ORIGINAL ARTICLE

The Convergence of Medicine and Neurotoxins: A Focus on Botulinum Toxin Type A and Its Application in Aesthetic Medicine—A Global, Evidence-Based Botulinum Toxin Consensus Education Initiative

Part II: Incorporating Botulinum Toxin into Aesthetic Clinical Practice

Jean Carruthers, MD, FRCSC, FRC(Ophth),* Nathalie Fournier, MD,† Martina Kerscher, MD,‡ Javier Ruiz-Avila, MD,§ Ada R. Trindade de Almeida, MD,¶ and Gina Kaeuper, MAcc††

BACKGROUND The new world of safe aesthetic injectables has become increasingly popular with patients. Not only is there less risk than with surgery, but there is also significantly less downtime to interfere with patients' normal work and social schedules. Botulinum toxin (BoNT) type A (BoNTA) is an indispensable tool used in aesthetic medicine, and its broad appeal has made it a hallmark of modern culture. The key to using BoNTA to its best effect is to understand patient-specific factors that will determine the treatment plan and the physician's ability to personalize injection strategies.

OBJECTIVES To present international expert viewpoints and consensus on some of the contemporary best practices in aesthetic BoNTA, so that beginner and advanced injectors may find pearls that provide practical benefits.

METHODS AND MATERIALS Expert aesthetic physicians convened to discuss their approaches to treatment with BoNT. The discussions and consensus from this meeting were used to provide an up-to-date review of treatment strategies to improve patient results. Information is presented on patient management and assessment, documentation and consent, aesthetic scales, injection strategies, dilution, dosing, and adverse events.

CONCLUSION A range of product- and patient-specific factors influence the treatment plan. Truly optimized outcomes are possible only when the treating physician has the requisite knowledge, experience, and vision to use BoNTA as part of a unique solution for each patient's specific needs.

This activity is supported by an educational grant from Merz. Jean Carruthers is a consultant for Merz and Allergan. Nathalie Fournier has ownership interest in EKKYO. Martina Kerscher is a consultant and contracted researcher for Merz, Loreal, Galderma, Q-Med, Proctor and Gamble, Anteis, and Kythera Biopharmaceuticals. Ada Regina Trinadade de Almeida is a consultant for Allergan.

We are truly in an "era of injectables," with access to a varied armamentarium of products that yield dramatic aesthetic results with minimal recovery downtime. Botulinum toxin (BoNT) type A (BoNTA) is an indispensable tool in this armamentarium, and its broad appeal has made aesthetic BoNTA injections a hallmark of modern culture.

University of British Columbia, Vancouver, British Columbia, Canada; †Centre Laser Dermatologie and Phlébologie, La Croisée, Clapiers, France; ‡Division of Cosmetic Sciences, University of Hamburg, Hamburg, Germany; §Cosmetic Dermatology, Trichology and Hair Disorders Specialist, Dermedica Clinic, México City, Mexico; ¶Clínica Dermatológica do Hospital do Servidor Público Municipal de São Paulo, São Paulo, Brazil; ††Freelance Writer, Knoxville, Tennessee

ISSN: 1076-0512 • Dermatol Surg 2013;39:510–525 • DOI: 10.1111/dsu.12148

The availability of newer BoNTA formulations, with more expected in the near future, poses an exciting opportunity for aesthetic practitioners to reach an everexpanding potential patient base and provide increasingly refined treatment. Critical to this endeavor is the ability to use BoNTA to its best effect; this requires, at minimum, an understanding of the scientific profile and physical characteristics of commercially available agents, but just as important are an understanding of the patient-specific factors that will determine the treatment plan and the ability to integrate consideration of each patient's individual needs into the development of a personalized treatment strategy.

Although BoNTA formulations have been a mainstay of aesthetic practice for 20 years, continued evolution in the aesthetic industry creates a dynamic and progressive environment. There is no lack of publications or education pieces that provide guidance on the use of BoNTA in aesthetic medicine, but product introductions, refinements in technique, and new tools that assist in aesthetic assessment support the need for continued discussion. Our focus in this monograph is on the considerations that have the greatest effect on the achievement of optimal outcomes.

In Part I of this monograph, our colleagues took a comprehensive look at the history, science, and clinical data behind the use of BoNTA for therapeutic and aesthetic purposes. In this section, we will expand on that background by providing guidance on current approaches to aesthetic BoNTA treatment. Rather than deliver merely a basic how-to on certain procedures, it is our intention to present international expert viewpoints on some of the contemporary best practices in aesthetic BoNTA so that beginner and advanced injectors may gain insights that provide practical benefits.

The Aesthetic Patient

Aesthetic medicine has evolved dramatically over the past 30 years. In the past decade alone, the U.S. Food and Drug Administration has approved more than 20 aesthetic injectable products. Increased consumer demand for nonsurgical procedures mirrors this significant market expansion. According to American Society for Aesthetic Plastic Surgery (ASAPS) annual statistics, the number of nonsurgical procedures that physicians performed increased 356% from 1997 to 2011.[1] BoNT and hyaluronic acid fillers are routinely the most popular procedures, highlighting the demand for injectable products.

A shift in U.S. consumer attitudes has accompanied the increased demand for aesthetic procedures. A 2009 American Academy of Cosmetic Surgery survey revealed that 71% of consumers surveyed felt that society was less judgmental about cosmetic surgery than just 5 years before, and almost 62% reported that this greater acceptance made them feel more comfortable about pursuing cosmetic enhancement.[2] According to a 2009 survey by The Aesthetic Surgery and Research Foundation, almost 90% of respondents felt comfortable discussing their BoNT and hyaluronic acid treatment with others.[3] Economic uncertainty does not appear to hamper consumer interest in facial rejuvenation; instead, patients turn to nonsurgical rejuvenation as a lower-cost option to surgery during leaner times.[4]

The aging of the U.S. population is an important driver of procedures that help maintain a youthful appearance.[5] A common motivation for patients seeking aesthetic treatment is a mismatch between mental "age" and physical appearance. Today's adults simply do not view themselves as aging, and they want to look as young and energetic as they feel. According to ASAPS statistics, more than 77% of BoNTA procedures reported in 2011 were administered to patients ages 35–64.[1] Patients also may seek aesthetic enhancement as an aid to achieving other goals (e.g., to boost their confidence, increase professional opportunities, and attract potential partners),[6] but is this motivation merely a matter of pure vanity?

A comprehensive analysis of 272 articles revealed detrimental effects of clinical dermatology conditions to patient self-esteem, as measured using the Dermatology Life Quality Index.[7] Simply put, these conditions are clearly more than skin deep—they are brain deep—and there is tremendous psychological benefit in restoring patients to a more "normal" appearance. Quality-of-life effects are not yet as well studied in association with cosmetic procedures, but evidence suggests that the benefits of aesthetic procedures may also go beyond appearance. In a 2009 study, Fried and colleagues administered questionnaires to 76 women receiving BoNT injections and found that the use of BoNT for cosmetic purposes was more than simply a cosmetic indulgence[8]; their findings suggest that treatment with BoNT noticeably improved patients' psychological state.

