FEATURE ARTICLE

CE 2.5 Contact Hours

Neuromodulators—Between the Lines

Lynn Consolmagno

ABSTRACT: The frequency of nonsurgical cosmetic procedures, specifically the injection of neuromuscular modulators produced by Clostridium botulinum type A exotoxin, frequently referred to as BoNTA, such as Botox Cosmetic (Allergan), Dysport (Medicis), and Xeomin (Merz), is increasingly common in the war on aging. Although the overall number of cosmetic surgical procedures has decreased, in the past decade, less-invasive injectable treatments have gained popularity. BoNTA agents are the most popular option for reducing or eliminating facial rhytids by causing dynamic muscle relaxation through chemodenervation of facial striated muscles. This article will provide an overview of indications, efficacy, risks, and product choices.

Key words: Aesthetics, Botulinum Toxin Type A, Facial Rejuvenation, Neurotoxin

In the United States, botulinum toxin type A (BoNTA) injections increased by 584% in the last decade to a total of 5,379,360 sites injected in 2010 (Bowers, 2011). According to GlobalData's (2011) new report, Botox Cosmetic (onabotulinumtoxinA; Allergan, Inc., Irvine, CA) has been the market leader globally, whereas other brands such as Dysport (abobotulinumtoxinA, Medicis Pharmaceutical Corporation; Scottsdale, AZ) and Xeomin (incobotulinumtoxinA, Merz Pharmaceuticals; Frankfurt, Germany) have followed in pursuit of gaining the market share among the devotees of wrinkle-free foreheads.

Since March 2012, Xeomin (Merz Pharma and Merz Aesthetics, Frankfurt, Germany) has not been readily available for use; a U.S. District court issued a 10-month injunction prohibiting sales in the facial aesthetic market. For the purposes of this article, discussion of BoNTA products will be limited to Botox (Allergan) and Dysport (Medicis) only as they pertain to facial aesthetics.

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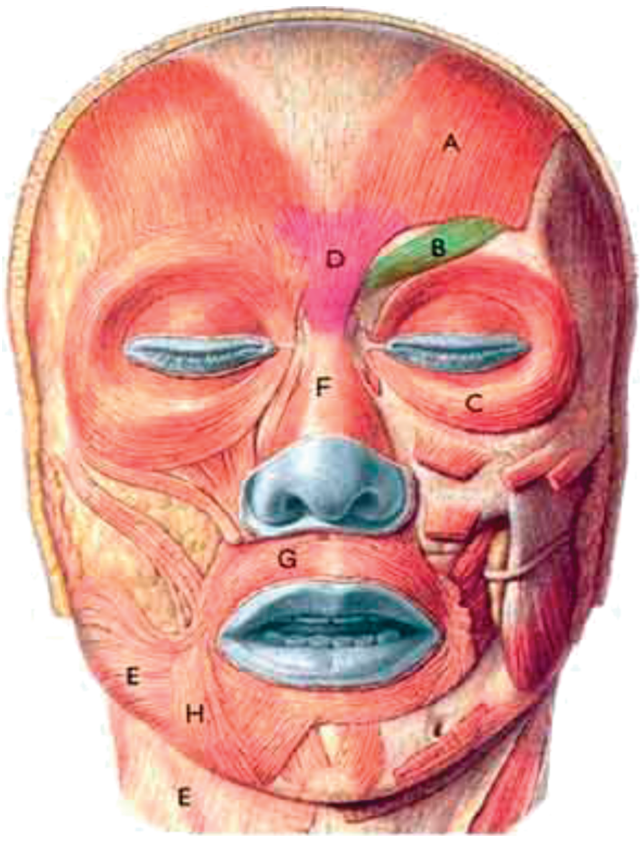
INDICATIONS

Use of BoNTA agents has become a fundamental tool in the facial aesthetic armamentarium available to the medical aesthetic practitioner. Before using these agents effectively, it is crucial to have a complete understanding of facial anatomy and neuromuscular actions (Balikian & Zimbler, 2007). Use of BoNTA provides a safe, affordable, and widely available method for many seeking amelioration of dynamic facial rhytids. Neuromuscular denervation is a consequence of interrupting the release of acetylcholine at the presynaptic neuromuscular junction. BoNTA agents bind to the receptor sites of motor or sympathetic nerve terminals and inhibit the release of acetylcholine, essentially obstructing the message telling the muscle to contract (American Academy of Facial Esthetics, 2012).

