A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Re-examining the Optimal Use of Neuromodulators and the Changing Landscape: A Consensus Panel Update

ISSN: 1545 9616

April 2020 • Volume 19 • Issue 4 (Supplement 1)

Disclosure of Commercial Support
This supplement to the *Journal of Drugs in Dermatology* is supported by an educational grant from Evolus, Inc.

RE-EXAMINING THE OPTIMAL USE OF NEUROMODULATORS AND THE CHANGING LANDSCAPE: A CONSENSUS PANEL UPDATE

Release Date: March 20, 2020 (Last Reviewed: January 3, 2020)
Expiration Date: March 20, 2021
Time to Complete Activity: 1.0 hour

This activity is provided by Paradigm Medical Communications, LLC.

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Learning Objectives

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

- Review the anatomy and pathophysiology of facial aging as they relate to aesthetic rejuvenation with neurotoxins
- Differentiate available neurotoxins for aesthetic facial rejuvenation, including their indications, preparation, mechanisms of action, efficacy, and safety
- Devise individualized treatment plans for natural, harmonious facial rejuvenation with neurotoxins based on appropriate patient assessment and consultation

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Re-examining the Optimal Use of Neuromodulators and the Changing Landscape: A Consensus Panel Update

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ABSTRACT

Since initial US Food and Drug Administration approval of botulinum toxin type A (BoNT-A) for aesthetic use in 2002, clinical evidence and experience with BoNT-A and understanding of facial anatomy have greatly increased, leading to rapid advances in treatment planning and implementation. BoNT-A use has expanded from the upper face to the midface, lower face, and neck, so that BoNT-A injection is the most common cosmetic procedure worldwide. Trends in facial aesthetics reflect growing patient diversity with respect to age, gender, and ethnicity. In October 2019, a multidisciplinary panel of 6 experts in minimally invasive injectable procedures in the specialties of dermatology and plastic surgery convened at the 2019 American Society for Dermatologic Surgery (ASDS) meeting in Chicago, IL. Their goal was to discuss recent advances in BoNT-A use in facial aesthetics, including implications of the introduction of new agents in light of an evolving patient population.

J Drugs Dermatol. 2020;19(4 Suppl 1):s5-15

INTRODUCTION

Selective weakening of the muscles of facial expression with BoNT-A has been found to improve the appearance of the overlying rhytides caused by muscle activity. Since the first BoNT-A was approved for aesthetic use, the evolution and creativity of BoNT-A use have been swift and ever changing. The number of approved BoNT agents and their indications have grown, with additional approvals expected in the future. With their high level of patient satisfaction,[1] BoNT-A injections are the most common nonsurgical cosmetic procedures in the United States,[2] confirming their integral role in facial aesthetics.

The aesthetic use of BoNT-As is driven by general principles common to all 4 BoNT-A products as well as unique characteristics of each. Knowledge of the science and innovation behind these different agents and the underlying anatomy enables aesthetic physicians to provide patients with a variety of treatment options.[3] Individual patient assessment, injection site selection, dosing, and follow-up are critical for optimal results.[4] Over time, there has been a paradigm shift toward neuromodulation with BoNT-As rather than paralysis[5] and an evolution in the patient base with regard to age, gender, and ethnicity, so that aesthetic physicians who want to excel must be dedicated to continued learning.

In October 2019, a multidisciplinary panel of 6 experts in minimally invasive injectable procedures in the specialties of dermatology and plastic surgery convened at the 2019 ASDS meeting in Chicago, IL. Their objective was to assess recent advances in BoNT-A use in facial aesthetics. This publication summarizes key discussions from the meeting and provides clinical considerations for current use of BoNT-A, including changes in the patient population, the impact of patient anatomy, similarities of and differences between the 4 approved agents, evolving use of BoNT-As throughout the face, how approval of a new BoNT-A affects clinical practice, and agents on the horizon. Nonreferenced statements represent the opinions of the panel and are not intended to be statements of fact.

THE EVOLVING AESTHETIC PATIENT POPULATION

While there has always been variation amongst practices, there has recently been an increase in the number of patients under age 30 coming in for initial BoNT-A treatment. Many aesthetic practices are also seeing a growing number of people age 70 and above for the first time, who traditionally hadn't come in before. There are many reasons for these demographic changes. Social media has become an essential way for people to connect and communicate. The importance of physical appear-

ance as dictated by social networking sites is more persuasive than ever, especially among younger people.[6] A substantial percentage (81%) of Americans report going online daily, including 28% who are online "almost constantly" and 45% who go online several times a day.[7] Social media plays a pivotal role in presenting aesthetic medicine as a feasible option for consumers active on these platforms. Traditional media channels are also creating enhanced awareness of aesthetic medicine. With the increasing shift from invasive to minimally invasive procedures, and new neurotoxins coming on the market, it's an exciting time. Even people who had never considered treatment have a wider appreciation of what's available. The consensus panel agreed it is imperative that physicians understand how various forms of media affect clients' daily decision-making.

The millennial generation (born 1981-1996) represents the largest generation in US history, now representing more than 25% of the US population.[8,9] To provide optimal counseling, preventions, and age-appropriate interventions for aesthetic patients, it is especially important that aesthetic clinicians be educated about generational differences in the manifestations of aging, since changes with aging often impact muscular activity as well as facial contours.[10,11] These changes can be ameliorated by multiple modalities, including BoNT-A, but frequently not BoNT-A alone.