Other studies offer additional insight into the relationship between BoNTA treatment and patient satisfaction and outlook. In a retrospective evaluation of 30 patients who had received BoNTA, Sommer and colleagues found that 77% felt more comfortable with their body's appearance after treatment of the upper facial lines, 55% felt more attractive, and 45% felt more confident as a result of treatment.[9] Carruthers and colleagues analyzed data from 295 patients from six clinical studies of BoNTA that captured patients' Self-Perception of Age.[10] The pooled data revealed that 40–60% of subjects who received BoNTA (percentages varied according to facial area treated) reported looking an average of 5 years younger than their actual age 4 weeks after treatment.[10]

Although significant progress in understanding of BoNTA science has driven some change in the practice of aesthetic medicine, patient considerations remain firmly at the center of successful treatment plans. Most physicians conduct a pretreatment patient assessment of sorts. Less common are physicians who seek to understand the patient's motivations, fears, and knowledge. Patient care is dramatically enhanced when we understand *who* our patients are, *why* they are in our office, and *what* they know about BoNTA treatment.

Communication

Communication may be the most effective tool in aesthetic medicine and should be the one used first and most often. Quality patient communication encompasses many aspects of aesthetic practice and can have a significant effect on patient satisfaction through enhanced knowledge, realistic expectations, and good treatment outcomes. Patients who are well-informed before their procedure will have a better understanding of possible outcomes and thus a better framework for assessing how the outcomes reflect their pretreatment vision. Effective pretreatment communication also enables physicians to understand unique patient-specific characteristics that determine the individualized treatment plan.

Education is an important facet of physician–patient communication. Despite the broad availability of information related to aesthetic products and procedures, many patients will have little correct information regarding the treatment they seek. In a 2003 patient satisfaction survey conducted by the American Academy of Dermatology, 78% of respondents did not know how long cosmetic procedures take or how long they last,[11] 67% were uncertain about what procedures would work best for them, and only 35% believed that cosmetic procedures were safe. These survey data are dated but highlight an important opportunity to ensure adequate patient knowledge about procedures before initiating a treatment plan. Some patients take an active role in their own education about aesthetic procedures, but this self-education may be problematic if unreliable Internet research or feedback from friends have influenced patient expectations.

Accurate information is essential for creating realistic expectations about treatment outcomes. Unrealistic expectations are associated with poor outcomes,[12] and before treatment, physicians should

ensure that patient expectations are in balance with reasonably achievable results. An ongoing physician challenge is to identify patients in whom psychological obstacles prevent satisfaction even with good technical outcomes. Certain communication clues signal patients for whom treatment may not yield satisfying results; these include repeated questions, poor listening or comprehension, and criticism of other doctors.

Objective assessment measures are useful in establishing appropriate expectations. These include patient photography and visual scales that aid patient understanding of their baseline status. We will discuss common visual anatomic severity scales and how they can benefit patient care in more detail below.

Surveys that assess patient perceptions of age and patient-reported outcomes are also beneficial at the practice level and can be easily integrated into practice habits.[10] Patient wait time, for example, can be effectively used by having patients complete a quick questionnaire on their perception of age and facial appearance. The information gleaned from surveys of this type can benefit the physician's understanding of the specific patient, as well as overall practice dynamics.

Patients begin receiving information from the moment they first contact your office. Your staff, your office, and your other patients all contribute to the patient's expectations, comfort, and confidence in your abilities.

Patient Assessment

Understanding the prospective patient's goals and aesthetic self-concept is critical for achieving satisfactory outcomes. Gender, cultural, and ethnic standards of attractiveness may significantly influence the patient's preference. Patients may express goals that fall outside what is considered the norm for their "group," and physicians should be prepared to recognize and respond to those goals. Even subtle differences in outcome can change patient happiness to extreme dissatisfaction, so knowing as much as possible about the particular characteristics and motivations of the individual patient is essential.

In addition to assessing the patient's goals and preferences, it is crucial to assess the patient's medical and physical considerations before treatment. The initial step in this process is to obtain the patient's medical history. Any contraindications or cautions to treatment should be identified and documented, as should the patient's prior experience with aesthetic treatments. Previous aesthetic treatments can dramatically influence patient outcomes, and patient attitudes about previous treatments may signal underlying psychological barriers to treatment satisfaction.

Physicians should carefully assess and document observations of patients' notable physical characteristics, including patterns of aging, skin elasticity, surface landmarks, and muscle distribution and mass. Aging is multifactorial, and each patient's lifestyle and genetics will yield a unique aging presentation. The physiology of the aging changes will significantly direct the aesthetic treatment plan and the extent to which BoNTA can provide benefit. Patient photography is essential as a reference point for posttreatment evaluation of these characteristics.

One of the most significant changes in recent aesthetic medicine has been a paradigm shift in how we view the face. In the 2008 consensus article on the aesthetic use of BoNTA and hyaluronic acid fillers,[13] Carruthers and colleagues noted an evolution in the approach to facial rejuvenation, from a two-dimensional focus on lines and wrinkles to a three-dimensional viewpoint that recognizes the primary influence of volume on the appearance of facial aging. This three-dimensional viewpoint is a cornerstone of aesthetic evaluation and treatment strategy. When we view the face in three dimensions, we can better select the aesthetic tools and

treatment approach that will create the desired outcome.

Muscle pattern, size, and dynamic action will have primary influence on the creation of the BoNTA injection strategy for a specific treatment area (Figure 1). Although facial anatomy is similar in most individuals, anatomic muscle patterns can vary. Underlying muscular variances have been observed through differences in surface characteristics, such as various patterns identified in smiles,[14] crow's feet distribution,[15] nasal wrinkles,[16] and forehead lines.[17] Trindade de Almeida and colleagues recently catalogued five types of glabellar contraction patterns and provided guidance on BoNTA injection strategy modifications that might enhance results.[18] MacDonald and colleagues demonstrated sex-based differences in the thickness, length, and depth of upper face muscles through cadaver research.[19] BoNTA dose and injection sites must reflect these variations to ensure optimized outcomes.

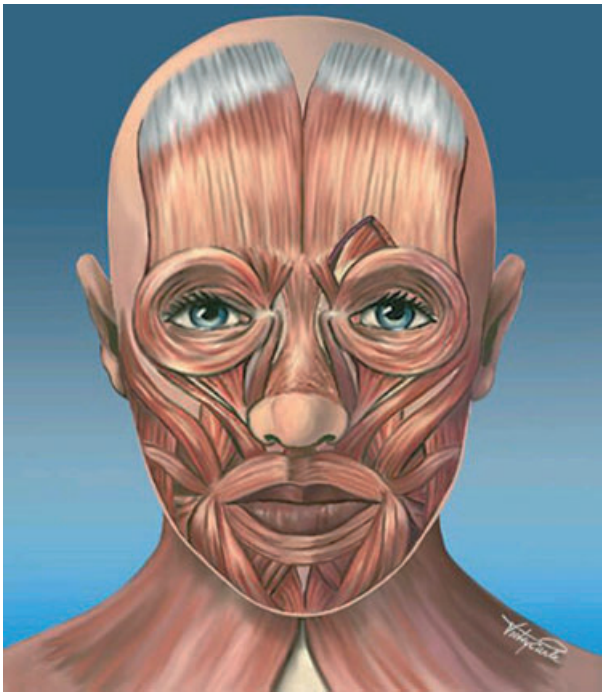

Figure 1. Facial musculature.