The Food and Drug Administration in the United States approved botulinum toxin for temporary treatment of moderate to severe dynamic glabellar frown lines in adults aged 18–65 years in 2002. Additional approval from the Food and Drug Administration for the treatment of primary axillary hyperhidrosis was granted in 2004 (Small & Hoang, 2012). Many studies have shown the improvement in the appearance of fine lines of the face after treatment with BoNTA products (Carruthers & Carruthers, 1998; Guerrissi & Sarkissian, 1997).

Basic off-label areas most commonly considered appropriate for treatment with BoNTA agents (see Figure 1) include horizontal forehead rhytids (frontalis muscle) and dynamic lateral canthal wrinkles or "crow's feet" (lateral obicularis occuli muscles; Mendez-Eastman, 2003).

Treatment of dynamic rhytids in the upper one third of the face has been fundamentally changed with readily available and affordable BoNTAs (Bassichis, 2007). Although historically cosmetic surgeons augmented eyebrow and eyelid imperfections and asymmetries surgically, BoNTA agents are now an integral component of treatment plans with advanced treatment techniques, as shown in Table 1. Aesthetic medical clinicians and cosmetic surgeons are utilizing these products intraoperatively, as postoperative



(A) Frontalis muscle – horizontal forehead lines
(B) Corrugator and Depressor supercilli complex -vertical frown lines
(C) Orbicularis oculi - crows feet
(D) Procerus - frown lines
(E) Platysma – vertical neck bands
(F) Nasalis - nose wrinkles
(G) Orbicularis oris – vertical lines around the lips
(H) Depressor anguli oris – downturned corners of the mouth

FIGURE 1. Common muscles of expression. From Emerging Pharma, Inc. (2006).

adjunctive enhancements and as primary treatment to the periorbital region (Balikian & Zimbler, 2007).

Although injection technique is not complicated, careful patient selection and thorough pretreatment evaluation of their skin and underlying anatomy and musculature is essential to outcome predictability (Bassichis, 2007). Mastery of these skills is vital for dermatology nurses and nurse practitioners to be considered indispensable providers within the rapidly changing dermatology workforce. Cosmetic injectable expertise is viewed as an essential skill for all cosmetic/dermatology nurses, dermatology nurse practitioners, and dermatologists (Bobonich & Cooper, 2012).

The most commonly treated area is deep vertical lines in the glabella area, between the eyebrows (see Figure 3; Botox Cosmetic, 2002). Musculature involved includes paired corrugator supercillii, procerus, orbicularis, and some contribution from the frontalis muscles. The creases between the eyebrows are best evaluated by observation and palpation, during dynamic action by frowning and at rest. By palpating the corrugators in motion, the clinician can better assess the size and strength of the muscles. Importantly, awareness of the dermal insertion of the corrugator muscles is essential for determining the lateral placement of the product. Maintaining a margin of 1 cm above the eyebrow (orbital rim) and keeping medial to the midpupillary line mitigates the potential risk of ptosis (Bassichis, 2007).

PRODUCT CHOICES

Botox Cosmetic and Dysport are the most popular and the most commonly used products within the neuromodulator class. Although their end point effect is similar, they are dissimilar in preparation, diffusion potential, onset and length of action, and effectiveness and should not be considered equivalent (Small & Hoang, 2012). In addition, the dosage and reconstitution are significantly different. Botox Cosmetic is supplied in 100-unit freeze-dried vacuum vials with instructions from Allergan requiring 2.5 ml of preserved sodium chloride for reconstitution. This formula yields the following:

4 units per 0.1 ml
2–4 units per injections site

There are alternative reconstitution formulas used by many practitioners such as the following:

2 ml of preserved sodium chloride in 100 units of Botox yielding 5 units per 0.1 ml.
1 ml of preserved sodium chloride in 100 units of Botox yielding 10 units per 0.1 ml.

The choice of concentration is determined by patient-specific anatomical profile and practitioner preference and experience. Dysport is supplied in 300-unit freeze-dried vacuum vials and, according to the product insert (PI), requires either 2.5 or 1.5 ml of preserved sodium chloride for reconstitution (Medicis, 2009). Using 2.5 ml of sodium chloride, the concentration will be 10 units per 0.08 ml, whereas using 1.5 ml of sodium chloride, the concentration will be 10 units per 0.05 ml.