Younger women often seek aesthetic treatments to retain a youthful appearance, particularly once they notice initial signs of aging.[12] Many come in because their friends are getting treated and there is far less stigma about talking about it as in the past. It has become much more the social norm than the exception. In the experience of the consensus panel, younger patients are especially likely to be interested in having only a single area treated with BoNT-A—glabella, forehead, or crow's feet, for example—rather than global treatment because they are thinking of it as preventative maintenance, are focused on a certain area, and are cost-conscious. Millennials typically have a limited budget, which can present its own unique challenges, but they are also starting treatment at a younger age than patients in the past. Because it's more preventative, the dosing strategy is often different. Younger patients tend to need a lower number of BoNT-A units and their treatment visits are less frequent, which enables them to better afford treatment. It is a different group, so the marketing strategy needs to be different. For example, many offices with a variety of clinicians at different ages are finding that millennials tend to gravitate toward the younger ones. The panel felt that it is likely a slightly better fit because patients just relate to them a little more closely.

The panelists agreed that younger patients are a little more challenging to treat than older patients they have traditionally seen. There are 2 distinct groups of young patients. At one extreme are those who have done research and have an opinion, but who also value the expertise of the physician to determine the best treatment options. These patients know the names of the BoNT-As, they sometimes know dosing, and they talk with their friends about it. When managing these patients, it is beneficial to anticipate that they will have done some online research and be ready to answer questions, which can help generate trust and demonstrate personal expertise of the physician above and beyond information found online.[8] Some of these patients actually understand when you talk about agonist and antagonist muscles and explain that if they only get their forehead treated, their brow might drop. They have typically also watched the procedures online, so have less phobias, which also simplifies treatment.

The other group of younger patients believes they know more than their clinicians because they read something on the internet and come in with their own detailed treatment plan. The panel agreed that managing patients like this can be challenging at times, because they may want something done that the clinician knows from experience isn't going to turn out well. The classic example is a patient who wants to totally get rid of her forehead lines—it's an earlier mindset that persists. That pretreatment discussion can take a long time. The panel suggests that aesthetic physicians explain that the paradigm has shifted away from total immobilization, and that patients don't need to be completely frozen to get great results. Patients who request treatment with high forehead doses often return a week later because their eyebrows are heavy. But they are frequently educated enough to learn from their experience and agree to listen more closely to physician recommendations.

Recent statistics from the American Society of Plastic Surgeons show that more Americans age 55 and older are increasingly seeking aesthetic procedures, with nearly 50,000 more procedures performed in 2018 in this group than in 2017.[13] The panelists shared that as a group, baby boomers are a different kind of patient than millennials. These patients tend to come in because of a friend who's looking great after aesthetic treatment or because they've had some sort of life change, like a divorce or the death of a spouse. These patients generally seek to reverse some negative effects of aging.[14] They care about reviews, referrals, and being treated by the right person, and often have more resources than younger patients, so are less price sensitive.[10]

Another recent trend is patients requesting a particular agent, which was rare in the past, and is likely related to the expansion of social media and overall awareness. As additional agents are introduced, more people understand that they might provide different outcomes. In the past, many patients were not interested in switching agents. But now, those who trust their physician's expertise often ask if they should try the latest agent. The panel felt that experienced aesthetic physi-

cians, unlike many non-core clinicians, are able to explain the actual differences, be it a quicker onset, a more specific effect, extended longevity, or something else. Another trend, according to the panel, is that patients are asking for treatment in a specific area rather than just asking the clinician what they should have done. Some ask for treatment in off-label areas because their medi-spa only treats on-label. The panel agreed that knowledgeable aesthetic physicians are better able to help guide patients based on their experience.

Several panelists suggested that it is beneficial, during the initial consultation, for aesthetic physicians to be upfront with patients and explain their own individual style. An analogy would be that if they were going to build a house, they'd want an architect with the same aesthetic sensibilities they're looking for. It is important to explain, for example, that the ultimate goal is for patients to look like the best version of themselves, with natural, smooth results. The definition of "natural" continues to evolve, making the discussion tricky, but essential. The fact that aesthetic preferences vary throughout the country should also be considered when creating treatment plans.

PATIENT ANATOMY AND EVOLVING USE OF BoNT-As

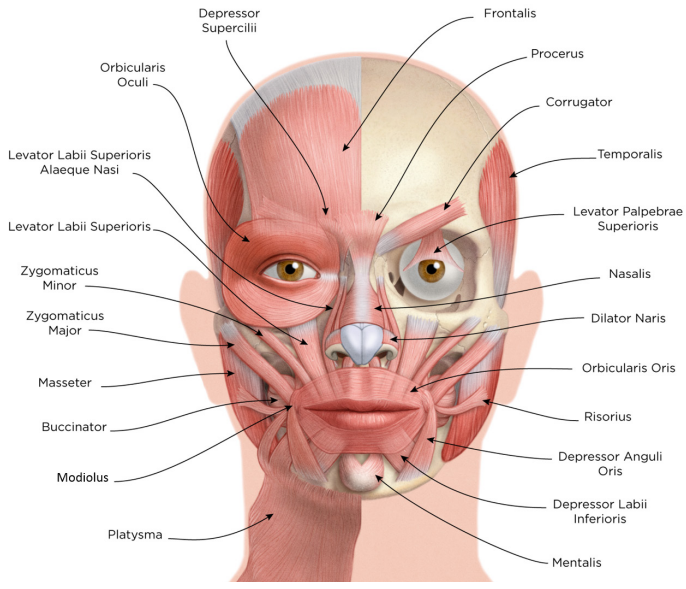
The increasing demand for aesthetic treatments in younger populations requires thoughtful and age-appropriate counselling for delivering preventions and interventions. The physiologic, age-related changes that occur with increasing age help guide suitable treatment selection.[11] The consensus panel agreed that anatomic considerations weigh very heavily into the appropriate use of BoNT-As. They related how all of the phase 3 BoNT-A clinical trials have been done with a standard 5-point pattern of glabellar injections, using fixed doses, as required for commercial release of a new drug. However, while studies using those doses and pattern give good results, they do not reflect normal clinical use, which varies widely based on patient-related factors.[15] The panel felt strongly that clinicians must consider that every person's face is different, not only due to varying gender, muscle mass, and age, but also to the contraction pattern of their muscles.[16] In the glabella, for example, some people's muscles converge, some pull down, some don't need the fourth and fifth injection points. The concept of there being 5 different types of glabellar contraction patterns[16] is particularly relevant. The standard 5-point pattern is really only appropriate for about 25% of the population. Some patients will get better results with a 2-point injection pattern, others a 3-point or even a 7-point pattern, depending on the muscles and their function.