Pretreatment assessment should include careful evaluation of the musculature at rest and when engaged, and changes in facial landmarks as the muscles are activated. This should be done with the patient's eyes open and closed and at repose, moderate animation, and maximum contraction. Clinicians should also spend a few minutes observing the patient speaking and should document specific facial movements, mannerisms, smile patterns, and other individual animations. Facial muscles work in coordination to create expressions and control facial movement; treatment of a specific muscle group without consideration of its whole-face effects can lead to less-optimal results.

The patient assessment process should be repeated at each visit, because patient preferences, goals, and health status will change over time. Aging is a dynamic process, and the best treatment strategy for the patient at age 30 will almost certainly be different from that of the same patient at age 60.

Aesthetic Scales for Optimized Outcomes

Another way the aesthetic industry is evolving is in the development and use of tools that enable standardized assessment of patient appearance, before and after treatment. It is challenging to "standardize" what is an inherently personal pursuit, but the emergence of newer anatomic severity scales has improved our ability to objectively establish the degree of aging and severity of facial wrinkles before treatment and to evaluate the level of improvement after. Standardized scales that visually and objectively demonstrate various aging pathologies are also a valuable resource in the patient communication process.

Commonly used scales evaluate anatomic severity or degree of aesthetic improvement after treatment in the clinical study setting. (See Table 1 for a summary of selected aesthetic facial assessment scales.) The 4-point Facial Wrinkle Scale (FWS)[20] is the one most often used; others include the 5-point Wrinkle Severity Rating Scale (WSRS)[21] and the Global

TABLE 1. Selected Aesthetic Facial Assessment Scales

Scale	*Description*	*Source*
Grading Scale for Hyperkinetic Facial Lines	6-point scale designed to quantify expression lines at rest and those created with effort (1 = no expression line; 6 = expression line at rest)	Goodman 1998[23]
Wrinkle Assessment Scale	6-point photonumeric rating scale designed to quantify improvement in facial wrinkles after injection of filler (0–5; more prominent folds receive a higher numeric rating)	Lemperle 2001[24]
Clinical Severity Scale for Glabellar Frown Lines	4-point photograph-based scale designed to evaluate the severity of glabellar lines (0 = no facial wrinkles; 3 = severe facial wrinkling)	Honeck 2003[20]
Global Aesthetic Improvement Scale	5-point relative improvement scale ranging from worse to very much improved	Narins 2003[22]
Wrinkle Severity Rating Scale	5-point photograph-based scale designed to quantify facial folds (1 = absent; 5 = extreme)	Validated by Day et al. 2004[21]
Clinical Severity Score for Lateral Canthal Lines	4-point photograph-based scale designed to determine severity of lateral canthal lines at rest and maximum smile (0 = none; 3 = severe)	Hund 2006[25]
Brow Positioning Grading Scale (Figure 2)	5-point photonumeric rating scale to evaluate eyebrow position at rest (0 = youthful, arched; 4 = flat, tired)	A Carruthers 2008[27]
Forehead Lines Grading Scale	5-point photonumeric rating scale to evaluate forehead lines at rest and expression (0 = no wrinkles; 4 = deeper wrinkles at rest and with expression)	A Carruthers 2008[28]
Crow's Feet Grading Scale	5-point photonumeric rating scale to evaluate lateral canthal lines at rest and maximum contraction (0 = no wrinkles; 4 = severe wrinkles)	A Carruthers 2008[29]
Lip Fullness Grading Scale	5-point photonumeric rating scale to evaluate fullness of the upper and lower lips (0 = very thin; 4 = full)	A Carruthers 2008[30]
Marionette Lines Grading Scale (Figure 3)	5-point photonumeric rating scale to evaluate melomental folds (0 = no visible fold; 4 = extremely long and deep fold)	A Carruthers 2008[31]
Modified Fitzpatrick Wrinkle Scale	Nasolabial wrinkle severity	Shoshani 2008[32]
6-Point Grading Scale	6-point scale designed to determine severity of nasolabial folds	Monheit 2010[33]
Lip Volume and Thickness Grading Scale	Photographic grading scale designed to evaluate lip volume and thickness	Rossi 2011[34]
Upper Face Validated Assessment Scales	5-point photonumeric rating scale to evaluate upper facial lines and sex-specific brow positioning (0 = no sign; 4 = very intense)	Flynn 2012[35]
Mid Face Validated Assessment Scales	5-point photonumeric rating scale to assess mid-face volume loss (0 = no sign; 4 = very severe)	J Carruthers 2012[36]
Lower Face Validated Assessment Scales	5-point photonumeric rating scale to evaluate lower facial lines and volume loss (0 = no sign; 4 = very intense)	Narins 2012[37]
Neck Volume Validated Assessment Scale	5-point photonumeric rating scale to evaluate neck volume (0 = no sagging; 4 = very severe sagging)	Sattler 2012[38]
Global Face Validated Composite Assessment Scales	Composite facial assessment approach, including results of principal component analysis (Figure 4) that identified facial areas with greatest contribution to global facial aging appearance in each sex	Rzany 2012[39]
Investigator's Global Assessment of Lateral Canthal Line Severity Scale	5-point scale designed to measure severity of lateral canthal lines at rest (0 = absent; 4 = severe)	Kane 2012[40]

Figure 2. Brow positioning grading scale.

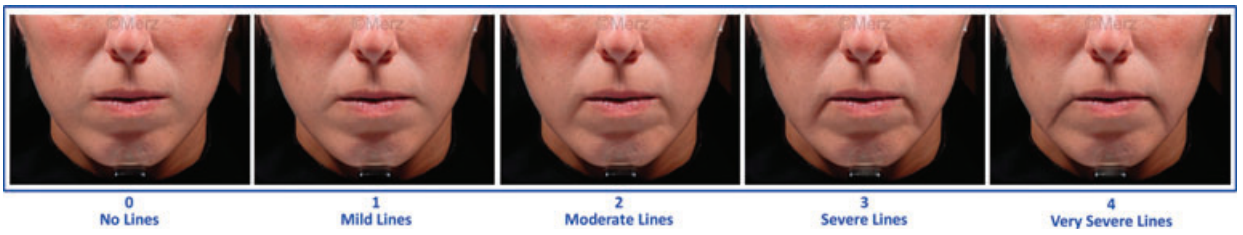

Figure 3. Marionette lines grading scale.

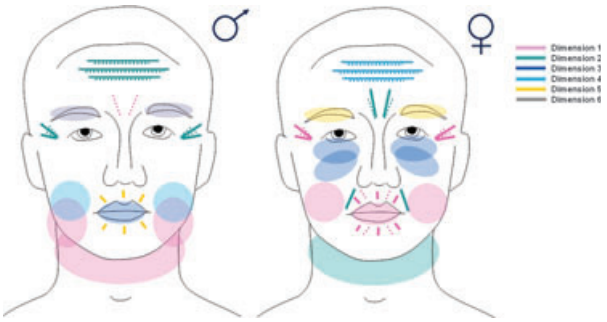

Figure 4. Illustration of principal component analysis for both sexes.

Aesthetic Improvement Scale (GAIS).[22] Studies will frequently use one of the wrinkle scales to establish a baseline and the GAIS to quantify the degree of improvement. The evolution of aesthetic medicine has demanded that aesthetic scales also evolve to better capture meaningful information in the context of the changing paradigm of facial aesthetic medicine. To effectively measure baseline anatomic severity and change after treatment, facial aging scales must be standardized and specific, provide objective measurement parameters, and enable consistent application from patient to patient. Many existing aesthetic scales, although useful for intrastudy comparisons, do not provide a way to compare results across studies, nor do they provide practice-level benefits.