PIs from Botox and Dysport reconstitution instructions include reconstitution with nonpreserved sodium chloride and refrigeration after reconstitution at 2°C–8°C (36°F–46°F); however, patient comfort is maximized using preserved sodium chloride for reconstitution, and it is this author's choice. There is no evidence to support the use of nonpreserved sodium chloride over preserved sodium chloride for reconstitution (Alam, Dover, & Arndt, 2002). Once reconstituted, both Botox and Dysport require refrigeration. Injection with an insulin or tuberculin syringe with a 31-gauge needle is recommended (Mariwalla, 2011). Removing the rubber stopper before withdrawing the product ensures sharpness of the needle, which increases patient comfort during injection.

During the cosmetic surgery forum in Las Vegas, December 2011, Dr. Heidi A. Waldorf (Waldorf Dermatology & Laser Associates, Nanuet, NY) indicated that the

TABLE 1. Advanced Treatment Techniques

Common Name	Medical Name	Muscles
Lower eyelid wrinkles	Infraocular rhytids	Inferior preseptal obicularis oculi
Eyebrow lift	Reduction of ptotic eyebrows and dermatochalasis	Superior lateral orbital orbicularis oculi
Bunny lines	Nasal rhytids	Nasalis
Vertical lip lines (smoker's lines)	Perioral rhytids	Orbicularis oris
Marionette lines	Melomental folds	Depressor anguli oris (DAO)
Downturn corners of the mouth	Depressed oral commissures	DAO
Nasolabial folds	Melolabial folds	Levator labii superioris alaeque nasi
Gummy smile	Gingival show	Levator labii superioris alaeque nasi
Chin line	Mental crease or labiomental crease	Mentalis
Chin puckering	Mentalis contraction	Mentalis
Neck bands	Platysmal bands	Platysma

Note. Adapted From (Small & Hoang, 2012).

choice of product is based on four characteristics: the patient, the price, the protein, and the profile. For experienced patients, their own choice of product is the first concern; the clinician's experience with each product is an additional consideration. There is a cost difference between Botox and Dysport, and utilizing Dysport with the appropriate patient may yield approximately 20% cost savings to the patient; however, it should be noted that these products are not interchangeable and careful patient selection is critical when choosing products. The profile of the product is of consideration with regard to reconstitution, dosages, and dispersion or remote spread into an unwanted area. An example of this is ptosis after glabella treatment because of undesired lateral spread of the product (Schlessinger, 2012). There is a lack of scientific data to support choosing one BoNTA agent over another based solely on risk of remote spread of the product. Some injectors have claimed ptosis risk increases with the use of Dysport; however, that side effect has not been seen in this author's experience.

EFFICACY

The PI for Botox (Allergan) states that glabellar frown lines will be temporarily improved within 3–5 days after treatment and remain improved for 120 days, whereas Dysport's (Medicis) PI states that the severity of glabellar frown lines will be diminished for up to 4 months. It is not unreasonable to counsel the patient to expect results within 1–14 days after injection, and the length of action is individual, ranging from 3–4 months of duration (see Figure 2). When discussing length of efficacy with patients, it is important to consider the patients' underlying musculature as well as lifestyle. BoNTAs maybe metabolized more rapidly in areas of larger muscles with greater dynamic muscle activity, thus necessitating retreatment in shorter intervals. Observed efficacy is also influenced by skin turgor, elasticity, and muscle mass (Mariwalla, 2011). Anecdotally, extreme heat, such as exposure to frequent high-temperature saunas or steam, may degrade the product and shorten the length of efficacy.

Manufacturer guidelines for Botox (Allergan) and Dysport (Medicis) recommend using the reconstituted product within 4 hours. Many studies have shown efficacy exceeding 5 weeks after reconstitution, and for most clinicians, no change in efficacy is seen if the product is used within 6 weeks of reconstitution, as long as it has been refrigerated between uses (Hexsel, de Ameida, & Rutowitsch, 2003; Klein, 1998).

Clinicians may choose from various dilutions, although efficacy of BoNTA agents is derived from the number of units opposed to dilution, and manufacturer recommended dosage and injection sites for effective glabella relaxation are the following (see Figure 3):

Botox (Allergan) 20 units: 4 units into each of five sites;

Dysport (Medicis) 50 units: 10 units into each of five sites.

RISKS

Most commonly reported adverse events are temporary and include pain, bruising, temporary erythema/edema at

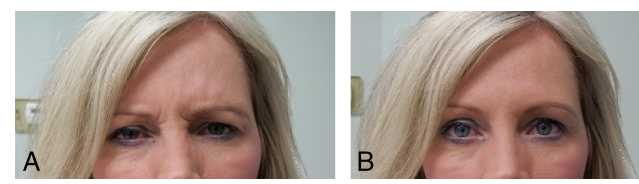


FIGURE 2. Botox treatment photographs. A. Before 20 units of Botox to glabella. B. 2 weeks after treatment.