The group agreed that it is challenging to correctly interpret how a patient's muscle function is affecting their face, and how BoNT-A treatment will alter it, which is widely variable. To get the best results with BoNT-As, aesthetic physicians need detailed knowledge of the facial musculature (Figure 1), the movement of these muscles alone and in relation to others, and the notion of compensatory strengthening. Clinicians must be able to evaluate each individual patient's presentation at rest and with normal and exaggerated animation,[17] as it provides information about muscle mass and function and identifies areas of stronger or weaker muscle contraction and other subtle variations in musculature such as facial asymmetry, compensatory muscle use, and palpebral weakness.

Anatomic assessment is crucial. One panelist gave the example of when assessing for brow elevation, if a patient doesn't have a significant lateral frontalis, they probably will not get a lot of brow lift. Alternately, if they have a very active frontalis that extends beyond the line of temporal fusion, the brow lift effect can sometimes be overly extreme. Judgement is more than just training and understanding the anatomy. Nuance is sophisticated, and something all aesthetic physicians should try to accomplish. It is a skill set that comes with experience and a detailed knowledge of anatomy. With BoNT-As, that ranks as a 10 on a scale of 1 to 10.

Because patient anatomy changes with aging, the panelists agreed that aesthetic physicians need to be aware of those changes and consider them when creating a treatment plan and discussing it with patients, especially younger educated ones. For example, one panelist explains BoNT-A dosing in females with a bell curve. Younger women need a little bit less BoNT-A, then need more as they age. But as patients get even older, they again need less. In older patients, the effects of BoNT-A may make lax skin more noticeable, so it makes sense to reduce the BoNT-A dosage and encourage patients to incorporate fillers and resurfacing because that will give them more value than increased BoNT-A doses. In general, males also need higher BoNT-A doses than females due to their larger muscle mass.

FIGURE 1. Facial Musculature



Careful placement of the correct dosing of BoNT-A offers the best chance of good patient outcomes, according to the group. Different areas require different doses of BoNT-A for a clinical effect, reflecting variations in muscular structure and function.[15] Some people also respond to a lower dose of an individual agent while others need higher doses. Specificity hitting the target is as important as dosing. Many clinicians waste a lot of BoNT-A, because once saturation is reached, more drug will not provide additional benefits and may be detrimental. Many physicians have reduced dosing in the frontalis to avoid brow ptosis. The group discussed that, in reality, it can be avoided with accurate injections. With increasing expertise, it is possible to be incredibly precise with a lower number of units.

Another panelist mentioned how the significance of injection depth is rarely talked about with BoNTs but is incredibly important. For the glabella, for example, clinicians have generally been taught that the lateral corrugator injection needs to be very superficial, but superficial injections also impact the frontalis, which can cause unwanted effects. While many clinicians avoid deep injections because of what they've been taught and because they're concerned about eyelid ptosis, it is important to be deep into the corrugator. Good injection technique is very specific to the muscle. Precision injection, based on a thorough assessment and understanding of the functional anatomy, is what's going to give the best results. The consensus group agreed that the field of effect of prabotulinumtoxinA-xvfs (Jeuveau®, Evolus, Inc.) may be more precise than that of other BoNT-As and may be helpful in that regard.

The panel agreed it is important to get the right results because BoNT-A treatment affects facial expression, which affects how patients are interpreted by others they interact with. The lack of immediate efficacy makes BoNT-A treatment complicated as compared with soft tissue fillers, where it is possible to see the immediate volume increase as an area is injected, as well as differences in symmetry. With BoNT-As, clinicians must envision what the results will be in 7 to 10 days based on individual patient characteristics. Injectors who don't understand this concept might get good results, but often are unable to attain great ones. The group felt that this is another issue that separates novice injectors from more experienced ones and is an important concept to try and get patients to understand.

According to the group, assessment at a follow-up visit after the first treatment can add a great deal of information about the individual patient and the way BoNTs affect them, which helps identify how to adjust treatment going forward. That information can't be obtained any other way. Follow-up can be especially helpful if the patient has asymmetry or an unusual forehead. Many patients, especially those who are BoNT-A-naïve, appreciate it when offered the opportunity to come back in for a follow-up visit, as it shows clinicians care enough to see what the results are going to be. If patients are concerned about the number of visits, they can be told they usually only need to come back after the first treatment, because the pattern and dosage will be evident after that. Another strategy for BoNT-A-naïve patients is to conservatively treat their glabella and have them come back in 2 weeks to see the results before treating other facial areas.