Over the past few years, a set of validated, objective, quantitative facial aging grading scales has emerged that is the first standardized comprehensive rating system designed to measure the skin's aging process. These validated aesthetic grading scales, known as the Merz Aesthetics Scales (MAS), are a step forward from earlier options because they facilitate interstudy comparisons and enable practice-level applications to enhance patient care.[26] The first set of these validated grading scales was published in 2008, and included separate scales to evaluate brow positioning, forehead lines, crow's feet, lip fullness, and marionette lines, as well as the appearance of aging in the hands.[27–31,41] In 2012, additional validated scales were released that build upon the previous scales and address larger facial units from a composite approach: upper face, mid face, lower face, neck volume, and the global face.[35–39]

The MAS provide several advantages distinct from earlier scales. A global multidisciplinary team of aesthetic experts developed and validated the scales, ensuring that the perspectives of different cultures

and specialties were considered when establishing ratings. Each individual area scale provides clear end points and a clear midpoint (using a 5-point rating system) and is supported by comprehensive photographic examples to guide the evaluation and rating of lines and volume in different areas of the face and body. Where appropriate, the scales are supplemented with two sets of photographs—one set that demonstrates static lines and a second that demonstrates dynamic lines. Inter- and intrarater reliability was generally high for all of the MAS; moderate variability was noted in scales that address areas that are typically more subjective, such as brow position and global assessment. Despite this variability, the MAS are the most-robust set of scales yet developed and can help promote better comparisons of results between studies and practices and potentially between products. We have found that their use as part of the patient pretreatment and follow-up communication process can help establish a common understanding of baseline and results, reducing the risk of unrealistic patient expectations before treatment and enhancing patient satisfaction afterwards.

Documentation and Consent

Photographic documentation is mandatory before any aesthetic treatment. "Before" photos should ideally be shown to the patient and used as part of the pretreatment assessment and communication process. Discussion of the upcoming treatment plan in the context of an objective view of relevant facial landmarks, aging pathologies, and any preexisting asymmetry will strengthen patient understanding of realistic treatment outcomes.

Before treatment, the patient must receive a thorough consultation on the potential risks of BoNTA treatment and limitations of treatment (e.g., BoNTA will not correct volume depletion.) Valid informed consent is essential and should capture any areas of caution, including whether the treatment is off label. (The FDA requires that patients receive the Patient Medication Guide for the specific BoNTA formulation to be used before *every* treatment.) In the event of legal proceedings with a dissatisfied patient, photographic and consent documentation will be critical.

Practical BoNTA Injection Strategy Considerations

Important among the myriad factors in developing a BoNTA injection strategy for a particular patient are decisions regarding dilution, dosing, and injection placement. The manufacturers of the three BoNTA formulations currently available in the United States provide specific instructions for product reconstitution, dosing, and administration in the glabellar region.[42–44] The guidance provided in the package insert for each product is an excellent resource for novice injectors and serves as a safe starting point. In practice, experienced physicians frequently depart from the package insert instructions. Only clinicians with sufficient education and experience to understand the potential clinical effects of that use should undertake any off-label use of BoNTA.

Dilution

All commercially available BoNTA products require reconstitution before use. The use of preservative-free 0.9% sodium chloride (saline) as the diluent is specified in each product's package insert, although some experts prefer to use preservative-containing saline.[45] Several studies have demonstrated greater patient comfort upon injection with BoNTA reconstituted with preserved saline than with nonpreserved saline; use of preserved saline does not appear to affect BoNTA potency.[46–49] Expert consensus supports the use of preservative-free or preservative-containing saline according to injector preference.[44,50]

The volume of saline used during the dilution process will also vary according to injector preference. The manufacturers of each product provide differing instructions regarding BoNTA dilution. The package insert for onabotulinumtoxinA (BoNTA-ONA) specifies a single diluent volume, abobotulinumtoxinA (BoNTA-ABO) has two options, and incobotulinumtoxinA (BoNTA-INCO) provides a table outlining eight diluent volume

choices. These differences among the package insert recommendations do not indicate specific product differences inherent to the dilution process; they more probably reflect the body of evidence in place at the time of each formulation's approval.

There has been considerable discussion about the possible influence of dilution choices on clinical effect, duration, and product diffusion. A study of the efficacy and safety of four dilutions of BoNTA-ONA in the treatment of glabellar lines found no obvious relationship between dilution and response or any greater incidence of adverse effects in any dilution group.[52] Similarly, the effects of two differing BoNTA-ONA dilution rates were studied in lateral orbital rhytides. Despite a fivefold difference in concentration between the two dilutions, no significant differences in efficacy or duration of effect were observed.[53] A study of two different dilutions of BoNTA-INCO in the glabellar lines also found no significant clinical differences in results.[54]

Almeida and colleagues reviewed studies and expert consensus about dilution rates across a range of indications.[55] Study results were somewhat varied, with some indicating greater diffusion or enhanced effect with greater volume, whereas others demonstrated no difference in efficacy. The review authors concluded that, in facial muscles, the clinical effect of dilution decisions does not appear significant, although they note the potential for less pain with more-concentrated solutions. More study of the potential clinical effect of dilution is warranted, although our position based on current evidence is that the choice of dilution rate, within reasonable parameters, is a matter of injector preference and convenience.

Dosing

BoNTA dosing has evolved as knowledge and skill with the product have advanced. Table 2 summarizes the recommended mean dosage of BoNTA for common upper face aesthetic indications across selected consensus publications from 2004 through 2010. Contemporary BoNTA injection strategy balances effective rejuvenation with enough facial movement to maintain a natural appearance,[56] and dosing decisions are important to finding that balance. Treatment response is dose-related. Dose-ranging studies in the forehead,[57] glabellar lines,[58,59] and periorbital rhytides[60] have shown a clear dose response with regard to treatment efficacy and duration of effect.

Treatment response also depends on patient-specific factors, such as sex and muscle mass. Based on the results of their dose-ranging studies of BoNTA-ONA

TABLE 2. Changes in Mean Botulinum Toxin Type A (BoNTA) Dosage in Aesthetic Indications from 2004 to 2010

	U (Injection Points)			
Location	*OnabotulinumtoxinA (2004)**	*OnabotulinumtoxinA (2007)†*	*OnabotulinumtoxinA (2008)‡*	*AbobotulinumtoxinA (2010)§*
Glabella				50 (5)
Women	20–30 (5–7)	20 (5)	10–30 (5–7)	
Men	30–40 (5–7)	30 (5)	20–40 (5–7)	
Horizontal forehead lines				20–60 (4–6)
Women	10–20 (4–8)	10–12 (4–8)	6–15 (4–8)	
Men	20–30 (4–8)	10–18 (4–8)	6–15 (4–8)	
Crow's feet				20–60 (3/eye)
Women	12–30 (3/eye)	6–10 (3/eye)	10–30 (2–5/eye)	
Men	12–30 (3/eye)	6–12 (3/eye)	20–30 (2–5/eye)	

