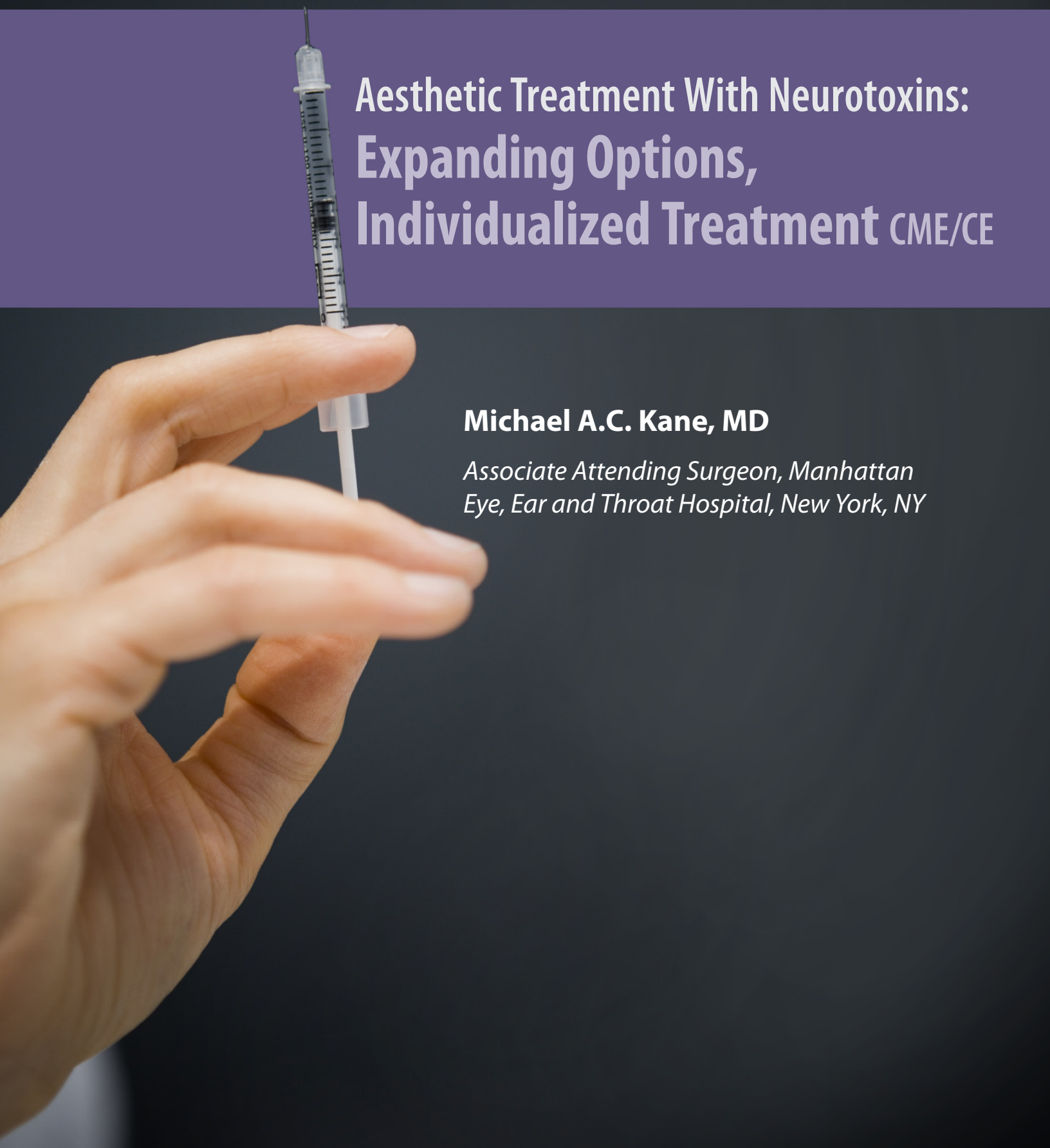

Aesthetic Treatment With Neurotoxins: Expanding Options, Individualized Treatment CME/CE

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This article is a CME/CE-certified activity. To earn credit for this activity visit: medscapecme.com/clinicalupdate/aestheticstreatment

CME/CE Released: 06/18/2010

Valid for credit through 06/18/2011

Target Audience
This activity is intended for dermatologists, plastic surgeons, primary care providers, and nurses who are involved in aesthetic procedures.

Goal
The goal of this activity is to review the background, clinical trials, and best injection practices for the use of botulinum neurotoxin type A products in aesthetic practice.

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

1. Review the clinical efficacy data supporting botulinum neurotoxin type A products for aesthetic use
2. Describe the similarities and potential differences between the 2 botulinum neurotoxin type A products that have been approved by the US Food and Drug Administration for aesthetic treatment
3. Design aesthetic neurotoxin treatment plans that minimize side effects and deliver optimal patient outcomes

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From MedscapeCME Dermatology

Aesthetic Treatment With Neurotoxins: Expanding Options, Individualized Treatment CME/CE

