Advancements and Refinement in Facial Neuromodulators

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Summary: The use of neuromodulators has increased by approximately 748 percent from 2000 to 2014 and has become an integral adjunct for facial rejuvenation. Knowledge of facial anatomy, accurate facial analysis, and familiarity with neurotoxin characteristics will minimize complications and optimize results. Current U.S. Food and Drug Administration–approved neurotoxins in the United States include onabotulinumtoxin A (Botox), abobotulinumtoxin A (Dysport), and incobotulinumtoxin A (Xeomin). The dosage and effect of these products are not interchangeable, so practitioners should master the utility and response of one product before trying the other products. All products have equivalent success in appropriately trained hands; the senior author (R.J.R.) favors no particular neurotoxin. This article provides a stepwise approach to treat dynamic facial rhytides with neuromodulators, including indications, facial analysis, preparation and injection technique, post-procedure care, and complications. (*Plast. Reconstr. Surg.* 138: 803, 2016.)

Clostridium botulinum toxin inhibits muscle contraction by cleaving presynaptic proteins involved in releasing acetylcholine at the neuromuscular junction. Carruthers and Carruthers[1] first described the cosmetic effect of these neurotoxins in 1992 when they noticed incidental improvement of glabellar rhytides in patients whom they were treating for ophthalmologic diseases. Although several different serotypes of the neurotoxin exist, serotypes A and B have been approved by the U.S. Food and Drug Administration for temporary improvement of moderate to severe glabellar and lateral canthal rhytides.[2,3]

According to the American Society of Plastic Surgeons 2014 statistics, the use of neuromodulators has increased by approximately 748 percent from 2000 to 2014 and has become an integral adjunct for facial rejuvenation.[4] Current U.S. Food and Drug Administration–approved neurotoxins in the United States include onabotulinumtoxinA (Botox; Allergan, Inc., Irvine, Calif.), abobotulinumtoxinA (Dysport; Galderma Laboratories, Lausanne, Switzerland), and incobotulinumtoxinA (Xeomin; Merz Pharma, Frankfurt am Main, Germany). The dosage and effect of these products are not interchangeable; practitioners should master the utility and response of one product before using the other products. All products have equivalent success in appropriately trained hands; the senior author (R.J.R.) favors no particular neurotoxin. This supplement provides a stepwise approach to treat dynamic and static facial rhytides with neuromodulators.

From the Department of Plastic Surgery, University of Texas Southwestern Medical Center.
Received for publication January 31, 2016; accepted May 17, 2016.
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DOI: 10.1097/PRS.0000000000002569

INDICATIONS

Accurate and comprehensive facial analysis is the cornerstone to nonsurgical facial rejuvenation. Failure to adequately assess and address certain areas will result in incomplete and asymmetric

Disclosure: *The authors have no financial interests in this research project or in any of the techniques or equipment used in this study. Dr. Rohrich is a volunteer member of the Allergan Alliance for the Future of Aesthetics and receives instrument royalties from Eriem Surgical, Inc., and book royalties from Taylor and Francis Publishing. No funding was received for this article.*

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correction. Examination of rhytides should be performed using a top-down approach and must include facial animation. Detailed detection and focused treatment of facial differences will lead to not only comprehensive rejuvenation but also improved symmetry.

As discussed, the aforementioned neuromodulators have been approved by the U.S. Food and Drug Administration to treat only glabellar rhytides and crow's feet; however, off-label cosmetic applications include frown lines, forehead creases, neck banding, and others. All muscles of facial expression may potentially benefit from cautious neurotoxin injection to diminish unwanted wrinkles; however, patients should be counseled regarding off-label use. Neurotoxins typically treat dynamic rhytides; static rhytides may require supplemental filler as well. In addition, several facial surgical treatments and procedures may benefit from the adjunctive use of neuromodulation.

Before injection, a complete history should always be taken, including medical conditions, medications, supplements, herbs, allergies, and previous surgical and nonsurgical facial rejuvenation procedures. The American College of Chest Physicians 2008 guidelines deems minor dermatologic procedures as low risk for bleeding and recommends continuing medically necessary anticoagulants; however, the practitioner must use appropriate medical judgment with any intervention.[5]

PREPARATION

As discussed previously, neurotoxin unit measurements are specific to each toxin and are not interchangeable given the varying degrees of potency and diffusion at the injection sites. As a general rule, 2.5 U of Dysport is comparable to 1 U of Botox, and 1 unit of Xeomin is comparable to 1 unit of Botox.[6,7] Of note, Dysport has been reported to diffuse more than the other agents.[8]

All products need to be reconstituted; reconstitution with preserved isotonic saline may result in less pain than nonpreserved isotonic saline.[9] The dilution volume does not contribute significantly to injection-site diffusion but, in general, a 100-U vial of Botox can be diluted in 2.5 ml of diluent for a final concentration of 4 U/0.1 ml.[10,11] Botox and Dysport require refrigeration; Xeomin does not need refrigeration until it has been reconstituted. Table 1 summarizes the differences among the neuromodulators.[12–14]

TECHNIQUE

The technique below documents a stepwise approach to facial rejuvenation with Botox; however, all neuromodulators can be used with similar efficacy in the appropriate concentrations. (**See Video, Supplemental Digital Content 1**, which demonstrates the authors' approach and technique of neuromodulator injection in the face, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/B844***.)