*Consensus recommendation United States, 2004.[45]
†Consensus recommendation Germany, 2007.[74]
‡Recommendation update, 2008.[13]
§International consensus recommendations, 2010.[51]

in the treatment of glabellar lines, Carruthers and Carruthers recommended a 40-U starting dose of BoNTA-ONA in men[58] and a 20-U starting dose in women.[59] The efficacy of variable dosing was tested as part of the clinical trial program for BoNTA-ABO. Kane and colleagues demonstrated that glabellar dosing based on sex and assessment of muscle mass improved response, especially in men who received higher doses.[61]

Commercially available BoNTA formulations are unique. Substantial evidence supports a 1:1 dose relationship between BoNTA-ONA and BoNTA-INCO[62–64]; thus, physicians can apply dosing guidelines for BoNTA-ONA to the use of BoNTA-INCO as a safe starting point. BoNTA-ABO units are not interchangeable with those of BoNTA-ONA or BoNTA-INCO, and a clear conversion ratio has not been established. An estimated dose ratio of 1:2.5 (BoNTA-ONA:BoNTA-ABO) may be assumed based on approved glabellar dosing with BoNTA-ABO in the United States. This ratio may be more convenient for clinicians who are familiar with BoNTA-ONA dosing and are attempting to find an appropriate dose for a BoNTA-ABO procedure. Physicians may also refer to consensus guidance on the use of BoNTA-ABO in practice for insight into dosing for various aesthetic procedures.[50,51]

As discussed in more detail in Part 1, some studies have found that there may be potential differences in the spread or field of effect of different formulations. Specifically, several studies have found that BoNTA-ABO may demonstrate greater spread than BoNTA-ONA or BoNTA-INCO.[65–67] Other study results found comparable spread.[68,69] Although additional research is needed to clarify the extent of any difference in this characteristic between formulations, physicians need to be aware of the potential and consider it when making dosing decisions.

Guidance on the Use of BoNTA in Specific Facial Areas

BoNTA dosing and injection points should be based on an assessment of the patient's anatomy, goals,

TABLE 3. Dosing Recommendations for Common Botulinum Toxin Type A Treatments of the Upper Face

Area	*OnabotulinumtoxinA*	*IncobotulinumtoxinA*	*AbobotulinumtoxinA*
Glabella (on label)	20 U divided evenly among 5 injection points	20 U divided evenly among 5 injection points	50 U divided evenly among 5 injection points
Glabella (see Figure 5)	Women: 10–50 U Men: 20–60 U Divided among 5 to 7 injection points.	Women: 10–50 U Men: 20–60 U Divided among 5 to 7 injection points.	Women: 50–70 U Men: 60–80 U Divided among 5 injection points, adjusted for muscle mass
Brow lift (see Figure 6)	3–7 U under tail of eyebrow plus inactivation of central depressors	3–7 U under tail of eyebrow plus inactivation of central depressors	5–10 U in the procerus; 5–10 U under tail of eyebrow
Forehead (see Figure 7)	5–15 U divided among 4 to 10 injection points.	5–15 U divided among 4 to 10 injection points.	20–60 U per side divided among 4 to 6 injection points
Periorbital rhytides	10–30 U total dose divided among 2 to 5 injection points per side	10–30 U total dose divided among 2 to 5 injection points per side	20–60 U per side divided among 3 injection points; optional fourth injection of 10 U

The treatment recommendations represent the general consensus of the authors based on clinical studies, consensus publications, and personal experience.
Each commercially available botulinum toxin product is unique. Dosing recommendations are expressed as units of that particular formulation.

TABLE 4. Dosing Recommendations for Common Botulinum Toxin Type A (BoNTA) Treatments of the Lower Face

Area	*OnabotulinumtoxinA*	*IncobotulinumtoxinA*	*AbobotulinumtoxinA*
Depressor anguli oris (see Figure 8)	1–7.5 U per side	1–7.5 U per side	2.5–10 U per side
Lip lines	4–6 U total dose divided among 2–6 injection points	4–6 U total dose divided among 2–6 injection points	Upper lip: 5–15 U divided among 2 or 4 injection points Lower lip: 5–15 U divided between 2 injection points
Mentalis	4–10 U total dose in 1–2 injection points	4–10 U total dose in 1–2 injection points	5–25 U total dose in 1–2 injection points
Nefertiti lift (see Figure 9)	15 U per side	15 U per side	30–45 U per side
Platysmal bands	30–60 U total dose divided among all injection points, as determined by patient assessment	30–60 U total dose divided among all injection points, as determined by patient assessment	30–120 U total dose, 30 U per band typical

Only injectors who have significant BoNTA treatment experience and comprehensive knowledge of facial anatomy should attempt BoNTA treatment in the lower face. The treatment recommendations represent the general consensus of the authors based on clinical studies, consensus publications, and personal experience.
Each commercially available botulinum toxin product is unique. Dosing recommendations are expressed as units of that particular formulation.

and preferences, as well as the physician's own professional experience with prior treatments. It is thus difficult to establish comprehensive dose and injection point templates for specific facial areas—the possibilities are virtually endless—although we provide some general injection strategy recommendations for common BoNTA treatments of the upper and lower face in Tables 3 and 4. Dosing and injection points are based on our personal experience and information from consensus guidelines. Illustrations of important musculature with potential injection sites are featured for selected treatment areas (Figures 5–9). This guidance should be used as a starting point but is not intended to replace professional judgment. Patient-specific factors or the treating physician's professional experience may dictate a modified approach.

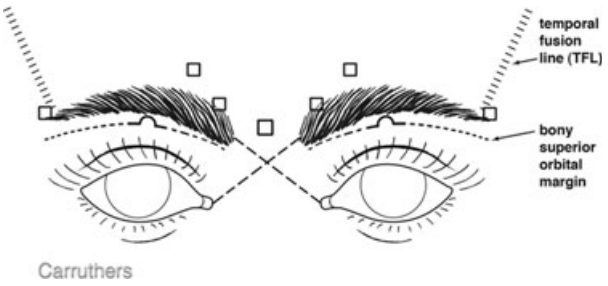

Figure 5. Glabella treatment approach.

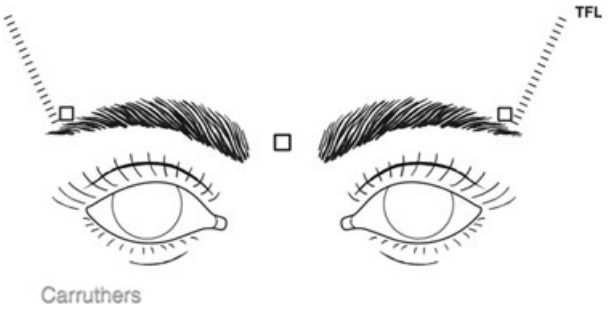

Figure 6. Brow lift treatment approach.

Preventing and Managing Adverse Events

BoNTA's aesthetic safety profile is exceptional, and adverse events are rare when the agent is used responsibly. In clinical practice, the most common adverse effects of aesthetic BoNTA injections are mild and transient and include injection-site pain, localized bruising, swelling, and short-term head-

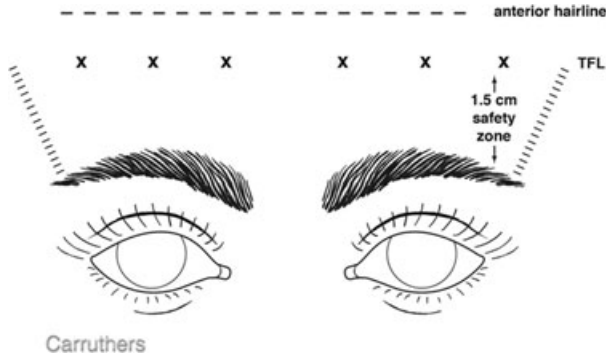

Figure 7. Forehead lines treatment approach.