DIFFERENCES IN THE 4 APPROVED BoNT-As

Each of the 4 commercially available BoNT-A formulations is approved for various indications in different countries. Despite sharing a similar mechanism of action and efficacies, there is continued discussion about their comparability.[18] Each agent

TABLE 1.

BoNT-As: Pharmacologic Similarities and Differences

	JEUVEAU[20]	BOTOX Cosmetic[21]	XEOMIN[22]	DYSPORT[23]
Vial size	100 U	50 U, 100 U	50 U, 100 U	300 U
Molecular weight	900 kDa	900 kDa	150 kDa	500-900 kDa
Stabilization	Vacuum-dried	Vacuum-dried	Lyophilized	Lyophilized
Composition	C botulinum toxin type A Wild type hemagglutinin complex	C botulinum toxin type A ATCC 3502 (Hall strain) hemagglutinin complex	C botulinum toxin type A ATCC 3502 (Hall strain)	C botulinum toxin type A ATCC 3502 (Hall strain) hemagglutinin complex
	0.5 mg HSA	0.25 mg HSA, 0.5 mg HSA	1.0 mg HSA (both vial sizes)	0.125 mcg HSA
	0.9 mg NaCl	0.45 mg NaCl, 0.9 mg NaCl	4.7 mg sucrose (both vial sizes)	2.5 mg lactose
Storage (packaged product)	36°F–46°F	36°F–46°F for 36 mo	68°F–77°F, 36°F–46°F, or -4°F–14°F until vial expiration	36°F–46°F until vial expiration
Storage (reconstituted)	36°F–46°F, use within 24 h	36°F–46°F, use within 24 h	36°F–46°F, use within 24 h	36°F–46°F, use within 24 h
On-label aesthetic indications	Glabellar lines	Glabellar lines; lateral canthal lines; forehead lines	Glabellar lines	Glabellar lines

HSA, human serum albumin.

is formulated differently, has a different manufacturing process, and demonstrates unique characteristics.[19] They vary in terms of composition, weight, chemical properties, and biologic activities (Table 1),[20-23] and subsequently are not exactly interchangeable.[24,25] An awareness of the differences between agents, particularly related to dosing and reconstitution, is critical.[26] Although each of the 4 BoNT-As can be used with comparable effect and duration and are quite similar in the opinion of the consensus group, the specific results obtained with each agent vary in practice and become more apparent as clinicians gain more expertise.

The panelists suggested that how the drug gets to the muscle may be different with the various agents, influencing the field of effect (spread), and the results, in some areas. However, the size of the field of effect, which helps prevent skip areas, is difficult to measure, and comparisons between preparations have yielded equivocal results.[27] In some areas, like the crows, feet, it is essential. In the experience of the group, the 4 BoNT-As fall on a spectrum with regard to field of effect. OnabotulinumtoxinA (Botox®, Allergan Inc.), the first approved agent, became the gold standard. AbobotulinumtoxinA (Dysport®, Galderma Laboratories, L.P.) appears to have a wider field of effect, and incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH) seems to have a narrower field of effect. The latest approved agent, prabotulinumtoxinA-xvfs, has a tight, precise field of effect. When using agents with a narrower field of effect, neighboring muscles may not be affected, requiring a change in strategy. This can be compensated for by increasing the dilution or by adding a few more injection points so they are closer together.

The panelists clarified that increased diffusion or field of effect is not necessarily a detriment unless BoNT-A is being injected midpupillary right on the brow, or periorally. Clinicians should understand how much each agent diffuses, and then determine how to best use that to an advantage based on the muscles being injected. Similar to soft tissue fillers, the 4 BoNT-As each function differently and aesthetic physicians need to know their nuances to get the best results.

Certain BoNT-As may work better than others in different areas of the face. According to the group, some patients may get profound results with a specific BoNT-A, and others not as much. That demonstrates how recruitment makes a big difference in some areas, and in some patients. In their initial experience, for example, some panelists believe prabotulinumtoxinA-xvfs provides "smoother" results than other BoNTs-As in select areas of the face. Similarly, several panelists felt that abobotulinumtoxinA provides a wider field of effect, which can be useful in areas such as the forehead and crow's feet. The group agreed that because of these nuances, it makes sense for injectors to get experience with all 4 agents rather than sticking with just 1 agent they may have become comfortable using. A few patients may benefit from treatment with several BoNT-As because they work a little differently.

The panel agreed that for aesthetic physicians to perform at an expert level, they need to understand how all the BoNT-As work as well as nuances of varying dilution and dosing and how they affect clinical results. The volume of saline depends on the concentration the clinician wishes to obtain from each vial.[26] The concentration can be adjusted to limit or increase the diffusion when treating localized or broad areas, respectively. Care must be taken, and concentration considered, however, when attempting highly selective facial muscle weakening. For onabotulinumtoxinA, prabotulinumtoxinA-xvfs, and incobotulinumtoxinA, most panelists reconstitute with 2 to 2.5 mL of saline per 100-U vial, although several use as much as 5 mL per 100-U vial. For abobotulinumtoxinA, the corresponding reconstitution is generally between 1.5 and 6 mL per 300-U vial. For example, some panelists use a 1.5 mL dilution of abobotulinumtoxinA in the glabella to increase precision and use a 6-mL dilution elsewhere in the face. The group generally agreed that using a higher dilution of prabotulinumtoxinA-xvfs in the forehead would increase its diffusion, making it behave more like onabotulinumtoxinA or abobotulinumtoxinA, likely because of the agent characteristics and baseline patient anatomy.