The injection site should be cleansed with alcohol. Ice packs may desensitize the area and minimize postprocedure bruising.

Detailed knowledge of facial anatomy is essential before any facial injections. The mimetic muscles traverse the face at various depths; awareness of specific facial structures will decrease the risk of neurovascular trauma and unwanted muscular injury or sequelae. Lights may also be positioned to allow visualization of the vasculature. Nonsurgical facial rejuvenation may begin with neuromodulator injections or fillers; if the practitioner is planning to massage the face significantly after filler injection, this should be done before

Table 1. Characteristics of Three Commonly Used Neuromodulators*

	Storage (°C)	Potency Relative to Botox	Excipient	Preservative	Complex Weight (kDa)	Duration (mo)	Onset (days)	Appearance after Reconstitution in Saline	Potential Allergic Reactions
Botox	2–8	1	Human albumin	None	900	3	4	Clear liquid	Botulinum toxin
Dysport	2–8	0.4	Human albumin, lactose, trace bovine milk proteins	None	~300	3	3	Clear liquid	Botulinum toxin, bovine milk proteins
Xeomin	20–25, 2–8	1	Human albumin, sucrose	None	150	3	4	Clear liquid	Botulinum toxin

*Merz Pharma. Xeomin full prescribing information. Frankfurt am Main, Germany: Merz Pharma; 2009; revision April of 2014; Allergan, Inc. Botox full prescribing information. Irvine, Calif: Allergan, Inc; 2009; revision October of 2014; Medicis Aesthetics, Inc. Dysport, abobotulinumtoxinA (full prescribing information). Scottsdale, Ariz: Medicis Aesthetics, Inc; 2009; revision March of 2012.

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neuromodulator injection to prevent excessive spread of neurotoxin.

Treatment of facial rhytides should be performed in a top-down approach. The frontalis should be injected in several sporadic, horizontal rows across the forehead in a superficial manner with approximately 6 to 15 U.[8] To prevent brow ptosis, the practitioner should stay at least one fingerbreadth above the brow. To prevent a peaked brow appearance, an additional 2 U may be injected in the midforehead superior to the junction of the middle and lateral brow.

Subsequently, the corrugators can then be injected with approximately 10 U of Botox per side, starting medially and proceeding approximately 30 degrees superolaterally with injections toward the tail of the muscle, the location of which varies in each individual. Next, the procerus and nasalis can be treated, localizing the sites of injection by having the patient dynamically animate the face.

The crow's feet may be softened with lateral periorbital injections. The side with the larger eyelid aperture should be injected more laterally compared with the contralateral side to balance eyelid opening in addition to softening of the crow's feet. These injections should be superficial to preferentially affect the orbicularis oculi and avoid the zygomaticus major. If the crow's feet are deep and fine rhytides are present more laterally, a second row of injections approximately 1 cm more lateral to the first row may be performed. Injection of 10 to 30 U per side is usually adequate.

Perioral rhytides are mainly addressed with fillers, but the upper lip may be injected laterally near the commissures with 1 to 2 U at the white roll to mildly soften those areas. To raise downturned commissures, the depressor anguli oris may also be injected superficially near its origin directly inferior to a vertical reference line from the lateral commissures. The 2- to 3-U injection must be at or slightly lateral to the vertical reference line of the commissures to avoid affecting the other lip depressors.

Injection of the mentalis should be with 4 to 10 U, usually in the midline; however, if there is asymmetry in elevation, the muscle is injected bilaterally in addition to the midline to preferentially weaken the stronger side. Finally, prominent platysmal bands may individually be injected with 2 to 4 U to help soften and produce a more youthful neck appearance.

POSTPROCEDURE CARE

Patients should not massage the area after injection, to prevent unwanted diffusion; otherwise, patients may resume normal activities immediately. The duration of action is approximately 3 to 4 months. Patients may have variable responses to each of the neurotoxins; thus, detailed procedure notes, including dosage and location, are instrumental for optimizing future outcomes. Animated photographs and/or videos may even supplement documentation and direct treatment.

COMPLICATIONS

Common adverse effects are related to poor injection techniques and may include localized pain, infection, inflammation, tenderness, swelling, erythema, and bruising. In addition, incorrectly administered injections may paralyze muscle unintentionally, causing upper eyelid ptosis, diplopia, smile asymmetry, drooling, and speech difficulties.[15] Caution is urged in patients with neuropathic diseases such as amyotrophic lateral sclerosis, myasthenia gravis, or Lambert-Eaton syndrome. These patients may be at increased risk for severe dysphagia or respiratory compromise; however, these sequelae are very rare. To counteract complications, an oral cholinesterase inhibitor may be used.

CONCLUSIONS

This summary provides our stepwise approach to facial analysis and subsequent treatment for dynamic facial rhytides. Of note, various

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neuromodulators can be used with equivalent outcomes. Knowledge of facial anatomy and neurotoxin characteristics will minimize complications and optimize results.

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PATIENT CONSENT

The patient provided written consent for the use of her images.

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