulinumtoxinA was used. Two injections of 2.5 U of incobotulinumtoxinA were injected at each lateral brow to enhance lifting (B).

Manufacturers recommend dividing the BTXA dose across 5 sites when treating glabellar lines and using total doses of 20 U for incoBTXA and onaBTXA and 50 U for aboBTXA.[1-3] This patient had a strong frown, so a higher dose was used to result in a greater duration of effect. In addition, it is safe to completely relax the glabellar complex. Although BTXA injection into the corrugator and procerus muscles will result in eyebrow elevation through relaxation of the depressor actions of the corrugator procerus muscle, administering 2 additional injections into the orbicularis oculi at each lateral brow results in enhanced browlifting by relaxing the depressor portion of the orbicularis oculi. Weakening of all of the depressors of the brow, central (including procerus) and lateral, will elevate the brow and can also result in reduction of lower forehead lines secondary to neurotoxin field of effect.

Eyelid ptosis can occur after BTXA treatment for glabellar lines. The risk can be minimized by keeping the injections into the corrugator muscle at least 1 cm above the brow and not lateral to the midpupillary line; applying digital pressure over the supraorbital rim during corrugator injection; and pointing the needle superiorly, away from the orbit.[31] Eyelid ptosis is self-limiting; if treatment is required, an ophthalmic alpha-adrenergic agonist (eg, apraclonidine, 0.5%) can be used to elevate the ptotic eyelid.

ABOUT Case: Treatment of Male Glabella

From the Files of Joely Kaufman, MD

A 54-year-old man presented to the office complaining of a "weird" look to his forehead after he was treated at another office 10 days prior. He was not sure which BTXA he had received. On examination, he had elevation of the lateral brow at rest and extensive peaking on animation ***(Figure 2A)****. Two 7.5-U doses of aboBTXA were administered to normalize the frontalis activation and give him a straighter, more natural looking male brow* ***(Figure 2B)****.*

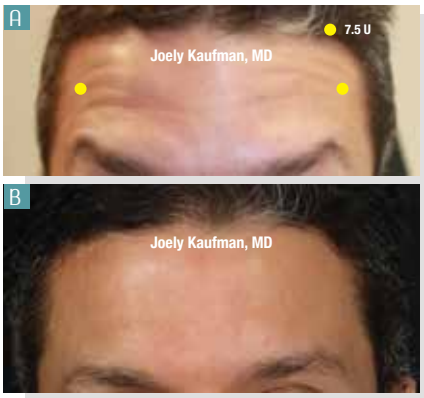

Figure 2. Corrective treatment of brow arching in a male patient using 2 injections of abobotulinumtoxinA (7.5 U each) in the lateral portions of the frontalis (A) to achieve a smoother, more natural appearance (B).

Sex differences in anatomy and facial aesthetics should be considered when treating glabellar lines with BTXA. Most men have a stronger frontalis than do women and look best with a straight, more masculine, brow. This changes the approach to the standard injection patterns used in women. The undesirable, "Spock-like" appearance described above is a side effect commonly seen in men after injection of the glabella with the typical 5-point injection pattern, which does not include injections into the lateral frontalis. Although the prescribing information for the BTXA products recommends 5 injection points,[1-3] a 7-point pattern with the addition of bilateral injections above the lateral superior orbital rim accounts for the likelihood that the lateral brow will elevate, and this injection pattern might be preferable in men to avoid brow arching.

Figure 3 demonstrates a 7-point injection pattern that could be followed on a male brow at the initial visit. A higher dose of neurotoxin is generally needed when treating men because they tend to have larger and stronger muscles than do women. For such injections using aboBTXA, the 300-U vial is reconstituted with 2 mL of diluent. A total aboBTXA dose would be 90 U—15 U injected at each of 5 sites in the glabellar complex and 7.5 U at each of 2 forehead sites. If using the other BTXA agents, the total dose for onaBTXA would be 30 U (5 U at each of the 5 glabellar sites and 2.5 U at each of the 2 forehead sites) and 42 U for incoBTXA (7 U for each glabellar site and 3.5 U per forehead site). If the tail of the corrugator is not strong, fewer units are injected at the lateral site.