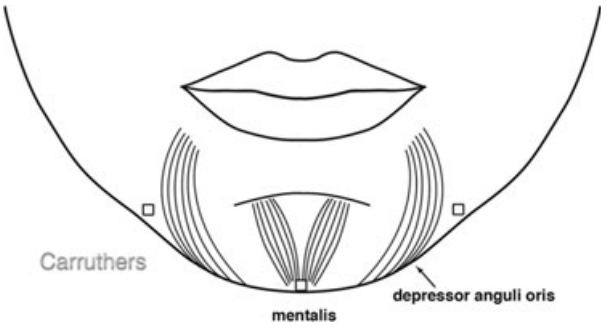

Figure 8. Depressor anguli oris treatment approach.

ache.[70,71] Although these adverse effects are possible after BoNTA administration by even the most educated and experienced injectors, certain strategies can help minimize their occurrence and impact.

Injection-site pain is typically transient, and most patients require little pain management. Using small-gauge needles, changing needles frequently during intensive treatment sessions, and careful technique can help minimize pain during injection. Distraction strategies (e.g., talking to the patient, providing a "stress ball" to squeeze, using a distraction device such as a massager) can be helpful. In patients who are pain sensitive or apprehensive, pretreatment application of ice or a topical anesthetic agent will lessen discomfort and at minimum will provide some psychological soothing. The use of preservative-containing saline as the diluent has been shown to reduce patient discomfort significantly during BoNTA injection.[46,47]

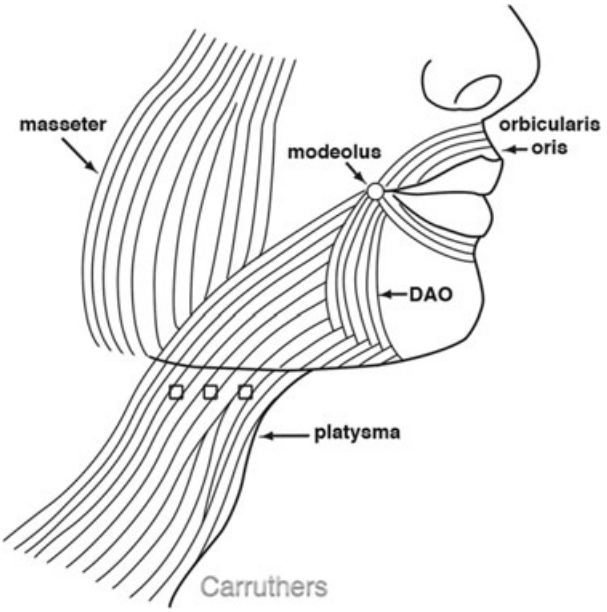

Figure 9. Nefertiti lift treatment approach.

Bruising after injection is fairly common, especially in thin-skinned areas such as the periorbital area (crow's feet). Bruising may be minimized by having the patient avoid using anticoagulant medications or supplements for up to 2 weeks before treatment.[70] For patients who cannot stop taking anticoagulants because of medical necessity, pretreatment patient information materials and counseling should involve cautions about bruising as a possible outcome. Physician-applied pressure and the application of ice to the injection site can help minimize the occurrence of bruising.[51]

Mild headache after BoNTA injection can be treated with over-the-counter analgesics if necessary. Severe, persistent headache after BoNTA injection has been noted in a small fraction of patients.[72] Although this is a rare outcome, some experts recommend that patients should be informed of the possibility of severe headache before treatment.[72]

Injection-Related Complications

Beyond these mild adverse effects, the most common complications after BoNTA treatment relate to the injection strategy. Even small missteps in dosing or

TABLE 5. Injection Strategies for Reducing Complications with Botulinum Toxin Type A (BoNTA) in the Lower Face

Muscle	*Suggested injection strategy to minimize complications*
Orbicularis oris	Dosing: 4–6 U (BoNTA-ONA or BoNTA-INCO units) Place balanced dose between upper and lower lips symmetrically on each side
Depressor anguli oris	Dosing: 5–7.5 U (BoNTA-ONA or BoNTA-INCO units) Inject just anterior to the anterior border of the masseter. Injection further anterior can weaken depressor labii inferioris.
Mentalis	Dosing: 5–10 U (BoNTA-ONA or BoNTA-INCO units) Inject centrally at the point of the mentum. Do not inject superior to this, or you will weaken the depressor labii inferioris and orbicularis oris.
Platysma	Dosing: 15–30 U (BoNTA-ONA or BoNTA-INCO units); 30–45 U (BoNTA-ABO units) It is safest to inject laterally in the neck just under the mandibular margin. Injecting large doses in the anterior platysmal bands can interfere with the function of the neck flexors and the muscles of deglutition (swallowing.)

Only injectors who have significant BoNTA treatment experience and comprehensive knowledge of facial anatomy should attempt BoNTA treatment in the lower face. The treatment recommendations herein represent the general consensus of the authors based on clinical studies, consensus publications, and personal experience.
Each commercially available botulinum toxin product is unique. Dosing recommendations are expressed as units of that particular formulation.

injection placement can yield poor outcomes. The adverse treatment results will be temporary, but your patient's dissatisfaction will most likely be long-lived. Although poor injection strategy in the upper face typically results in mostly aesthetic inconvenience, BoNTA mistakes in the lower face can have a serious effect on patient quality of life. The musculature of the lower face is highly integrated and integral to essential life functions such as speaking and eating. Excessive dosing is the primary cause of complications in the lower face; malplacement of the injected product is the second most common cause. Table 5 provides guidance on specific injection strategies to avoid complications when treating the lower face with BoNTA.

Best Practices for Avoiding Complications

Many of the most common complications associated with BoNTA aesthetic use can be prevented. The most powerful tools for the prevention of adverse events are the physician's own aesthetic knowledge and injection competence. Before attempting aesthetic treatment with BoNTA, physicians should possess knowledge of the aging process and underlying causes of observed surface characteristics; facial musculature, its potential individual variations, and the interplay between muscles; essential characteristics of the BoNTA formulation selected for use; and the effect of injection strategy decisions, including dilution, dosing, and specific injection sites.

Moreover, physicians should be sure that their injection expertise is sufficient for the procedure. Experience with less-complex procedures is required before attempting procedures that are more complicated. Educated staff and an organized office with clear protocols for the safe handling and application of products are additional measures that promote safe and effective treatment and higher levels of patient satisfaction.

Like beauty, adverse outcomes are in the eye of the beholder. Simply put, if your patient does not like the outcome, the result represents an adverse effect from the patient's perspective—yet another reminder that aesthetic medicine is fundamentally patient-centered. The patient's expectations, goals, and vision are foundational considerations in the treatment strategy, and how well these are fulfilled is an important measure of success.