Michael A.C. Kane, MD

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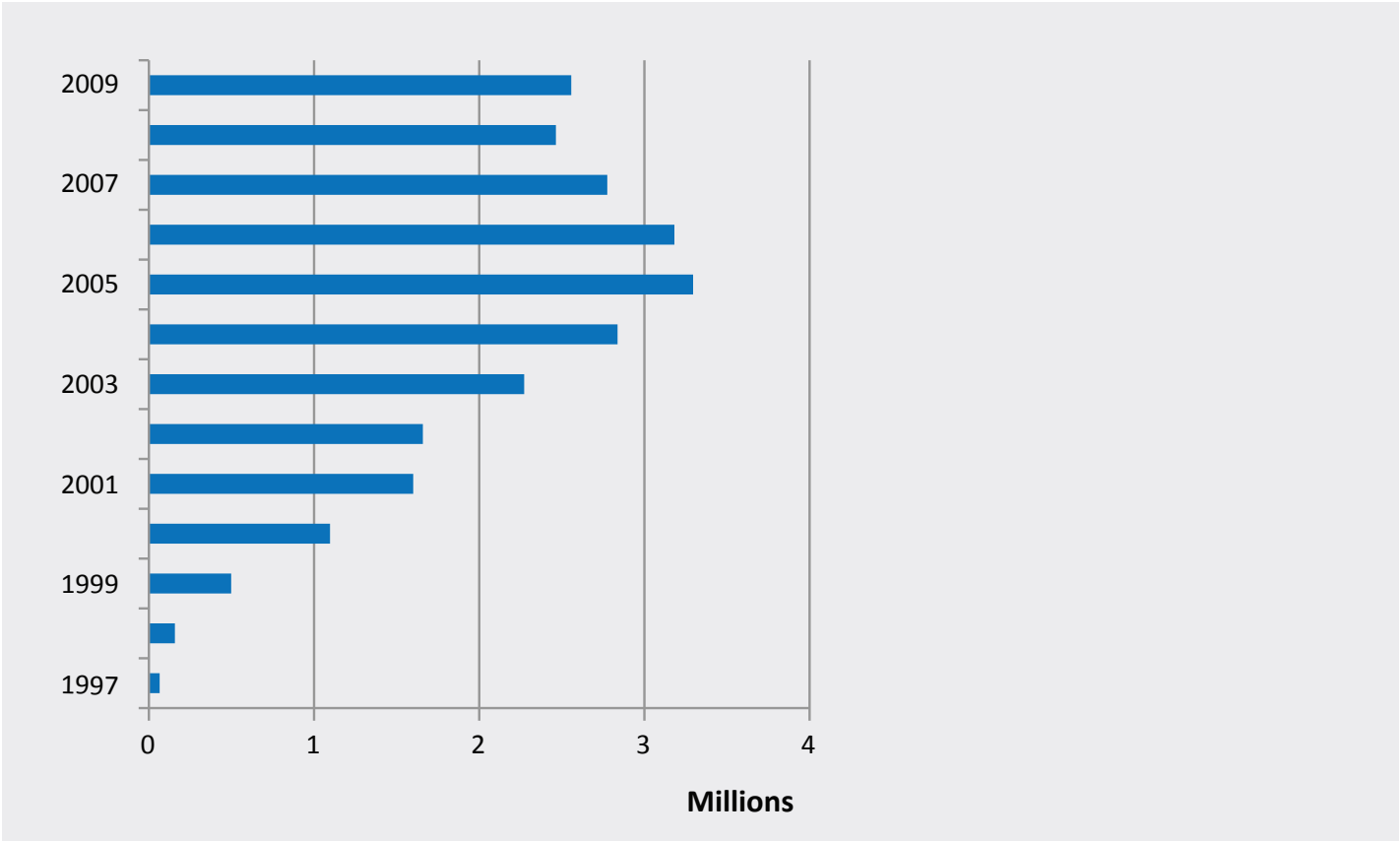
Introduction

Botulinum neurotoxin (BoNT) has transformed the field of aesthetic medicine since its recognition as an aesthetic tool 20 years ago. Its first reported cosmetic use was described in a 1992 study limited to the glabella.[1] Since that time, its use has been described in every mimetic muscle.[2-6] According to the American Society for Aesthetic Plastic Surgery, botulinum neurotoxin type A (BoNTA) injection has remained the most popular aesthetic procedure since 2000, with more than 2.5 million procedures performed in 2009 alone (Figure 1).[7] Although much of the US history of aesthetic BoNTA use has been defined by onabotulinumtoxinA (BoNTA-ONA; Botox® Cosmetic; Allergan, Inc; Irvine, California), the 2009 approval of abobotulinumtoxinA (BoNTA-ABO; Dysport™; Medicis Pharmaceutical Corporation; Scottsdale, Arizona) provides today's aesthetic practitioner with an additional therapeutic option. As we look to the future, more products will arrive over the coming years, and this expanding landscape will offer us the ability to continually refine and individualize treatment for each patient. To effectively use each new option, the clinician must be familiar with the similarities and differences among products and achieve a level of comfort regarding their unique qualities and practical applications.

Figure 1. Aesthetic BoNTA annual procedures.

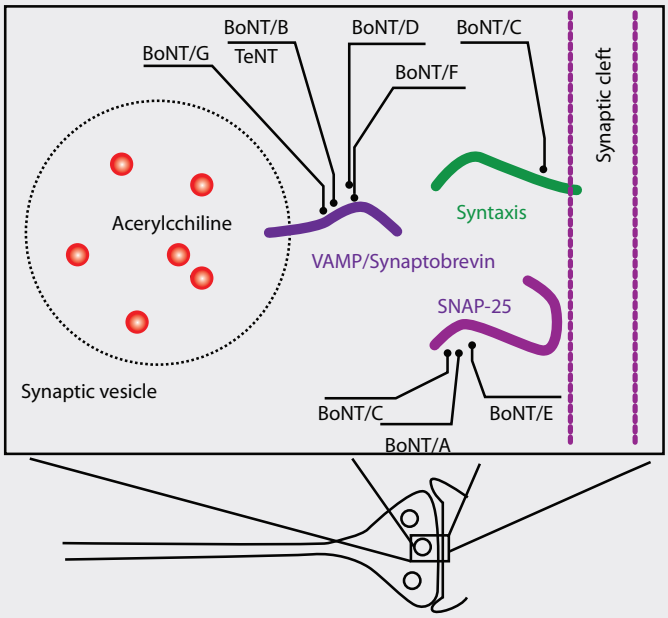


Botulinum Neurotoxin Clinical Background

BoNT is a product of *Clostridium botulinum*, an anaerobic, gram-positive, spore-forming bacterium. Different strains of *C botulinum* produce 7 distinct neurotoxins, each with unique functional and immunologic characteristics that affect biologic potency and, ultimately, clinical usefulness to human medicine.[8,9] Botulinum toxin types A and B (BoNTA and BoNTB, respectively) are currently the only serotypes approved for human use. Commercial preparations of BoNTA are the most widely used worldwide and currently hold the only approvals for aesthetic use.

Despite their unique qualities, different BoNT serotypes demonstrate the same basic mechanism of action (Figure 2). Whether ingested (in nature) or injected (in medicine) or perhaps applied topically (in the future), BoNT travels to the neuromuscular junction where it binds, cleaving a membrane protein responsible for acetylcholine exocytosis, thus blocking the release of acetylcholine and inducing functional paralysis. The specific serotype determines which membrane protein is disturbed. BoNTA cleaves synaptosomal-associated protein 25 (SNAP-25), one of the SNARE proteins necessary for the fusion of the acetylcholine-containing vesicle with the cell membrane.[10]