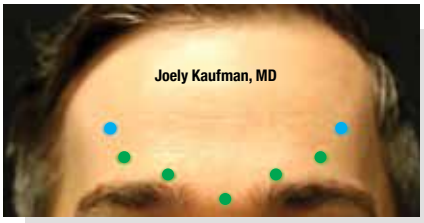

Figure 3. A 7-point injection pattern prevents elevation of the brow, especially in male patients. Total dose of abobotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA administered would be 90 U, 42 U, and 30 U, respectively, using this 7-point pattern in a typical case involving a male patient.

Swelling, bruising, pain at the injection site, and headache can occur after all BTXA treatments, but these adverse events are generally mild and temporary. Complications specific to treatment of glabellar rhytides include eyebrow ptosis, upper eyelid ptosis, and eyelid sensory disorder.[32]

ABOUT Case: Treatment for Perioral Rhytides

From the Files of Joel L. Cohen, MD

A 28-year-old woman presents for rejuvenation of perioral etch lines. She was treated with 6 U of onaBTXA into the orbicularis oris muscle, using a 0.3-cc insulin needle with a 31G short hub ***(Figure 4A)****. Treatment with a low dose of BTXA can help delay the development or worsening of permanent etching, and repeat treatments every few months might soften the appearance of existing lines* ***(Figure 4B)****.*

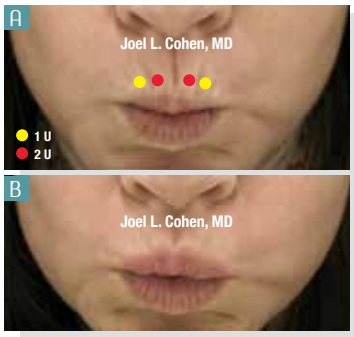

Figure 4. Perioral lines in the upper lip treated with 6 U of onabotulinumtoxinA as shown (A). In similar cases, total dose ranges for other botulinum neurotoxin type A agents are 10 to 22 U of abobotulinumtoxinA and 4 to 8 U of incobotulinumtoxinA. A low dose of botulinum neurotoxin type A softens the wrinkles in the upper lip without hindering function and expression (B).

Repetitive dynamic activity of the orbicularis oris muscle can lead to development of static radial perioral rhytides. BTXA can relax the orbicularis oris, but the key is to use a low enough dose that will soften the musculature around the philtrum without significantly affecting the lateral orbicularis in a manner that will interfere with facial expressions and lip function. In a study investigating onaBTXA treatment of hyperdynamic perioral lines, doses of 7.5 and 12.0 U were associated with similar improvement and duration, but the higher dose was associated with more adverse events, including changes in the ability to whistle, drink from a straw, purse the lips, and enunciate the letters "p" and "b".[33] There might also be feelings of general oral incompetence.

Appropriate patient selection is essential because of the potential for impairing muscle sphincter function. Clinicians should be very cautious about administering BTXA in the orbicularis oris in certain patients, including wind instrument players, singers, broadcast journalists, and scuba divers. Such patients should be treated with a low dose, and only after thoroughly explaining the risks.

Optimal rejuvenation of the perioral region/lower face often requires a multimodal approach that combines BTXA with additional procedures that address other age- or photodamage-related changes, including skin texture and laxity. According to clinician experience, the best use of BTXA around the mouth is as an adjuvant therapy to resurfacing. Treating the orbicularis oris approximately 1 week before ablative resurfacing weakens the muscle and limits the extent to which it can contract, thereby preventing imprinting of lines in the skin during the healing process.[34] Studies have also shown that pretreatment with neuromodulators before other procedures, including surgery involving skin cancer repairs, can lead to a more favorable effect on the cytokine and chemokine pathways, leading to a better result.[35-37]

ABOUT Case: Treatment of a Small Eye

From the Files of Ava Shamban, MD

A 52-year-old woman presented for treatment to correct eye size asymmetry. Note the smaller palpebral aperture on the left side of her face, which was thought to be at least partly hereditary; the differences in vermilion contour, which conferred a sneering appearance at rest; and the development of a dimple in the medial aspect of the upper left cheek upon animation due to synkinesis ***(Figures 5A and 5B)****. A total of 20 U of onaBTXA (4 U/0.1 mL) was injected subcutaneously, using a 32G, 0.5-in aesthetic needle* ***(Figure 5B)****. After BTXA injection, the treated eye no longer appeared "squinty", and its size resembled the contralateral eye* ***(Figure 5C)****. The patient was delighted with the outcome and continues to be treated every 4.5 months.*