BoNT-As each have different personalities, just like fillers. Expert clinicians have learned how to use multiple fillers and understand how one filler may be better in a specific area than another. The introduction of a new neurotoxins should help aesthetic clinicians adjust their clinical practices, providing opportunities for growth. The consensus panel noted that new agents must be treated as unique. As clinicians use new agents, they need to re-evaluate their techniques for the other agents and the results they are getting, and then adjust their practices as part of the ongoing learning process. The group generally felt that starting dosages for the latest agent, prabotulinumtoxinA-xvfs, should be the same as for onabotulinumtoxinA, or maybe 10% more, depending on the area being treated. It was recommended that clinicians start using prabotulinumtoxinA-xvfs just like onabotulinumtoxinA—the same reconstitution and the same injections technique—until they are able to gauge its nuances. For incobotulinumtoxinA, the number of units is usually increased by 20% to 30%. AbobotulinumtoxinA is injected similarly but requires a different dosage calculation of about 2.5:1 to onabotulinumtoxinA.

The panelists agreed that the adverse events and safety profiles of the 4 agents seem to be the same. They believe that adverse events, when they occur, are often the result of substandard technique and training. The major tools for preventing adverse effects from BoNT-A are knowledge and skill, especially proper techniques of dilution, storage, and injection, as well as the

careful exclusion of patients with any contraindications.[28]

EVOLVING USE OF BoNT-A THROUGHOUT THE FACE

The use of BoNT-As is a very important component of non-surgical rejuvenation. The science behind the agents injected and the facial anatomy are important factors in the final result. The panelists were in general agreement regarding the number of injection points and dosing in the upper and midface (Table 2) and the lower face and neck (Table 3) but there was some disagreement on the extremes, resulting in wide ranges. These values reflect differences in agent reconstitution, injection technique, and patient presentation. The most important variables, however, are the skill, experience, and artistic eye of the injector.[17] The wide range of opinions reflects the variety of strategies that can be used to achieve safe, successful results in the hands of experienced aesthetic physicians.

Glabellar Lines

The first FDA-approved aesthetic use of BoNT-A was for treatment of glabellar rhytides. With frowning, the paired corrugator and depressor supercilii muscles contract primarily horizontally, contributing to vertical rhytides. Together, with occasional contribution from the medial orbicularis oculi and frontalis, these muscles form the glabellar complex.[29] The typical targets of injection are the procerus, corrugators, and depressor supercilii muscles, the latter of which are highly variable in angle of insertion and length. Injection points are best determined by observing muscle contraction, although muscle palpation and reference to surface landmarks can sometimes be useful, as can bony landmarks and anatomic diagrams, to a lesser extent.[27]

BoNT-A injections into the glabellar complex can have significant impact on brow height and position. The brows are critical to the unspoken messages that humans send to others, as low medial brows can signal hostility and anger and lower lateral brows can signal uncertainty, concern, or distress.[17] Product labeling recommends 20 units of onabotulinumtoxinA, prabotulinumtoxinA-xvfs, or incobotulinumtoxinA, divided into 5 equal injection points (2 in each corrugator and 1 in the procerus) of 4 units each.[20-22] For abobotulinumtoxinA, the recommended dosage is 50 units divided into 5 equal injection points (2 in each corrugator and 1 in the procerus) of 10 units each.[23] The range of units and injection points recommended by the panel, reflecting real world BoNT-A experience, are listed in Table 2. Lower values reflect patients who may need only a medial corrugator injection, 1 or 2 procerus injections, or perhaps both medial corrugator and procerus variations.

To minimize risk of eyelid and/or brow ptosis, it is important to inject more superficially at the tail of the corrugator or at the

TABLE 2.

Panel Dosing Recommendations for BoNT-As: Upper and Middle Face

Upper Face	Target Muscle(s)	Injection Points, n	JEUVEAU, JUs	BOTOX Cosmetic, BUs	XEOMIN, XUs	DYSPORT, DUs
Glabellar lines	Procerus, corrugator supercilii, depressor supercilii	3-8 (total)	Women: 6-35 Men: 8-40	Women: 6-35 Men: 8-40	Women: 10-35 Men: 12-50	Women: 12-75 Men: 16-105
Frontalis	Frontalis	2-12 (total)	Women: 4-20 Men: 4-30	Women: 2-18 Men: 4-30	Women: 4-24 Men: 4-36	Women: 4-25 Men: 4-50
Brow lift	Lateral: orbicularis oculi	4-11 (total for both sides, including crow's feet)	10-45	10-45	10-50	20-135
Crow's feet	Medial: procerus, corrugator supercilii, depressor supercilii, orbicularis oculi	2-6 (per side)	6-20	6-20	6-25	12-60
Bunny lines	Orbicularis oculi	1-2 (per side)	2-10	2-10	2-16	5-15

TABLE 3.