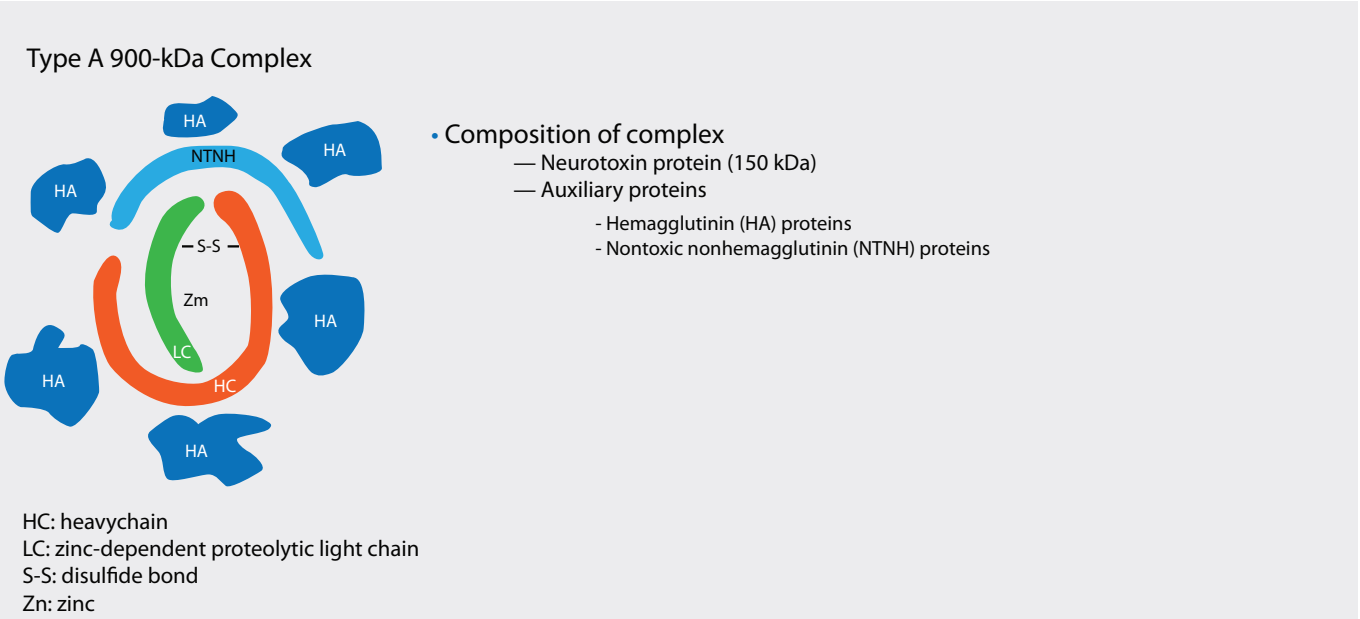
Figure 2. BoNT mode of action.



- Polypeptide chain; inert before activation
- Activated in process called nicking (or cleaving) to form a heavy chain linked by disulfide bonding to a light chain
- 7 different serotypes (A, B, C, D, E, F, G) are structurally similar but have functional and immunologic differences
- All toxins naturally exist as complexes that dissociate under physiologic pH

The natural physical structure of BoNTA is a large complex consisting of the core neurotoxin protein (150 kDa) in combination with auxiliary proteins (Figure 3). These secondary proteins appear to have a protective role, shielding the neurotoxin from acidic stomach conditions.[10] They may also have a secondary role in shielding parts of the neurotoxin from antibody formation.[11] Each commercial formulation of BoNTA has a unique complex, and the impact of the complex's size and composition is a subject of increasing interest and discussion. Studies suggest that the function and properties of botulinum neurotoxins are affected by the presence of secondary proteins and the structure of the complex.[12-16]

Figure 3. The BoNTA complex.



It is not known whether and how accessory proteins may affect a product's clinical effects in aesthetic treatment. A neurotoxin protein cannot act until it is freed from its complexing proteins; therefore, all BoNTA neurotoxin complexes must dissociate following injection. Several studies conducted on commercially available toxins have indicated that dissociation occurs rapidly. In 2008, Eisele and colleagues[17] presented findings from their study of complex dissociation under physiologic conditions (900 kDa complex). They reported that the neurotoxin protein is released from the complex less than 1 minute after being exposed to physiologic pH conditions. Due to this rapid dissociation rate, the study authors concluded that the presence of complexing proteins cannot be considered a significant stabilizing factor, nor can it significantly affect product diffusion.[17] Similarly, Friday and associates[18] evaluated the stability of 3 commercial toxin products (Botox®, Dysport™, and Myobloc®) under physiologic pH and temperature conditions and found that the neurotoxins for all 3 commercial preparations were dispatched from their complexes as soon as they were exposed to physiologic conditions, and all showed significant paralytic activity at zero incubation time. Although further exploration of this issue is needed, these studies suggest that the presence, size, and composition of the complex do not greatly influence the neurotoxin protein's ability to act.

Commercially Available Botulinum Neurotoxin Products

As of 2010, 3 neurotoxin products are approved for use in the United States: onabotulinumtoxinA (BoNTA-ONA, Botox Cosmetic®; Allergan Inc; Irvine, California), abobotulinumtoxinA (BoNTA-ABO, Dysport™; Medicis Pharmaceutical Corporation; Scottsdale, Arizona), and rimabotulinumtoxinB, a type B neurotoxin (Myobloc®; Solstice Neurosciences; Malvern, Pennsylvania). These 3 products are indicated for many medical applications; however, BoNTA-ONA and BoNTA-ABO are the only products with an approved indication for aesthetic use.

We can expect to see additional BoNT products attempt to enter the US market in the coming years because a number of neurotoxins are available internationally or are in development for possible future use. As new products arrive, we will see products that "look" different from existing options. Two BoNTA products formulated without complexing proteins are in US clinical trials: PurTox® (Mentor Corporation; Santa Barbara, California) and Xeomin® (Merz Pharmaceuticals GmbH; Frankfurt, Germany). Revance Therapeutics (Newark, California) is developing a topical delivery system for BoNTA.

We do not currently know how characteristics such as complex size/composition or delivery vehicle will affect aesthetic clinical outcomes, but we do know that each neurotoxin product will have a unique clinical profile and will offer an additional therapeutic choice for the clinician. As we become more experienced with a range of neurotoxin products, we may find that some are poor substitutes for those currently at hand, while others may join our armamentarium as assets to aesthetic practice. The discussion in this review will focus on products currently approved for aesthetic indications in the United States: BoNTA-ONA and BoNTA-ABO.

OnabotulinumtoxinA

BoNTA-ONA has a long history of use worldwide, with over 20 therapeutic indications across 75 countries. Its safety and efficacy are well-established in many facets of medicine. As we discuss BoNTA-ONA along with newer and future products, a brief review of its aesthetic clinical program is warranted.

The US aesthetic clinical trials for BoNTA-ONA consisted of 2 phase 3, randomized, multi-center, double-blind, placebo-controlled studies[19,20] and an open-label, repeat-injection study.[21] Patients in the placebo-controlled studies received 1 fixed-dose treatment. Day-30 response rate was approximately 80% (by investigator's assessment, rate across both placebo-controlled studies), with response beginning to fade by 90 days.[22] Adverse events were similar to those with placebo, with the exception of blepharoptosis (3% vs placebo, across both placebo-controlled studies).[22] Patients enrolled in the open-label, repeat-injection extension study of these 2 pivotal trials received 2 additional fixed-dose treatments (at 0 months and 4 months; cycles 1 and 2, respectively). The overall incidence of blepharoptosis was 2.2% in cycle 1 and 0.8% in cycle 2.[21]

Beyond these first aesthetic clinical trials, BoNTA-ONA has certainly maintained a visible presence in the scientific literature and in clinical practice. It has proven to be a safe, effective, and flexible product with many potential applications. Any new entry to the market will understandably be subject to comparisons with this agent.