Combination Therapy

As we enter the second decade of the 21st century, the aesthetic clinician has access to an everexpanding and differentiated armamentarium of products from which to craft effective treatment plans that address individual patient needs. Although BoNTA is a powerful agent that will benefit most patients, no single aesthetic tool can address the myriad presentations of aging. Combining modalities and products often provides benefits beyond those experienced with any modality alone. Beer nicely captures the potential of this combined approach, stating "the most interesting development in the arena of facial rejuvenation is not the advent of any single product or technology but rather the possibilities of combining the various treatments and products in ways heretofore not possible."[73] To take advantage of the exponential aesthetic possibilities inherent in combination therapy, physicians must have the requisite knowledge and experience with each component to use it to its best effect.

Conclusion

BoNTA is a powerful and flexible tool in the aesthetic physician's armamentarium. Progress in aesthetic medicine has provided contemporary insights into practices that maximize its use. A range of product- and patient-specific factors influences the treatment plan, and truly optimized outcomes are possible only when the treating physician has the requisite knowledge, experience, and vision to use BoNTA as part of a unique solution for each patient's specific needs. If history is any indication, demand for aesthetic BoNTA will continue to grow, and innovative new approaches will further refine its use. The most successful physicians will be those who can grow and innovate in pace with the industry.

References

1. American Society for Aesthetic Plastic Surgery. 15th Annual Cosmetic Surgery National Data Bank Statistics. 2011 Statistics. [online] Available from: http://www.surgery.org/media/statistics Accessed March 27, 2012.
2. American Academy of Cosmetic Surgery. 2010 American Academy of Cosmetic Surgery cosmetic surgery attitudes fact sheet. [online] Available from: http://www.cosmeticsurgery.org/media/consumerfact-Overall-V2.pdf Accessed March 27, 2012.
3. American Society for Aesthetic Plastic Surgery. Survey reveals injectable procedures are mainstream and accepted medical aesthetic treatment options [Press Release]. [online] Available from: http://www.surgery.org/media/news-releases/survey-reveals-injectable-procedures-are-mainstream-and-accepted-medical-aesthetic-treatment-options Accessed March 27, 2012.
4. American Society for Aesthetic Plastic Surgery. Facing the economy: patients seek out less-costly facial treatments, but prefer treatments with longer-lasting results over immediate effects [Press Release]. [online] Available from: http://www.surgery.org/media/news-releases/facing-the-economy Accessed March 27, 2012.
5. Zins JE, Moreira-Gonzalez A. Cosmetic procedures for the aging face. Clin Geriatr Med 2006;22:709–28.
6. American Society for Aesthetic Plastic Surgery. How do our attitudes about beauty change as we age? New survey from the two leading plastic surgery societies reveals surprising answer [Press Release]. Available from: http://www.surgery.org/media/news-releases/how-do-our-attitudes-about-beauty-change-as-we-age Accessed March 27, 2012.
7. Basra MKA, Fenech R, Gatt RM, Salek MS, et al. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008;159:
997–1035.
8. Fried RG, Werschler WP, Floirendo T. The botulinum toxin experience: results of a patient self-report questionnaire. J Clin Aesthet Dermatol 2009;2:37–40.
9. Sommer B, Zschocke I, Bergfeld D, Sattler G, et al. Satisfaction of patients after treatment with botulinum toxin for dynamic facial lines. Dermatol Surg 2003;29:456–60.
10. Carruthers A, Carruthers J. Patient-reported outcomes with botulinum neurotoxin type A. J Cosmet Laser Ther 2007;9 (Suppl 1):32–7.
11. American Academy of Dermatology. Facing the age old question…how to turn back the hands of time. New Academy of Dermatology survey finds women overwhelmed by anti-aging treatment options [Press Release]. Available from: www.aad.org Accessed November 6, 2003.
12. Honigman RJ, Phillips KA, Castle DJ. A review of psychosocial outcomes for patients seeking cosmetic surgery. Plast Reconstr Surg 2004;113:1229–37.
13. Carruthers JDA, Glogau RG, Blitzer A, 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.
14. Rubin L. The anatomy of a smile: its importance in the treatment of facial paralysis. Plast Reconstr Surg 1974;53:384–7.
15. Kane MA. Classification of crow's feet patterns among Caucasian women: the key to individualizing treatment. Plast Reconstr Surg 2003;112:33S–9S.

16. Tamura B, Odo M, Chang B, Cuce LC, et al. Treatment of nasal wrinkles with botulinum toxin. Dermatol Surg 2005;31:271–5.

17. Braz AV, Sakuma TH. Patterns of contraction of the frontalis muscle. Surg Cosm Dermatol 2010;2:191–4.

18. De Almeida AR, Da Costa Marques ER, Banegas R, Kadunc BV. Glabellar contraction patterns: a tool to optimize botulinum toxin treatment. Dermatol Surg 2012;38:1506–15. doi: 10.1111/j.1524-4725.2012.02505.x. [Epub ahead of print]

19. Macdonald M, Spiegel J, Raven R, Kabaker SS, et al. An anatomical approach to glabellar rhytids. Arch Otolaryngol Head Neck Surg 1998;124:1315–20.

20. Honeck P, Weiss C, Sterry W. Reproducibility of a four-point clinical severity score for glabellar frown lines. Br J Dermatol 2003;149:306–10.

21. Day DJ, Littler C, Swift R, Gottlieb S. The wrinkle severity rating scale: a validation study. Am J Clin Dermatol 2004;5:49–52.

22. Narins R, Brandt F, Leyden J, Lorenc Z, et al. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of restylane versus zyplast for the correction of nasolabial folds. Dermatol Surg 2003;29:588–95.

23. Goodman G. Botulinum toxin for the correction of hyperkinetic facial lines. Australas J Dermatol 1998;39:158–63.

24. Lemperle G, Holmes R, Cohen S, Lemperle S. A classification of facial wrinkles. Plast Reconstr Surg 2001;108:1735–50.

25. Hund T, Ascher B, Rzany B. Reproducibility of two-four-point clinical severity scores for lateral canthal lines (crow's feet). Dermatol Surg 2006;32:1256–60.

26. Gladstone H, Coleman K. Editorial. Dermatol Surg 2012;38:293.

27. Carruthers A, Carruthers J, Hardas B, Kaur M, et al. A validated brow positioning grading scale. Dermatol Surg 2008;34:S150–4.

28. Carruthers A, Carruthers J, Hardas B, Kaur M, et al. A validated grading scale for forehead lines. Dermatol Surg 2008;34:S155–60.

29. Carruthers A, Carruthers J, Hardas B, Kaur M, et al. A validated grading scale for crow's feet. Dermatol Surg 2008;34:S173–8.

30. Carruthers A, Carruthers J, Hardas B, Kaur M, et al. A validated lip fullness grading scale. Dermatol Surg 2008;34:S161–6.

31. Carruthers A, Carruthers J, Hardas B, Kaur M, et al. A validated grading scale for marionette lines. Dermatol Surg 2008;34:S167–72.

32. Shoshani D, Markovitz E, Monstrey SJ, Narins DJ. The modified Fitzpatrick wrinkle scale: a clinical validated measurement tool for nasolabial wrinkle severity assessment. Dermatol Surg 2008;34(Suppl 1):S85–91.

33. Monheit GD, Gendler EC, Poff B, Fleming L, et al. Development and validation of a 6-point grading scale in patients undergoing correction of nasolabial folds with a collagen implant. Dermatol Surg 2010;36(Suppl 3):1809–16.