Panel Dosing Recommendations for BoNT-As: Lower Face

Lower Face	Target Muscle	Injection Points, n	JEUVEAU, JUs	BOTOX Cosmetic, BUs	XEOMIN, XUs	DYSPORT, DUs
Perioral lines	Orbicularis oris	2-8 (total)	2-10	2-10	4-16	4-24
Marionette lines	Depressor anguli oris	1-2 (per side)	2-6	2-6	2.5-8	5-15
Mentalis	Mentalis	1-4 (total)	2-10	2-10	5-12	4-24
Masseter hypertrophy	Masseter	2-6 (per side)	5-35	5-35	10-40	15-60
Platysma bands	Platysma	2-10 (per band)	4-40	4-40	6-60	8-80
Nefertiti lift	Platysma	4-7 (per side)	5-14	5-14	8-20	15-35

subdermal insertion points and somewhat deeper (intramuscularly) at the more medial body of the corrugator muscles based on frown pattern. To prevent unpleasant results, it is critical to avoid the frontalis fibers that lie superficial to the corrugators. In men, brows are optimally low and flat. As such, care should be taken to avoid arching the male brow, which can be feminizing.[17]

The panelists agreed that all 4 agents act similarly in the glabella. In the clinical studies for the newest BoNT-A, prabotulinumtoxinA-xvfs, treating the glabella knocked out the corrugators and the procerus[30] just like other BoNT-As. Some members of the group noted an observable difference between prabotulinumtoxinA-xvfs and onabotulinumtoxinA in the glabella, which could be used to some advantage.

Frontalis

The frontalis muscle is an elevator of the eyebrow. The muscle fibers are oriented vertically, and contraction is associated with development of horizontal forehead rhytides.[29] Significant anatomic variability exists among patients, with many showing significant medial overlapping and structural difference between medial and lateral aspects.[31] Some patients show several fine rhytides, where others exhibit 1 or 2 deep creases. BoNT-A treatment of this area is highly variable due to the anatomic variability of the frontalis muscle and characteristics of each patient's animation patterns.[29]

Complete immobilization is generally not desirable, even if some rhytides remain, because it can prevent normal facial expression.[27] The group agreed that the primary objective is to modulate the depth and magnitude of the effect of BoNT-As based on the patient's muscle mass, thus improving rhytides and maintaining some movement of the frontalis muscle without causing brow ptosis or paralysis and a "frozen" appearance. When patients come in and express concern that they can move their forehead, the group agreed it is best to emphasize that a little bit of motion evokes natural results. But when a patient has a hyperfunctional frontalis, or wants it knocked out completely, the more extensive diffusion of abobotulinumtoxinA may be advantageous.

Treating the forehead with agents that have a smaller field of effect can be an issue in some patients, but the group agreed that the issue can be circumvented by increasing BoNT-A dilution or dose. The group recommended that in areas like the forehead, and occasionally the crow's feet, clinicians can draw up 8 to 10 units and then draw up more diluent to increase the diffusion. Some members of the group have observed a difference between prabotulinumtoxinA-xvfs and onabotulinumtoxinA in the frontalis. For example, one panelist was able to get rid of the little "comma" above the lateral brows with prabotulinumtoxinA-xvfs, something they were unable to do with other BoNT-As.

Brow Lift

The group agreed that it is much more important to raise and shape the brow, than to eradicate every wrinkle. Because appearance is based on shadows and light, positioning of the eyebrows and the corners of the mouth, and expression, some movement is also important. BoNT-As can also be used to correct brow asymmetry from lax skin or mild ptosis on one side and resulting compensation of the frontalis to lift the lower, sagging side.[17] Brow ptosis occurs over time, due to bone loss and descent and shrinkage of the underlying fat pad in the brow area.[32] In general, 2-3 units of onabotulinumtoxinA, prabotulinumtoxinA-xvfs, or incobotulinumtoxinA, or 6-9 units of abobotulinumtoxinA above the stronger brow corrects asymmetry.[17]

Crow's Feet

Lateral periorbital rhytides appear bilaterally upon smiling in a fan-shaped pattern that may extend as far as the temporal hair line. They are formed by a combination of lateral orbicularis oculi muscle contraction and photoaging.[33]The identification of multiple fan patterns suggests that individuals may use different regions of the orbicularis oculi when smiling and, in some cases, recruit cheek elevators. Baseline severity of crow's feet lines, age, and gender may predict fan pattern, which may progress with age from central to lower fan or full fan.[34] Injection points are located based on observed muscle action and superficial landmarks; bony landmarks and anatomic diagrams also may be useful, but muscle palpation is of little value.[27] Overall efficacy rates in the onabotulinumtoxinA pivotal trials[35,36] suggest that 1 of the 2 distinct injection patterns used would be appropriate for the majority of individuals with moderate or severe dynamic crow's feet lines.[34]

The BoNT-A dose should be adjusted based on the desired degree of effect and the expanse and number of wrinkles. Care should be used to stay 1 cm from the lateral canthus in most indications and over the lateral orbit as opposed to injecting over the eye adnexa.[27] Any regional veins should be noted and avoided. It is extremely important to inject superficially in this area to avoid or minimize bruising. In patients with lax lower eyelids, caution should be used when injecting medially to avoid disrupting proper lid function.[29]

The panelists mentioned that over time, they see atrophy with most muscles that they treat, but that treatment of crow's feet is different. The target is not the temporalis, yet there can be temporalis atrophy over time, especially in hyperfunctional young women. A recommendation was made to inject BoNT-A further posteriorly when targeting the temporalis muscle, beyond the hairline, so that any atrophy is hidden for the most part. By inducing muscle paresis, BoNT produces atrophy and reduction of muscle diameter.[37] Muscle atrophy can be the aim of the treatment (in masseter reduction, for example) or an unintend-

ed and undesirable effect.[24] One panelist was unsure whether it is temporalis muscle atrophy or fat loss that is being noted over time, in that the long-term effects of treatment are not well understood. In patients with significant atrophy, the group generally recommends use of soft tissue fillers and discontinuation of BoNT-A.