AbobotulinumtoxinA

BoNTA-ABO was approved by the US Food and Drug Administration (FDA) in 2009, but carries more than 15 years of experience into this new approval. It is approved in more than 70 countries for therapeutic indications, and has an aesthetic indication in more than 25 countries. The product has been studied in more than 150 clinical trials worldwide.[23]

The US clinical trial program for BoNTA-ABO consisted of 3 randomized, placebo-controlled, double-blind, multicenter trials[24-26] and 2 open-label studies,[27-29] including one to evaluate long-term safety.[27] More than 3500 patients were treated with BoNTA-ABO during these trials. The efficacy of BoNTA-ABO was well-established through multiple treatment protocols: single- and repeat-injection treatments with fixed dosing and a single-injection study using variable dosing based on patient gender and muscle mass assessment. The median duration of effect was 85 days for the fixed-dosing regimen[24] and 109 days for the variable-dosing regimen.[26] The median time to onset of effect was 3 days,[24] with some results as early as 24 hours.[24,26] A repeat-injection study demonstrated continuing efficacy without tachyphylaxis after multiple treatments.[29]

Clinical study results demonstrate that BoNTA-ABO is well tolerated in the treatment of glabellar lines. Adverse events were similar to those with placebo, with the exception of "eye disorders" (defined as eyelid edema and eyelid ptosis).[30] The rate of blepharoptosis in the clinical studies was 2%, and the incidence did not increase in the long-term safety studies of repeat administrations. The overall incidence of adverse events remained relatively constant or decreased over repeated treatment cycles.[27] Testing and study of BoNTA-ABO is ongoing, with a second phase 3, open-label extension study currently in process.

Important Safety Issues

The availability of multiple BoNT formulations has brought to the forefront safety issues related to possible misunderstandings regarding each product's unique characteristics. In April 2009, the FDA issued requirements for the inclusion of a boxed safety warning in the prescribing information and the implementation of a risk evaluation and mitigation strategy for each commercially available BoNT product.[31] These requirements were the result of concerns regarding possible distal spread of BoNT. It is important to note that although no instances of distal spread have been identified following aesthetic treatment, the safety language and risk evaluation and mitigation strategy requirements apply to all products and all uses. In August 2009, the FDA issued unique generic names for each commercially available BoNT product, in a move that formalizes the warning that BoNT products are not interchangeable.[32]

Similarities and Differences in Approved Botulinum NeurotoxinA Products

As more BoNT options become available, an understanding of the similarities and differences among products will enable informed decisions about their usefulness in aesthetic medicine. BoNTA-ONA and BoNTA-ABO are both BoNTA products, an important similarity. However, each product is derived through the proprietary processes of their respective manufacturers, with resultant differences between the formulations.[33] BoNTA-ONA and and BoNTA-ABO are believed to have differing complex sizes (900 kDa and 500 kDa-900 kDa, respectively). Pickett notes that data regarding the molecular weight of BoNTA-ABO have not been published,[34] and in his article with Wortzman[10] states that the collection of data to support the assertion of any complex particle size is "exceptionally difficult." Despite the lack of concrete information regarding the complex size of BoNTA-ABO, certainly the proprietary process involved in producing a commercial BoNTA formulation would likely result in differing complex sizes between BoNTA-ABO and BoNTA-ONA.

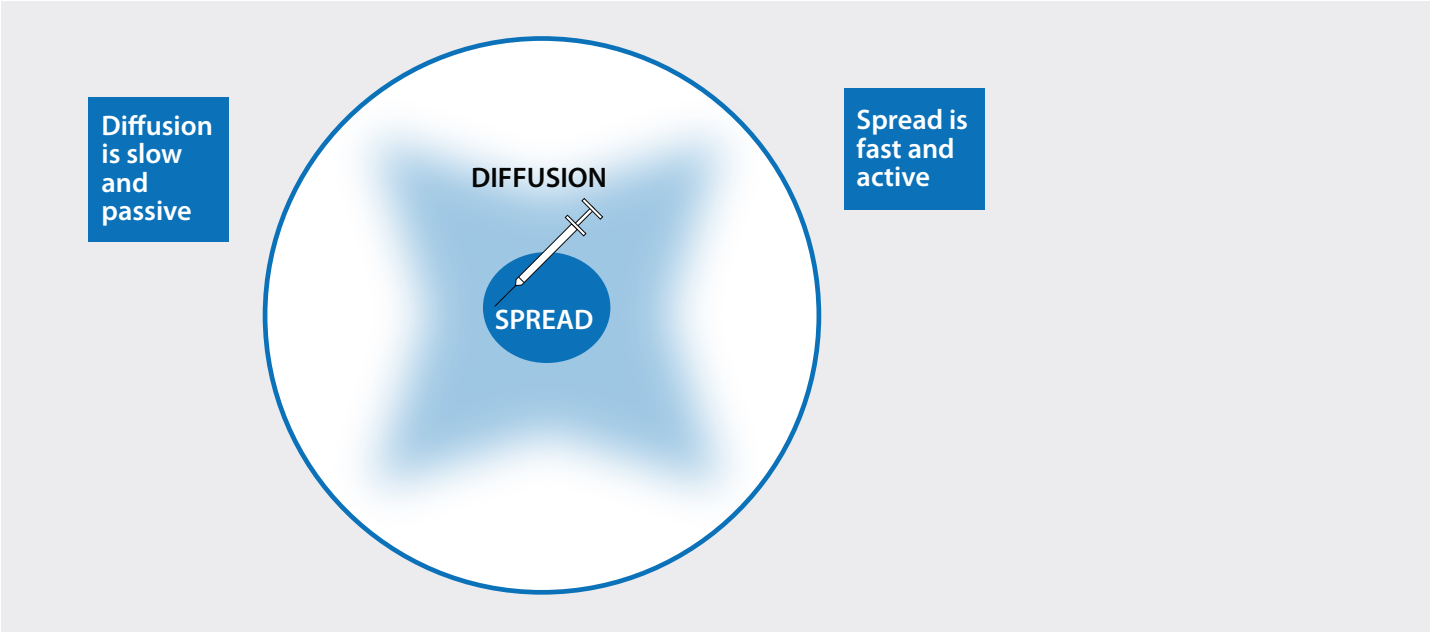
Diffusion vs Spread

The reputed complex size difference between formulations is at the root of a primary discussion topic related to the potential clinical impact of product differences — specifically, toxin movement from the site of injection. This movement is commonly referred to as diffusion. Differences in commercially available formulations are associated with differing diffusion rates, yielding corresponding concern about possible resultant adverse events.

It is important to understand that diffusion is a kinetic process whereby the toxin molecules move to attain concentration equilibrium. All toxins diffuse, because it is a natural process for any high local concentration of molecules to diffuse to a lower concentration. During diffusion, the toxin complex dissociates and the neurotoxin proteins will begin to bind. In an animal model study, Tang-Liu and colleagues[35] found no difference in the distribution or diffusion rate between a 900-kDa complex and a complex-free BoNTA.