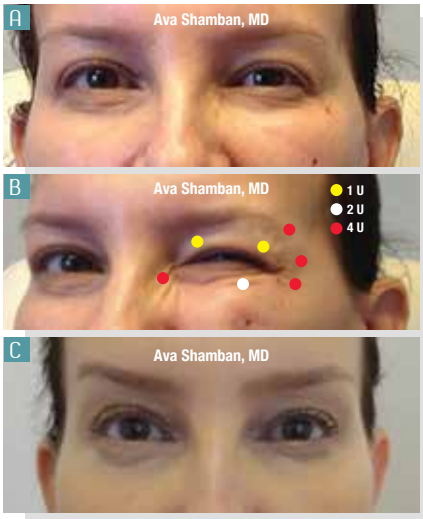

Figure 5. Eye asymmetry (A) is treated with a total of 20 U of onabotulinumtoxinA subcutaneously as shown (B). In similar cases, a total of 60 U of abobotulinumtoxinA or 20 U of incobotulinumtoxinA would be used. After the injection, the eye appeared more symmetrical (C).

Injection of BTXA just inferior to the lower lash margin widens the palpebral aperture by weakening the orbicularis oculi, but it is important to use a low dose (1-2 U of onaBTXA) so that the patient will maintain some control of the upper lid and retain the ability to close the eye during sleep. Injection directly at the site of the dimple would risk paralysis of the zygomaticus minor, resulting in an asymmetric smile.

ABOUT Case: Treatment for Perioral and Chin Dimpling

From the Files of Dee Anna Glaser, MD

A 71-year-old man presented for lower face rejuvenation to address chin dimpling and downward turning of the oral commissures ***(Figure 6A)****. He was treated with aboBTXA; a 300-mL vial was diluted with 3 mL of diluent. Using a 30G needle, a total of 30 U was injected in 3 equal aliquots into the depressor anguli oris muscles on either side of the face and the central mentalis muscle. When the patient returned after 2 weeks, he was pleased with the outcome* ***(Figure 6B)****.*

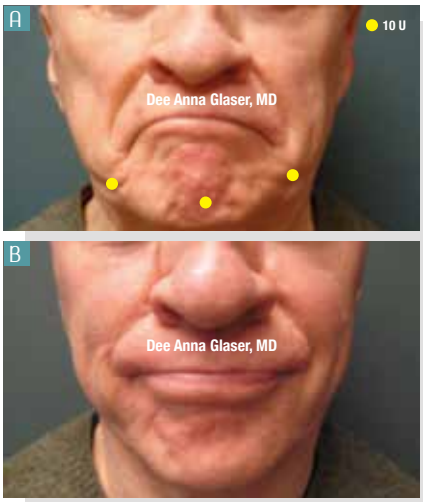

Figure 6. A total of 30 U of abobotulinumtoxinA to treat a dimpled chin and downturned corners of the mouth (A). Ten units were injected in each of the locations. To achieve similar results with other agents, 5 U of onabotulinumtoxinA or 6 U of incobotulinumtoxinA would be administered in each site. Major improvement was seen at follow-up 2 weeks after the injection (B).

Appropriate dose selection and proper placement of the neurotoxin is important to avoid complications, which can include lower lip dysfunction and change in lower lip contour. To minimize risk, the injections should be delivered into the inferior portion of the depressor anguli oris and lateral to the oral commissures. When selecting the appropriate dose of BTXA to administer in areas of the lower face, a conservative approach is recommended in order to reduce the risk of administering toxin into the wrong muscle and to limit the field of effect that could result from administering a dose that is too high. Patient follow-up is crucial; having the patient return 2 to 3 weeks after the initial injection allows the clinician to determine if there is an optimal improvement, or to re-treat if the results are not optimal.