Bunny Lines

Horizontal and oblique lines form across the bridge and side of the nose due to contraction of the transverse nasalis muscle and often become more prominent after BoNT-A treatment of the glabella.[17,27] Rhytides are oriented perpendicular to the muscle fibers of the underlying nasalis muscle.[29] Wrinkle severity, muscle mass, degree and duration of effect, and adjacent muscle function are the primary considerations in adjusting the BoNT-A dose. To prevent excessive paralysis of the deeper and more inferior levator labii superioris and levator labii alaeque nasi, important elevators of the upper lip, injection sites should be high on the nose and superficial. Excessive chemodenervation of these muscles may lead to upper lip ptosis.[29]

Perioral Lines

Smoking, aging, and habitual facial expressions can result in changes to the appearance of the lips, particularly the formation of vertical perioral rhytids. The muscles in the region most commonly addressed with BoNT-As are the orbicularis oris, depressor anguli oris (DAO), and mentalis.[29] The patient's pattern of recruitment of the orbicularis oris (the "pout" pattern) can guide the location of injections.[26] In general, injections should be symmetrical and superficial.[26] Overdosing can result in perioral muscle weakness, lip elevation, or lip depression, and slight differences in injection depth or placement on either side of the midline can lead to facial asymmetry.[38] Considerations for dose adjustment include muscle mass, wrinkle severity, desired degree and duration of effect, and function of adjacent muscles.[27] The number of injection sites varies. Outcomes are often enhanced when BoNT-A is combined with soft tissue fillers and/or resurfacing.[26]

Marionette Lines

The DAO muscle depresses the angle of the mouth and pulls down on the oral commissures, creating rhytides from the corners of the mouth to the jaw that can be particularly troubling as patients age. Weakening the DAO with BoNT-A minimizes downward pull on the dermal insertions of the muscle and can raise the oral commissures.[26] Observed muscle action is of primary importance for locating injection points, but superficial landmarks can play a secondary role. Muscle weakness and an asymmetric smile resulting from BoNT-A diffusion into the depressor labii inferioris are possible adverse events in this area. Careful, symmetric placement of injections away from the oral commissures, along with proper dosing, reduces the risk of adverse effects.[27] The lower third of the DAO should be targeted to avoid injecting the depressor labii inferioris.[39] Dosing is adjusted based on muscle mass and adjacent muscle function, as well as wrinkle severity to a lesser extent.[27]

Mentalis

The appearance of a dimpled chin due to mentalis muscle contraction can be reduced with the use of BoNT-A, although toxin is best used conservatively in this area.[26] Injection points should be located mostly by observed muscle action but also based on superficial landmarks. Muscle mass, adjacent muscle function, desired degree and duration of effect, and wrinkle severity are important factors when adjusting the usual dose.[27]

There were differing opinions about injection depth in this area, as well as the number of injection points. Several panelists keep injections superficial in the chin because the mentalis muscle is intercalated with the skin, and that is one way to avoid complications, since it keeps BoNT-A out of the lip depressor areas. Others do 4 injections, with the 2 lower injections deep and the 2 upper injections superficial, noting it gives excellent results while avoiding lip dysfunction. One panelist believes that with paired injections, the needle might actually be at different levels, resulting in some lip dysfunction and asymmetry. This panelist typically uses a single, deep, central bolus retrograde injection, almost down to the bone, and continues to inject as the needle is withdrawn, so it is deep and superficial. This affects the body of the medial portion of the paired mentalis as well as getting near the dermal insertions to improve skin texture in this area.

The group agreed that treating the mentalis can be difficult due to the amount of recruitment in the area. When using a BoNT-A with a tight field of effect, there is good paralysis in the injection area, but the lateral part of the mentalis may start bulging. It was suggested that increasing the dilution to get a little bit more diffusion or increasing the number of injection points would be beneficial in that situation.

Masseter Hypertrophy

Hypertrophy of the masseter muscle can create a square-jawed profile that can be considered unattractive, especially in women and in certain cultures.[27,29] Unlike most other aesthetic uses of BoNT-A, which diminish wrinkles or correct asymmetry, treatment of the masseter is intended to reduce muscle mass by atrophy, slimming the jawline.[27,29] Observed muscle action and muscle palpation are the most important factors for locating injection points, with minor roles for superficial landmarks and anatomic diagrams. Treatment of this area is challenging even for experienced aesthetic physicians.[27] Care should be taken to avoid excessive paralysis, as it can weaken mastication.[29] The panel agreed that they see more masseter hypertrophy in young women under age 35 than in older patients. Recognizing and treating these young women with tremendous masseter

hypertrophy can positively affect how they look and feel. The group agreed that patient age must be considered when treating the masseters with BoNT-As, and that if you use more than 10 units for anybody age 40 or older, their skin might be more prone to sagging, and they'll be very unhappy.

Several panel members mentioned they are getting very good results with prabotulinumtoxinA-xvfs for treating masseter hypertrophy, perhaps somewhat better than with other BoNT-As. They related that such results were difficult to explain, given that some diffusion would seem beneficial. They suggested the agent may be spreading mechanically due to vigorous muscle action. In addition, it was stated that more effective aesthetic injections of prabotulinumtoxinA-xvfs require deep injection in the masseters to prevent superficial herniation when patients clench, chew, or bite.