Another factor in the discussion of toxin movement is spread — the actual physical movement of the injected product, due primarily to clinician-controlled variables (eg, injection depth, pressure, syringe volume, dilution volume, needle length and gauge). All toxin products are subject to spread due to these multiple variables. Diffusion and spread are not identical (Figure 4).

Figure 4. Diffusion and spread.



In their 2009 article, Wortzman and Pickett[10] discuss reports that BoNTA-ABO demonstrates greater local diffusion following injection vs comparative agents, and the resulting inference that this diffusion is due to a smaller complex particle size. The authors found that most reports of greater diffusion were the result of dosing — specifically, that the studied doses of BoNTA-ABO were too high in comparison with the comparative agent. They additionally state that "there is no link or relationship between BoNTA complex size, dissociation, and diffusion." In conclusion, all toxins dissociate rapidly and diffuse until bound. Wortzman and Pickett hold that complex size has not been shown to have a practical effect on those natural actions.

Unit Potency

The question of unit equivalence between different BoNTA formulations is one of the most common practical concerns expressed by clinicians. Before discussing this topic, the clinician must understand that unit measurement is a clear clinical difference between products. Quite simply, BoNTA-ABO units and BoNTA-ONA units are not interchangeable.

As stated earlier, each commercial BoNTA product is the result of a proprietary manufacturing process. This results in a proprietary unit potency measurement for each product as well; a unit of BoNTA-ONA bears no direct relationship to a unit of BoNTA-ABO. This is not to say that unit conversion templates are not helpful — they may be, especially as a safety step in dosing. However, it is best to remember that these are simply estimates and that even experts experienced with multiple formulations find it difficult to agree on unit equivalence ratios.

In the consensus panel that I co-chaired,[5] there were varying opinions regarding a dosing ratio. This variance aligned mostly according to geography, with US physicians recommending slightly higher ratios than the panel members from South America and Europe. I was a bit of an outlier on the panel, expressing disagreement with the use of unit equivalence ratios as a standard treatment approach. The panel recommended that physicians experienced with BoNTA-ONA who seek guidance on initiating BoNTA-ABO treatment use a dose conversion ratio in the range of 1:2.5 to 1:3 (BoNTA-ONA:BoNT-ABO). We emphasized that this ratio is provided only as a "safety net" until the physician is sufficiently experienced and comfortable to make independent BoNTA-ABO dosing decisions.

In a 2010 publication, Hexsel and colleagues[36] asserted that "clinical use and recent unpublished studies suggest that 2.5 U of Dysport™ [BoNTA-ABO] is slightly more potent than 1 U of Botox® [BoNT-ONA]." The authors' recommendation is that a dose ratio of 1:2.5 (BoNT-ONA:BoNT-ABO) is appropriate for use in the upper face. It is interesting that they suggest a more conservative ratio of 1:2 in the lower face. Despite the differences between BoNTA products, clinical data and years of worldwide experience have proven that both commercially available formulations are safe and effective. Optimal outcomes are based on the clinician's understanding of each as a unique product and the application of professional judgment to issues of dosing and aesthetic application.

Practical Use of Botulinum NeurotoxinA in Aesthetic Practice

Although BoNTA-ONA and BoNTA-ABO are unique products, the aesthetic clinician will find that the preparation and practical use of each product are extremely similar. Many of the common methods of preparation and most uses of these products depart from the approved labeling. These departures result from years of experience and are not intended to represent a cavalier disregard for the products' approvals. Rather, off-label practices should be adopted based on an educated, judicious decision by the practitioner to improve overall patient care and treatment outcomes, and accompanied by appropriate storage, handling, and patient-related safety measures.

Indications and Contraindications

BoNTA-ONA and BoNTA-ABO are FDA-approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients younger than 65 years of age,[22,30] but the practical aesthetic use of BoNTA varies greatly beyond that indication. BoNTA is still most commonly used in upper-face applications, such as treatment of the glabella and frontalis and the correction of periorbital lines. However, the evolution of aesthetic practice has yielded the broad use of BoNTA for the treatment of other facial concerns. The use of BoNTA to lift and reshape the brows is a very effective part of the upper-face treatment plan. In the lower face, treatment of the depressor anguli oris and the platysma are offered by many experienced aesthetic clinicians. Additional specialized applications include treatment of the overactive mentalis, correction of "bunny lines" and "gummy smile," and softening of lip lines.[3,5,6,36-39]

The aesthetic use of BoNTA is contraindicated for some individuals. Prescribing instructions for both BoNTA-ONA and BoNTA-ABO contraindicate their use in patients with infection at the injection site or with known hypersensitivity to any BoNT products or components of the formulation (the excipients also vary slightly between the 2 products).[22,30] BoNTA products should be used with caution in individuals with neuromuscular disorders, or who are on certain types of drug therapies (eg, aminoglycoside antibiotics, muscle relaxants).[22,30] Both approved products are pregnancy category C, and their use should be avoided in patients who are pregnant or who are breastfeeding. Patients with cow's milk-protein allergies are contraindicated from use of BoNTA-ABO due to the presence of lactose in the preparation.[30] It should be noted that Hexsel and colleagues[36] state that this risk has not been shown to be clinically relevant and there are no documented allergic reactions at this time.

Reconstitution

The package inserts for BoNTA-ONA and BoNTA-ABO outline specific diluent instructions for the reconstitution of the vials.[22,30] The package insert for BoNTA-ONA (100-U vial) requires 2.5 mL preservative-free saline as the diluent. The package insert for BoNTA-ABO (300-U vial) also requires preservative-free saline, but provides the option of 2.5 mL or 1.5 mL dilutions. In practice, clinicians frequently depart from these standards.

The 2004 consensus recommendations on the use of BoNTA-ONA in aesthetics stated that the use of preserved saline was "preferred,"[3] and pointed to a study indicating less patient discomfort when preserved saline was used as the diluent.[40] Two 2010 practice guides for BoNTA-ABO concur that either diluent is acceptable for use as a reconstituting agent.[5,36]

Aesthetic practitioners commonly use a range of dilutions, with each practitioner having an individual preference. Within reasonable ranges, the dilution rate selected by the individual practitioner appears to have no effect on overall efficacy and safety.[41] In their publication, Hexsel and colleagues[36] state that "the dose of toxin is more important than the volume of toxin injected" in determining the overall efficacy of the treatment.