ABOUT FACE Summary Points

Four BTXA products are commercially available for cosmetic use.
- They are not interchangeable
- The products vary compositionally and in their manufacturing processes
- Potency units are product specific
- Differences in NAP content among products is thought to have no effect on efficacy or safety

There is no universally accepted conversion ratio among BTXA products.
- Several reviews and experts suggest the ratio for aboBTXA:onaBTXA is between 2:1 and 3:1
- Several reviews suggest the ratio for incoBTXA:onaBTXA is 1:1, but some experts believe it is higher (between 1.2:1 or 1.5:1)

Practitioners might vary the diluent volume used to reconstitute BTXA products, depending on site of injection, treatment goals, patient-specific characteristics, and mathematical ease of dose conversion among products.

Movement of BTXA away from the site of injection affects efficacy and safety outcomes.
- Field of effect, which represents the overall area affected, can vary according to injection characteristics, BTXA dose and concentration, injection site, postinjection massage, facial exercises, and manipulation
- Some experts believe that reported differences in field of effect among products reflect differences in dose or other injection parameters rather than any product-specific characteristic

Reported rates of neutralizing antibody development with cosmetic use of BTXA products is low or absent.

Careful dose selection and proper placement of BTXA injections is needed to achieve the desired cosmetic result and to avoid complications.
- Swelling, bruising, pain at the injection site, and headache can occur after all BTXA treatments