(Botox PI, 2002)

FIGURE 3. Recommended glabella injection sites (Botox Cosmetic, 2002).

the injection site, transitory mild headache, dry eye symptoms, ptosis, and asymmetry (Bassichis, 2007). BoNTA injection side effects vary with site injected, dose, frequency of injections, and mastery of injection technique.

Bruising risk can be mitigated by counseling the patient to avoid aspirin, nonsteroidal anti-inflammatory drugs, vitamin E, garlic, fish oil, warfarin, clopidogrel, alcohol, prednisone, and ginkgo biloba type of products for 2–7 days before treatment. However, patients should not stop any prescription medication without discussing it with their healthcare provider. According to the Botox manufacturer's insert, the risk of ptosis is 3%; however, this author has experienced considerably less. Proper product choice and correct placement technique should make ptosis preventable (Carruthers, Lowe, & Menter, 2002). Rarely reported adverse events include diplopia, blurred vision, and brief flu-like symptoms (Mendez-Eastman, 2003).

Contraindications to usage of BoNTA agents include known sensitivity to BoNTA and known neuromuscular disorders such as myasthenia gravis, Lambert–Eaton syndrome, amyotrophic lateral sclerosis, and muscular dystrophy. These agents are categorized as pregnancy C, but because safety data on treatment in pregnancy are not available, most practices include pregnancy and lactation in the list of contraindications. Further concerns include patients who are taking aminoglycoside antibiotics, quinine, and calcium channel blockers as these agents may increase the potential effect of the neurotoxin (Bassichis, 2007). In addition, some studies have indicated a cross-reactivity with milk proteins (Dysport) and flu vaccines (Botox) as well (Mariwalla, 2011). Dysport is freeze dried in lactose and albumin; consequently, there are trace amounts of cow milk protein in Dysport. In patients with milk allergy, Botox is a treatment alternative. Botox PI indicates known allergy to human albumin/egg white as one of the contraindication to treatment criteria. Because influenza vaccine is cultured in fluid from chicken embryos, people who have had reaction to flu vaccine are discouraged from receiving Botox.

DISCUSSION

Rejuvenation procedures are increasingly more readily available as they have gained popularity. Most patients are looking to ameliorate and soften the lines of the face; they are not seeking a "frozen" or paralyzed appearance. Although many extrinsic factors (sun exposure, smoking, alcohol use, etc.) are involved in the aging process, much of the intrinsic aging process involves the loss of facial bone mass and subsequent loss of muscle attachments within the facial structure. These changes are seen readily in the middle to lower thirds of the face, and although BoNTA agents cannot restore volume in these areas, they can dramatically improve the appearance of moderate to severe rhytids in the upper one third of the face. It is an important difference and consideration to explore with the patient. Patient understanding with regard to potential outcomes is critical in measuring success. For example, a neurotoxin will diminish or eliminate the muscle contraction that precipitated the crease between the eyebrows; however, if the skin is etched from repeated underlying muscle contraction over time, the line will still be visible even if the muscle is not active. The patient's ability to understand the difference relies on the clinician's ability to educate the patient before treatment. Theoretically, over time and reexposure to the neurotoxin, the muscles will weaken, and with good skin care, the lines will become less apparent.

Individual differences between population groups—men and women and skin types—are important considerations when utilizing BoNTA products. The use of these products and their commercial availability has revolutionized the practice of aesthetic medicine. Choice of product largely remains with the clinician. Factors influencing one's choice often include experience with specific product, comfort level to discriminate between product choices, patient population, and cost and availability of product. These agents have an outstanding safety record; desired outcomes are easily attainable with proper patient evaluation and selection and an experienced injection technique.

CLINICAL PEARLS

Patient education should include written and verbal immediate posttreatment instructions: avoid manipulation of the treated area; within 4 hours, avoid supine position and bending over to minimize undesired spread of the product. Generally, all other facial treatments should be scheduled with 3- to 4-week interval between neuromodulator treatments to avoid unnecessary manipulation of the treated areas. However, facial fillers to alternate areas maybe utilized during the same appointment in conjunction with BoNTA agents for overall facial rejuvenation. Posttreatment follow-up appointments are recommended at the 2-week

interval to evaluate efficacy and assess patient satisfaction. It is common practice to provide additional treatment, "touch up," at follow-up with no additional charge to the patient. Recommendations often include repeat treatment 3–4 months subsequent to original treatment because muscle function typically returns 2–5 months after treatment. ■

REFERENCES

Alam, M., Dover, J. S., & Arndt, K. A. (2002). Pain associated with injection of botulinum A exotoxin reconstituted using isotonic sodium chloride with and without preservative: A double-blind, randomized controlled trial. *Archives of Dermatology, 138*, 501–514.