Storage and Use

Each vial of BoNTA-ONA and BoNTA-ABO is approved for single patient use — BoNTA-ONA within 24 hours of reconstitution[22] and BoNTA-ABO within 4 hours of reconstitution.[30] However, the practical considerations of this approval can result in significant waste of product, ultimately increasing expense.[5] The consensus panel that I co-chaired concluded that a single-use vial can be safely used for multiple patients, as long as sterile procedures are carefully followed.[5] This view is supported by the results of a clinical study with BoNTA-ONA in which the vials remained sterile under multiple-use conditions.[42]

The consensus of expert clinicians also supports the use of reconstituted BoNTA beyond the approved usage period, as long as proper storage procedures are followed.[3,5,36] Studies report continued potency and efficacy of BoNTA for weeks or months following reconstitution.[43-47]

Individualized Therapy

Although clinical data and consensus articles provide helpful guidance on aesthetic applications, reconstitution, and other practical matters related to BoNTA use in aesthetic practice, a determining factor for optimal outcomes is the creation of an individualized treatment plan for each patient. Patient satisfaction depends on the clinician's ability to visualize and recommend a treatment plan that meets the patient's goals and needs. Factors such as gender, personal aesthetic preferences, and the structure, action, and mass of the muscles to be treated all have a dramatic effect on the optimal approach.

This author reported the results of a phase 3, randomized, multicenter, double-blind, placebo-controlled study conducted as part of the BoNTA-ABO clinical program.[26] The study was unique because it evaluated the results of variable dosing based on gender and corresponding muscle mass assessment. Variable dosing in practice is off label yet routine. Subject patients were categorized by the results of a muscle-mass index system created for the study. Patients then received a single dose of BoNTA-ABO according to their gender and the results of the muscle mass assessment (ie, small, medium, large). The overall 30-day response rate was 85%, with a median clinical duration of 109 days and no significant dose-related adverse events. The response rate for men in particular was much higher than that seen in the fixed-dose studies. These study results highlight the large impact of small changes in our approach to patient treatment.

Botulinum NeurotoxinA Dosing in Facial Aesthetic Rejuvenation

Of particular interest to the clinician considering the use of BoNTA-ABO are dosing guidelines for specific treatment areas. Several recently published guidelines for BoNTA-ABO use include dosing recommendations.[5,36,48] Each guideline reflects the preferences and practices of the contributing authors and, as such, dose ranges vary somewhat. Despite this variance, a review of these publications can be extremely helpful to the clinician seeking guidance on the use of BoNTA-ABO.

Tables 1 and 2 summarize suggested BoNTA dose ranges for common aesthetic treatments. The dose ranges are referenced and adapted from published scientific literature and are suggestions based on the consensus of physicians experienced with each product. It bears reminding that the units of each product are proprietary and these recommendations do not attempt to use or establish a dose conversion ratio between products; rather, they reflect the range in which experienced physicians have found favorable treatment results.

Additionally, dosing recommendations are intended to be a starting point for the practicing physician and should not replace individual professional judgment. Clinicians should rely on their individual experience, as well as patient anatomy and goals, to select and refine the dose for a specific treatment. Consideration of the overall treatment plan, including adjunctive therapies, will ultimately guide the dose selection.

Table 1. Dosing Recommendations for BoNTA Treatment of the Upper Face

Treatment	BoNTA-ONA	BoNTA-ABO
Glabella	Women: 10-30 U[37] Men: 20-40 U[37] Divided among 5-7 injection points; men may require more sites[37]	Women: 50-70 U[26] Men: 60-80 U[26] Divided among 5 injection points; dose adjusted for muscle mass[26]
Forehead	6-15 U, divided among 4-8 injection points[37] Men may require more than 15 U[37]	20-60 U total dose, divided among 4-6 injection points distributed in a single line[5,48]
Crow's feet	10-30 U total dose, divided among 2-5 injection points per side[37]	20-60 U per side, divided among 3 injection points[5,48] Optional fourth injection of 10 U[5]
Bunny lines	2-5 U total dose, divided between 2 injection sites (1 injection per side)[3]	10-20 U, divided into 2 injection points [5,48]

Table 2. Dosing Recommendations for BoNTA Treatment of the Lower Face

Treatment	BoNTA-ONA	BoNTA-ABO[5]
DAO	1-7.5 U per side[49]	2.5-10 U per side
Lip lines	4-5 U, evenly divided among 2-6 injection points (includes upper and lower lip)[37]	Upper lip: 2.5-16 U, divided among 2 or 4 injection points Lower lip: 2.5-7.5 U, divided between 2 injection points
Chin	4-10 U divided between 1-2 injection points [37]	5-20 U total dose, divided between 1-2 injection points
Platysma	40-60 U, divided among all injection points[37]	30-120 U total dose, usual dose 30 U per band

DAO = depressor anguli oris

Combination Therapy With Botulinum NeurotoxinA

The efficacy of combined treatment modalities to achieve optimal results is now well accepted in the aesthetic community. BoNTA administration is successfully combined with dermal fillers, light/energy therapy, and even surgery to enhance treatment outcomes.[5,36,37,39,50,51] In keeping with the individualized approach discussed earlier, the therapeutic approach must be appropriate for the physiology of the demonstrated aging process, asymmetry, or other pathology. This practical consideration dictates that a combination approach will frequently prove to be the best choice for achieving natural, long-lasting, cost-effective outcomes.

In a 2008 consensus article, Carruthers and colleagues[37] discussed this evolution of aesthetic treatment, and provided practice guidelines for approaching minimally invasive aesthetic treatment with multiple modalities, with a specific focus on the roles of BoNTA-ONA and hyaluronic acid dermal fillers. They noted that the approach to facial rejuvenation had undergone a paradigm shift from a 2-dimensional focus on lines to an increased understanding of the role of volume loss on facial aging and the importance of this consideration to the treatment plan. This 3-dimensional viewpoint necessitates the use of multiple modalities, because no single aesthetic tool can address the myriad presentations of aging and associated pathologies.

BoNTA and dermal fillers lend themselves especially well to combined use. The most commonly used fillers are minimally invasive and yield long-lasting, but not permanent, results — qualities shared with BoNTA injections. As such, these agents work well together in crafting a flexible treatment plan that can achieve dramatic results and evolve with the patient's changing needs over time. This author has had very satisfactory results using fillers and BoNTA, both solo and in combination, across all facial regions. It is advised that clinicians with less experience approach treatment in a conservative manner until they are comfortable with the treatment area and the modality. For example, a BoNTA-ABO consensus panel recommended that a less-experienced clinician may wish to use fillers as the primary treatment of the lower face, following up with the judicious and selective application of BoNTA as needed to achieve desired results.[5]

A common question about combination therapy is how to approach the practical application of each treatment. Specifically, is there a preferred order for the application of each modality? Carruthers and colleagues stated that the general consensus of their panel was to perform BoNTA injections first in the upper face, and follow up to assess the need for treatment of residual lines and folds with dermal filler injections.[37] Conversely, the majority of the panel reported using fillers as the initial treatment in the lower face, and proposed the advantages of applying treatment over multiple sessions, allowing for reassessment during the treatment process.