34. Rossi A, Nkengne A, Stamatas G, Bertin C. Development and validation of a photonumeric grading scale for assessing lip volume and thickness. J Eur Acad Dermatol Venereol 2011;25:523–31.

35. Flynn T, Carruthers A, Carruthers J, Geister TL, et al. Validated assessment scales for the upper face. Dermatol Surg 2012;38:309–19.

36. Carruthers J, Flynn T, Geister T, Gortelmeyer R, et al. Validated assessment scales for the mid face. Dermatol Surg 2012;38:320–32.

37. Narins R, Carruthers J, Flynn T, Geister T, et al. Validated assessment scales for the lower face. Dermatol Surg 2012;38:333–42.

38. Sattler G, Carruthers A, Carruthers J, Flynn T, et al. Validated assessment scale for neck volume. Dermatol Surg 2012;38:343–50.

39. Rzany B, Carruthers A, Carruthers J, Flynn T, et al. Validated composite assessment scales for the global face. Dermatol Surg 2012;38:294–308.

40. Kane MA, Blitzer A, Brandt FS, Glogau RG, et al. Development and validation of a new clinically-meaningful rating scale for measuring lateral canthal line severity. Aesthetic Surg J 2012;32:275–85.

41. Carruthers A, Carruthers J, Hardas B, Kaur M, et al. A validated hand grading scale. Dermatol Surg 2008;34:S179–83.

42. BOTOX Cosmetic [package insert]. Irvine, Calif: Allergan, Inc; 2011.

43. DYSPORT [package insert]. Scottsdale, Ariz: Medicis Aesthetics Inc; 2010.

44. Xeomin [package insert]. San Mateo, Calif: Merz Aesthetics Inc; 2010.

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

46. Alam M, Dover J, Arndt K. Pain associated with injection of botulinum A exotoxin reconstituted using isotonic sodium chloride with and without preservative. Arch Dermatol 2002;138:510–4.

47. Allen SB, Goldenberg NA. Pain difference associated with injection of abobotulinumtoxinA reconstituted with preserved saline and preservative-free saline: a prospective, randomized, side-by-side, double-blind study. Dermatol Surg 2012;38:867–70. doi: 10.1111/j.1524-4725.2011.02284.x. [Epub ahead of print].

48. Kwait D, Bersani T, Bersani A. Increased patient comfort utilizing botulinum toxin type A reconstituted with preserved versus nonpreserved saline. Ophthal Plast Reconstr Surg 2004;20:186–9.

49. Sarifakioglu N, Sarifakioglu E. Evaluating effects of preservative-containing saline solution on pain perception during botulinum toxin type-A injections at different locations: a prospective, single-blinded, randomized controlled trial. Aesthetic Plast Surg 2005;29:113–5.

50. Hexsel DM, Spencer J, Woolery-Lloyd H, Gilbert E. Practical applications of a new botulinum toxin. J Drugs Dermatol 2010;9:s31–7.

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

52. Carruthers A, Carruthers J, Cohen J. Dilution volume of botulinum toxin type A for the treatment of glabellar rhytids: does it matter? Dermatol Surg 2007;33:S97–104.

53. Carruthers A, Bogle M, Carruthers J, Dover J, et al. A randomized, evaluator-blinded, two-center study of the safety and

effect of volume on the diffusion and efficacy of botulinum toxin type A in the treatment of lateral orbital rhytides. Dermatol Surg 2007;33:567–71.

54. Prager W, Zschocke I, Reich C, Brocatti L, et al. Beeinflusst die verdunnung das kosmetische ergebnis von BoNT/A? Hautarzt 2009;60:815–20.

55. De Almeida AR, Secco L, Carruthers A. Handling botulinum toxins: an updated literature review. Dermatol Surg 2011;37:1553–65.

56. Carruthers A, Carruthers J. Botulinum toxin type A treatment of multiple upper facial sites: patient-reported outcomes. Dermatol Surg 2007;33:S10–7.

57. Carruthers A, Carruthers J, Cohen J. A prospective, double-blind, randomized, parallel-group, dose-ranging study of botulinum toxin type A in female subjects with horizontal forehead rhytides. Dermatol Surg 2003;29:461–7.

58. Carruthers A, Carruthers J. Prospective double-blind, randomized, parallel-group, dose-ranging study of botulinum toxin type A in men with glabellar rhytids. Dermatol Surg 2005;31:1297–303.

59. Carruthers A, Carruthers J, Said S. Dose-ranging study of botulinum toxin type A in the treatment of glabellar rhytids in females. Dermatol Surg 2005;31:414–22.

60. Lowe NJ, Ascher B, Heckman M, Kumar C, et al. Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of botulinum toxin type A in subjects with crow's feet. Dermatol Surg 2005;31:257–62.

61. Kane MA, Brandt F, Rohrich RJ, Narins RS, 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.

62. Sattler G, Callander MJ, Grablowitz D, Walker T, et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. Dermatol Surg 2010;36:2146–54.

63. Roggenkamper P, Jost WH, Bihari K, Comes G, et al. Efficacy and safety of a new botulinum toxin type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm 2006;113:303–12.

64. Benecke R, Jost WH, Kanovsky P, Ruzicka E, et al. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology 2005;64:1949–51.

65. Kerscher M, Roll S, Becker A, Wigger-Alberti W. Comparison of the spread of three botulinum toxin type A preparations. Arch Dermatol Res 2012;304:155–61. Epub 2011 Oct 15.

66. De Almeida AR, De Boulle K. Diffusion characteristics of botulinum neurotoxin products and their clinical significance in cosmetic applications. J Cosmet Laser Ther 2007;9(Suppl 1):17–22.

67. Trindade de Almeida AR, Marques E, De Almeida J, Cunha T, et al. Pilot study comparing the diffusion of two formulations of botulinum toxin type A in patients with forehead hyperhidrosis. Dermatol Surg 2007;33:S37–43.

68. Hexsel D, Dal Forno T, Hexsel C, Do Prado D, et al. A randomized pilot study comparing the action halos of two commercial preparations of botulinum toxin type A. Dermatol Surg 2008;
34:52–9.

69. Nestor M, Ablon G. Comparing the clinical attributes of abobotulinumtoxinA and onabotulinumtoxinA utilizing a novel contralateral frontalis model and the frontalis activity measurement standard. J Drugs Dermatol 2011;10:1148–57.

70. Carruthers J, Carruthers A. Complications of botulinum toxin type A. Facial Plast Surg Clin North Am 2007;15:51–4.

71. Hirsch R, Meghan S. Complications and their management in cosmetic dermatology. Dermatol Clin 2009;27:507–20.

72. Alam M, Arndt K, Dover J. Severe, intractable headache after injection with botulinum A exotoxin: report of 5 cases. J Am Acad Dermatol 2002;46:62–5.

73. Beer K. Dermal fillers and combinations of fillers for facial rejuvenation. Dermatol Clin 2009;27:427–32.

74. Sommer B, Bergfeld D, Sattler G. Consensus recommendations on the use of botulinum toxin type A in aesthetic medicine. J Dtsch Dermatol Ges 2007;5:S1–29.

Address correspondence and reprint requests to: Jon Kaeuper, Fortis Spectrum, 5150 Palm Valley Road, Suite 200, Ponte Vedra Beach, FL 32082, email: jon.kaeuper@fsmeded.com