American Academy of Facial Esthetics, (2012). *The beauty of facial esthetics*. Retrieved from http://www.facialesthetics.org/esthetics/wrinkle-treatment/botox/

Balikian, R., & Zimbler, M. (2007). Primary and adjunctive uses of botulinum toxin type A in the periorbital region. *Otolaryngologic Clinics of North America, 40*(2), 291–303.

Bassichis, B. (2007). Cosmetic use of botulinum toxin in the upper face. *Operative Techniques In Otolaryngology—Head & Neck Surgery, 18*(3), 248–253.

Bobonich, M. A., & Cooper, K. D. (2012). A core curriculum for dermatology nurse practitioners: Using Delphi technique. *Journal of Dermatology Nurses' Association, 4*(2), 108–120.

Botox Cosmetic. (2002). *Package insert: Allergan*. Irvine, CA: Allergan, Inc.

Bowers, J. (2011). Reversing the ravages of time: New injectable agents help dermatologists meet growing demand for anti-aging treatments. *American Academy of Dermatology*. Retrieved from http://www.aad.org/dermatology-world/monthlyarchives/2011/june/reversing- the-ravages-of-time

Carruthers, A., & Carruthers, J. (1998). Clinical indications and injection technique for the cosmetic use of botulinum A exotoxin. *Dermatological Surgery, 24*, 1189–1194.

Carruthers, J. A., Lowe, N. J., & Menter, M. A. (2002). A multicentre, double-blind, randomized, placebo-controlled study of efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *Journal of the American Academic Dermatology, 46*, 840–849.

Emerging Pharma, Inc. (2006). *Common muscles of facial expression*. Retrieved from http://images.google.com/search?num=10&hl=en&site=&tbm=isch&source=hp&biw=1280&bih=656&q=common+facial+muscles+of+expression&oq=common+facial+muscles+of+expression&gs_l=img.3..2428.15108.0.15430.35.14.0.21.1.0.358.997.12j3-1.13.0..0.0..1ac.1.oDwQOR6TEs8#hl=en&tbo=d&tbm=isch&sa=1&q=common+facial+muscles+of+expression+botox &oq=common+facial+muscles+of+expression+botox&g s_l=img.3..149137.150639.0.150860.6.6.0.0.0.0.106.326.5j1.6.0..0.0..1c.1.UifcYThecjU&bav=on.2,or.r_gc.r_pw.r_qf.&bvm=bv.1355325884,d.eWU&fp=565f2a4d6b847f1c&bpcl=39967673&biw=1280&bih=656

GlobalData. (2011). *Facial aesthetics (Botox, dermal fillers, collagen products)—Global pipeline analysis, competitive landscape and market forecasts to 2017*. Retrieved from http://www.marketresearch.com/GlobalData-v3648/Facial-Aesthetics-Botox-Dermal- Fillers-6234307/

Guerrissi, J., & Sarkissian, P. (1997). Local injection into mimetic muscles of botulinum toxin A for the treatment of facial lines. *Annals of Plastic Surgery, 39*, 447–453.

Hexsel, D. M., de Ameida, A. T., & Rutowitsch, M. (2003). Multicenter, double-blind study of the efficacy of injections with botulinum toxin type A reconstituted in 6 consecutive weeks. *Dermatological Surgery, 29*, 523–529.

Klein, A. W. (1998). Dilution and storage of botulinum toxin. *Dermatological Surgery, 24*, 1179–1180.

Mariwalla, K. (2011). Rejuvenation of the upper face. *Medscape Education Dermatology*.

Medicis Pharmaceutical Corporation. (2009). *Dysport package insert*. Scottsdale, AZ: Author.

Mendez-Eastman, S. (2003). Botox: A review. *Plastic Surgical Nursing, 23*(2), 64–70.

Niamtu, J. (2008). Botulinum toxin type A (Botox) for the neuromuscular correction of excessive gingival display on smiling (gummy smile). *American Journal of Orthodontics & Dentofacial Orthopedics, 133*(2), 195–203.

Schlessinger, J. (2012). Aesthetics management: New frontiers in neurotoxins. *Practical Dermatology,* 22–25.

Small, R., & Hoang, D. (2012). *A practical guide to botulinum toxin procedures* (pp. 10–13). Philadelphia, PA: Lippincott Williams & Wilkins.