In the consensus statement in which I participated focusing on the use of BoNTA-ABO, it was agreed that practical and economic considerations frequently determine the order and timing of product/procedure use in multimodal therapy.[5] It is important that the practicing clinician understand the purpose and expected outcomes of each modality to optimize the patient's results and minimize costs and downtime. This consensus regarding how to approach multimodal treatment with BoNTA is summarized in Table 3.[5]

Table 3. Recommendations for Botulinum NeurotoxinA Use in Combination Therapy

Treatment	Recommendations
BoNTA + Injectable fillers	BoNTA and injectable fillers can be administered the same day or separate days. However, it may be preferable to inject the first agent, wait until effects are clinically evident, and then follow up with second agent as needed. Upper face: Typical to inject BoNTA first. Mid and lower face: Typical to inject filler first.
BoNTA + Ablative laser resurfacing	Inject BoNTA several days prior to the ablative procedure and wait until BoNTA effects are clinically evident.
BoNTA + Nonablative lasers/chemical peels	Nonablative procedure first. Inject BoNTA 10-15 minutes after nonablative procedure.
BoNTA + Surgery	Avoid injecting BoNTA on day of surgery. Follow-up BoNTA injections can continue beginning 3 months after surgery.

From Kane M, et al.[5]

Treatment-related Complications and Adverse Effects

Adverse effects associated with BoNTA are rare and temporary, and the primary tool for managing these complications is prevention. A solid knowledge of facial anatomy, thorough patient assessment, proper treatment dosing, and precise injection placement are all tools that help prevent treatment-related complications.

Despite the use of best practices, some adverse effects may occur. Matarasso and Shafer found that some injection-site pain and localized bruising are the most common adverse effects and are sometimes inevitable.[39] Mild adverse effects such as headache, bruising, or swelling are typically transient and require little clinician intervention. This author recommends a single dose of acetaminophen for headache and pressure/ice application for bruising or swelling.[5]

However, treatment-related complications associated with dosing decisions, improper injection placement, pre-existing muscle weakness, anatomic variations, or the migration of toxin into unintended areas may require clinician action. Despite their unpleasant effects, these complications typically fade after several weeks. Clinician intervention in the interim can mitigate the overall effects. For example, unwanted lateral brow elevation ("Spock" or cocked brow) can be treated with the selective injection of additional neurotoxin into the lateral frontalis fibers. Suggested doses are 1-3 U of BoNTA-ONA[52] or 5 U of BoNTA-ABO.[5] Similarly, asymmetry following treatment can be addressed with small doses of additional BoNTA on one side as needed.[5] Occurrence of transient lid ptosis can be managed with the application of alpha-adrenergic agonist ophthalmic drops.[5]

Common Treatment-related Adverse Effects Following Botulinum Neurotoxin

- Headache;
- Bruising/swelling;
- Asymmetry;
- Unwanted lateral brow elevation;
- Blepharoptosis;
- Brow ptosis;
- Upper lip flattening; and
- Oral incompetence.

The lower-face musculature is highly integrated and overtreatment in this area can result in significant effects on patient quality of life (eg, oral incompetence). Adverse events will be more difficult to manage in this area and, in general, complications must resolve over time. Conservative dosing and precise injection technique are key to prevention of adverse events.

Conclusion

The 2009 approval of BoNTA-ABO has further expanded the therapeutic options available to the aesthetic clinician. Clinical data and physician experience support BoNTA-ABO as a safe and effective addition to the practitioner's armamentarium. It is important to remember that BoNTA-ABO and BoNTA-ONA, although very similar in many respects, do have important differences — differences that may yield unique applications for each product in the aesthetic practice.

Regardless of which BoNTA product is selected, the hallmarks of quality treatment remain the same. Treatment individualization is essential for patient satisfaction and optimal outcomes, and will dictate many elements of the treatment plan. As we look to the future, the continued development of enhanced products, including new BoNT therapeutic options, will provide expanded choices with which to address specific patient goals and lifestyle needs.

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References

1. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. J Dermatol Surg Oncol. 1992;18:17-21.

2. Carruthers J, Carruthers A. Botulinum toxin A in the mid and lower face and neck. Dermatol Clin. 2004;22:151-158.

3. Carruthers J, Fagien S, Matarasso SL; Botox Consensus Group. Consensus recommendations on the use of botulinum toxin A in facial aesthetics. Plast Reconstr Surg. 2004;114:1S-22S.

4. Dayan SH, Maas CS. Botulinum toxins for facial wrinkles: beyond glabellar lines. Facial Plast Surg Clin North Am. 2007;15:41-49.

5. Kane M, Donofrio L, Ascher B, et al. Expanding the use of neurotoxins in facial aesthetics: a consensus panel's assessment and recommendations. J Drugs Dermatol. 2010;9;7-22.

6. Kane, MA. Botox injections for lower facial rejuvenation. Oral Maxillofac Surg Clin North Am. 2005;17:41-49.

7. Americian Society for Aesthetic Plastic Surgery 1997-2009 Cosmetic Surgery National Data Bank Statistics. Available at: www.surgery.org Accessed April 12, 2010.

8. Lamanna C. The most poisonous poison. Science. 1959;130:763-772.

9. Simpson, LL. Botulinum toxin: a deadly poison sheds its negative image. Ann Intern Med. 1996;125:616-617.

10. Wortzman MS, Pickett A. The science and manufacturing behind botulinum neurotoxin type a-abo in clinical use. Aesthet Surg J. 2009;29;S34-S42.

11. Chen F, Kuziemko GM, Amersdorfer P, Wong C, Marks JD, Stevens RC. Antibody mapping to domains of botulinum neurotoxin serotype A in the complexed and uncomplexed forms. Infec Immun. 1997;65:1626-1630.

12. Sharma SK, Singh BR. Enhancement of the endopeptidase activity of purified botulinum neurotoxins A and E by an isolated component of the native neurotoxin associated proteins. Biochemistry. 2004;43:4791-4798.

13. Matsumura T, Jin Y, Kabumoto Y, et al. The HA proteins of botulinum toxin disrupt intestinal epithelial intercellular junctions to increase toxin absorption. Cell Microbiol. 2008;10:355-364.

14. Cheng LW, Onisko BC, Johnson EA, et al. Effects of purification on the bioavailability of botulinum neurotoxin type A. Toxicology. 2008;249:123-129.

15. Hasegawa K, Watanabe T, Suzuki T, et al. A novel subunit structure of clostridium botulinum serotype D toxin complex with three extended arms. J Biol Chem. 2007;282:24777-24783.

16. Kukreja RV, Singh BR. Comparative role of neurotoxin-associated proteins in the structural stability and endopeptidase activity of botulinum neurotoxin complex types A and E. Biochemistry. 2007;46:14316-14324.

17. Eisele K-H, Taylor HV. Dissociation of the 900 kDa neurotoxin complex from C. botulinum under physiological conditions. Program and abstracts of the International Conference on Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins; June 14, 2008; Baveno (Lake Maggiore) Italy.

18. Friday D, Bigalke H, Fevert J. In vitro stability of botulinum toxin complex preparations at physiological pH and temperature. Naunyn-Schmeideberg Arch Pharmacol. 2002;365:R20.