References

1. Botox [package insert]. Irvine, CA: Allergan; 2018.
2. Dysport [package insert]. Wrexham, UK: Ipsen Biopharm Ltd; and Dallas, TX: Galderma Laboratories, LP; 2018.
3. Xeomin [package insert]. Raleigh, NC: Merz Pharmaceuticals, LLC; 2018.
4. US Food and Drug Administration. Drug approval package: JEUVEAU. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761085Orig1s000TOC.cfm. Published March 9, 2019. Accessed May 13, 2019.
5. Brin MF, James C, Maltman J. Botulinum toxin type A products are not interchangeable: a review of the evidence. *Biologics.* 2014;8:227-241.
6. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. *J Clin Aesthet Dermatol.* 2014;7(2):31-39.
7. Jeuveau [package insert]. Santa Barbara, CA: Evolus Inc; 2019.
8. Eisele KH, Fink K, Vey M, Taylor HV. Studies on the dissociation of botulinum neurotoxin type A complexes. *Toxicon.* 2011;57(4):555-565.
9. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. *Toxins (Basel).* 2016;8(3).
10. Frevert J. Pharmaceutical, biological, and clinical properties of botulinum neurotoxin type A products. *Drugs R D.* 2015;15(1):1-9.
11. Karsai S, Raulin C. Current evidence on the unit equivalence of different botulinum neurotoxin A formulations and recommendations for clinical practice in dermatology. *Dermatol Surg.* 2009;35(1):1-8.
12. Yu KC, Nettar KD, Bapna S, Boscardin WJ, Maas CS. Split-face double-blind study comparing the onset of action of onabotulinumtoxinA and abobotulinumtoxinA. *Arch Facial Plast Surg.* 2012;14(3):198-204.
13. Kaufman J, Cohen JL, Peredo MI, Jonas B, Down R, Nogueira A. Clinical assessment of 2 licensed abobotulinumtoxinA injection volumes for the treatment of glabellar lines [published online ahead of print March 18, 2019]. *Dermatol Surg.* doi:10.1097/DSS.0000000000001926.
14. Alam M, Geisler A, Warycha M, et al. Effect of postinjection facial exercise on time of onset of botulinum toxin for glabella and forehead wrinkles: a randomized, controlled, crossover clinical trial. *J Am Acad Dermatol.* 2019;80(4):1144-1147.
15. Carruthers A, Carruthers J, Cohen J. Dilution volume of botulinum toxin type A for the treatment of glabellar rhytides: does it matter? *Dermatol Surg.* 2007;33(1 spec no.):S97-S104.
16. Pickett A. Dysport: pharmacological properties and factors that influence toxin action. *Toxicon.* 2009;54(5):683-689.
17. Samizadeh S, De Boulle K. Botulinum neurotoxin formulations: overcoming the confusion. *Clin Cosmet Investig Dermatol.* 2018;11:273-287.
18. Lim EC, Seet RC. Botulinum toxin: description of injection techniques and examination of controversies surrounding toxin diffusion. *Acta Neurol Scand.* 2008;117(2):73-84.
19. Carli L, Montecucco C, Rossetto O. Assay of diffusion of different botulinum neurotoxin type A formulations injected in the mouse leg. *Muscle Nerve.* 2009;40(3):374-380.
20. Trindade de Almeida AR, Marques E, de Almeida J, Cunha T, Boraso R. Pilot study comparing the diffusion of two formulations of botulinum toxin type A in patients with forehead hyperhidrosis. *Dermatol Surg.* 2007;33(1 spec no.):S37-S43.
21. Hexsel D, Dal'Forno T, Hexsel C, Do Prado DZ, Lima MM. A randomized pilot study comparing the action halos of two commercial preparations of botulinum toxin type A. *Dermatol Surg.* 2008;34(1):52-59.
22. Hexsel D, Brum C, do Prado DZ, et al. Field effect of two commercial preparations of botulinum toxin type A: a prospective, double-blind, randomized clinical trial. *J Am Acad Dermatol.* 2012;67(2):226-232.
23. Hexsel D, Hexsel C, Siega C, Schilling-Souza J, Rotta FT, Rodrigues TC. Fields of effects of 2 commercial preparations of botulinum toxin type A at equal labeled unit doses: a double-blind randomized trial. *JAMA Dermatol.* 2013;149(12):1386-1391.
24. Dover JS, Monheit G, Greener M, Pickett A. Botulinum toxin in aesthetic medicine: myths and realities. *Dermatol Surg.* 2018;44(2):249-260.
25. Fabi SG, Sundaram H, Guiha I, Goldman MP. A two-center, open-label, randomized, split-face study to assess the efficacy and safety of one versus three intradermal injection sites of abobotulinumtoxinA in the treatment of lateral periocular rhytides. *J Drugs Dermatol.* 2013;12(8):932-937.
26. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. *J Neural Transm (Vienna).* 2013;120(2):275-290.
27. Joshi SG, Elias M, Singh A, et al. Modulation of botulinum toxin-induced changes in neuromuscular function with antibodies directed against recombinant polypeptides or fragments. *Neuroscience.* 2011;179:208-222.
28. Naumann M, Carruthers A, Carruthers J, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX®) across multiple indications. *Mov Disord.* 2010;25(13):2211-2218.
29. Frevert J, Dressler D. Complexing proteins in botulinum toxin type A drugs: a help or a hindrance? *Biologics.* 2010;4:325-332.
30. Fabbri M, Leodori G, Fernandes RM, et al. Neutralizing antibody and botulinum toxin therapy: a systematic review and meta-analysis. *Neurotox Res.* 2016;29(1):105-117.
31. King M. Management of ptosis. *J Clin Aesthet Dermatol.* 2016;9(12):E1-E4.
32. Carruthers A, Carruthers J. Glabella. In: Dover JS, ed. *Botulinum Toxin: Procedures in Cosmetic Dermatology.* 4th ed. Edinburgh, UK: Elsevier; 2017:95-102.
33. Cohen JL, Dayan SH, Cox SE, Yalamanchili R, Tardie G. OnabotulinumtoxinA dose-ranging study for hyperdynamic perioral lines. *Dermatol Surg.* 2012;38(9):1497-1505.
34. Kadunc BV, Trindade DE, Almeida AR, Vanti AA, Di Chiacchio N. Botulinum toxin A adjunctive use in manual chemabrasion: controlled long-term study for treatment of upper perioral vertical wrinkles. *Dermatol Surg.* 2007;33(9):1066-1072.
35. Gassner HG, Brissett AE, Otley CC, et al. Botulinum toxin to improve facial wound healing: a prospective, blinded, placebo-controlled study. *Mayo Clin Proc.* 2006;81(8):1023-1028.
36. Flynn TC. Use of intraoperative botulinum toxin in facial reconstruction. *Dermatol Surg.* 2009;35(2):182-188.
37. Oh SH, Lee Y, Seo YJ, et al. The potential effect of botulinum toxin type A on human dermal fibroblasts: an in vitro study. *Dermatol Surg.* 2012;38(10):1689-1694.

For instant processing, complete the CME/CE Post Test online at http://tinyurl.com/AboutFaceDT