19. Carruthers JA, Lowe NJ, Menter MA, et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. J Am Acad Dermatol. 2002;46:840-849.

20. Carruthers JD, Lowe NJ, Menter MA, Gibson J, Eadie N. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. Plast Reconstr Surg. 2003;112:1089-1098.

21. Carruthers A, Carruthers J, Lowe NJ, et al. One-year, randomized, multicenter, two-period study of the safety and efficacy of repeated treatments with botulinum toxin type A in patients with glabellar lines. J Clin Res. 2004:1-20.

22. BOTOX Cosmetic [package insert]. Irvine, Ca: Allergan, Inc; 2009.

23. Jewell ML, Monheit GD. An overview of clinical trial data on a new formulation of botulinum neurotoxin type A. Aesthet Surg J. 2009;29;31-33.

24. Brandt F, Swanson N, Baumann L, Huber B. Randomized, placebo-controlled study of a new botulinum toxin type a for treatment of glabellar lines: efficacy and safety. Dermatol Surg. 2009;35:1893-901.

25. Rubin M, Dover J, Glogau R, Goldberg D, Goldman M, Schlessinger J. The efficacy and safety of a new US botulinum toxin type A in the retreatment of glabellar lines following open-label treatment. J Drugs Dermatol. 2009;8:439-444.

26. Kane MA, Brandt F, Rohrich RJ, et al. Evaluation of variable-dose treatment with a new US botulinum toxin type a (Dysport) for correction of moderate to severe glabellar lines: results from a phase III, randomized, double-blind, placebo-controlled study. Plast Reconstr Surg. 2009;124:1619-29.

27. Cohen JL, Schlessinger J, Cox SE, Lin X. An analysis of the long-term safety data of repeat administration of botulinum neurotoxin type a-abo for the treatment of glabellar lines. Aesthet Surg J. 2009;29:S43-S49.

28. Monheit G, Cohen J. Long-term safety of repeated administration of a new formulation of botulinum toxin type A in the treatment of glabellar lines: interim analysis from an open-label extension study. J Am Acad Dermatol. 2009;61:421-425.

29. Moy R, Maas C, Monheit G, et al; for the Reloxin Investigational Group. Long-term safety and efficacy of a new botulinum toxin type A in treating glabellar lines. Arch Facial Plast Surg. 2009;11:77-83.

30. DYSPORT [package insert]. Scottsdale, AZ: Medicis Aesthetics Inc; 2009.

31. FDA Requires Boxed Warning for All Botulinum Toxin Products [news release]. US Food and Drug Administration; April 30, 2009. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149574.htm Accessed April 10, 2010.

32. FDA Gives Update on Botulinum Toxin Safety Warnings; Established Names of Drugs Changed [news release]. US Food and Drug Administration; August 3, 2009. Available at: http://www.fda.gov/NewsEvents/Newsroom-–/PressAnnouncements/ucm175013.htm Accessed April 10, 2010.

33. Panjwani N, O'Keefe R, Pickett A. Biochemical, functional and potency characteristics of type A botulinum toxin in clinical use. Botulinum J. 2008;1:153-166.

34. Pickett A. Dysport: pharmacological properties and factors that influence toxin action. Toxicon. 2009;54:683-689.

35. Tang-Liu DD, Aoki KR, Dolly JO, et al. Intramuscular injection of 125I-botulinum neurotoxin complex versus 125I-botulinum-free neurotoxin: time course of tissue distribution. Toxicon. 2003;42:461-469.

36. Hexsel D, Spencer JM, Woolery-Lloyd H, Gilbert E. Practical applications of a new botulinum toxin. J Drugs Dermatol. 2010;9:31-37.

37. Carruthers JDA, Glogau RG, Blitzer A; and Facial Aesthetics Consensus Group Faculty. Advances in facial rejuvenation: botulinum toxin type A, hyaluronic acid dermal fillers, and combination therapies — consensus recommendations. Plast Reconstr Surg. 2008;121:5S-30S.

38. Kane MA. The functional anatomy of the lower face as it applies to rejuvenation via chemodenervation. Facial Plast Surg. 2005;21:55-64.

39. Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport): clinical indications and practice guide. Aesthet Surg J. 2009;29;S72-S79.

40. Alam M, Dover JS, Arndt KA. Pain associated with injection of botulinum a exotoxin reconstituted using isotonic sodium chloride with and without preservative: a double-blind, randomized controlled trial. Arch Dermatol. 2002;138:510-514.

41. 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:S97-104.

42. Alam M, Yoo SS, Wrone DA, et al. Sterility assessment of multiple use botulinum A exotoxin vials: a prospective simulation. J Am Acad Dermatol. 2006;55:272-275.

43. Hexsel D, Rutowitsch MS, de Castro LC, et al. Blind multicenter study of the efficacy and safety of injections of a commmercial preparation of botulinum toxin typle A reconstituted up to 15 days before injection. Dermatol Surg. 2009;35:933-939.

44. Hexsel DM, De Almeida AT, Rutowitsch M, et al. Multicenter, double-blind study of the efficacy of injections with botulinum toxin type A reconstituted up to six consecutive weeks before application. Dermatol Surg. 2003;29:523-529.

45. Hui JI, Lee WW. Efficacy of fresh versus refrigerated botulinum toxin in the treatment of lateral periorbital rhytids. Ophthal Plast Reconstr Surg. 2007;23:433-438.

46. Parsa AA, Lye KD, Parsa FD. Reconstituted botulinum tupe A neurotoxin: clinical efficacy after long-term freezing before use. Aesthetic Plast Surg. 2007;31:188-191.

47. Yang GC, Chiu RJ, Gillman GS. Questioning the need to use Botox within 4 hours of reconstitution: a study of fresh vs 2-week-old Botox. Arch Facial Plast Surg. 2008;10:273-279.

48. Ascher B, Talarico S, Cassuto D, et al. International consensus recommendations on the aesthetic usage of *botulinum toxin* type A (Speywood Unit) — part I: upper facial wrinkles. J Eur Acad Dermatol Venereol. [published online ahead of print March 24, 2010].

49. Sengelmann RD, Tull S, Flynn TC. Botulinum toxin in the lips, mid, and lower face. In: Carruthers A, Carruthers J, eds. *Botulinum Toxin*. 2nd ed. Philadelphia, Penn: Elsevier; 2008:55-64.

50. Flynn TC. Update on botulinum toxin. Semin Cutan Med Surg. 2007;26:196-202. Abstract

51. Klein AW, Fagien S. Hyaluronic acid fillers and botulinum toxin type a: rationale for their individual and combined use for injectable facial rejuvenation. Plast Reconstr Surg. 2007;120:81S-88S.

52. Carruthers J, Carruthers A. Complications of botulinum toxin type A. Facial Plast Surg Clin North Am. 2007;15:51-54.