Panelists discussed 2 ways of shrinking the masseter. For example, in Asian women who are really looking for facial shaping and masseter reduction, some clinicians use 30 to 45 units or more of onabotulinumtoxinA or prabotulinumtoxinA-xvfs per side in a single visit to shrink the masseter quickly. The other option is to use fewer units and shrink it slowly over time. This allows titration over time and prevents jowling or masseter atrophy from high-dose treatment, but results don't usually last as long.

Platysma Bands

The platysma is a broad, thin muscle that covers the lower face, throat, and upper chest, and can raise bands on the neck upon contraction.[27] Although classically depicted as a distinct muscle on either side of the anterior neck, fibers often decussate across the midline.[29] Injections of the platysma in different locations in the lower face and neck with BoNT-A can attenuate lower face rhytides, soften platysma bands, improve the shape of the jawline, and diminish horizontal neck lines.[40] By reducing the degree of downward pull, injection of the platysma can also improve lateral cheek lines and marionette lines, lifting the lower face.[39] Care should be taken to inject specifically into the bands, as diffusion of BoNT-A to other muscles of the neck can cause difficulty swallowing, neck weakness, asymmetric smile, or life-threatening breathing difficulties.[27,29] Observed muscle action is the primary factor for determining the location of injections, although superficial landmarks, muscle palpation, and anatomic diagrams may be useful.[27] Platysma bands can be identified by having the patient grimace and jut out the lower jaw.

The amount of BoNT-A for treating the platysma is highly variable, depending in part on the muscle mass, the number of prominent bands, and the length of the neck.[39] Less important factors include desired degree and duration of effect, wrinkle severity, and adjacent muscle function.[27] While the panelists had a variety of injection techniques, they agreed that just "chasing" platysma bands is not effective. The more recent trend is to use BoNT-As as sculpting agents through paralysis. Several member of the group grasp the contracted band and inject BoNT-A very superficially every 1 to 2 cm down the length of the band to the clavicle. One group member related how crucial it can be to include injection with 5 or so units where the platysma merges with the mandible, and triangulates, perhaps because treatment is shrinking the maxillary salivary gland.

Recruitment can be an issue in the platysma since it is such a wide muscle. In a study by Matarasso and colleagues of 1,500 patients treated in 3 different practices, one of the authors used up to 250 units of onabotulinumtoxinA in some necks, which caused a significant degree of dysfunction in some patients.[41] Panel recommendations to help prevent adverse events in this area include staying away from the midline when injecting. In addition, it was suggested that higher doses in the lateral part of the band, which are affecting the jowl, can provide great results with a proper safety margin.

The group agreed that treated correctly, the platysma can be an area of high patient satisfaction, although patients may consider it as being expensive. If a patient is budget-conscious and they are concerned about the cost of treating the entire platysma, it makes sense to treat them with a few units on each side, which can help with jowling. Many patients are not aware that it is possible to define the jawline with BoNTs. When patients notice their jowls improving, they often come back for treatment of the entire platysma. Another option is to treat the platysma at every other patient visit, or every 6 to 9 months, which amortizes the price over time. That's possible because results can last longer than in other areas. A little soft tissue filler along the jawline on the same visit can also improve results.

The group agreed that a limited and carefully selected population of patients can benefit from treatment of the platysma from the mandibular border to the corner of the mouth (Nefertiti neck lift) to weaken the depressor action of the top part of the platysma and augment the elevator action, redefining the jawline and reducing neck rhytides.[32] Best patients typically have good retention of tissue quality and palpable platysma muscle mass, especially posteriorly, with a band that obscures the mandibular border when platysma is contracted while the patient is seated. In many cases, combining this technique with injection of individual platysma bands produces superior results.

VALUE OF COMBINATION THERAPY

The group agreed it is impossible to resolve all facial aesthetic issues with just BoNT-As. Combination treatment with soft tissue fillers is now considered standard of care.[14] While the original paradigm was to relax the upper face, fill the midface, and relax and fill the lower face,[42] this has evolved toward more equal use of BoNT-As and fillers throughout the face. BoNT-As

are used to target muscles whose excessive contraction is the primary cause of changes seen, while fillers are used when volume loss is the primary cause.[5] Soft tissue fillers play a valuable role, for example, in treating residual forehead lines after BoNT-A treatment, since it circumvents brow drooping due to use of higher BoNT-A doses. So, having the dual skill sets for soft tissue fillers and BoNT-As is essential to providing great results. Skin resurfacing can also be of value in some patients.

HOW APPROVAL OF A NEW BoNT-A AFFECTS CLINICAL PRACTICE

Novice injectors and experienced injectors using a new product should consider seeing patients back in 2 weeks. Even if an injector has used a new agent in a study, it probably was injected in the standard 5-point way, so they need to identify its nuances outside of that protocol. How much does the product move? What's the field of action? How does the dosing need to be adjusted?

The introduction of a new BoNT-A provides the opportunity to readdress anatomic considerations. It should make every injector reconsider what they have been doing, and why, and how a new agent can improve on that. Less experienced injectors may think all BoNT-As are pretty much like onabotulinumtoxinA, but they're not, they're all different. Each new BoNT needs to be thoroughly evaluated to determine its differences and how they can be used to an advantage, to give better results based on how they affect specific musculature as well as the interplay between muscles.

Patients should not be looking for a provider who advertises the cheapest price by the unit, but rather one who uses all 4 of the available agents and understands how each works. This is an essential part of the recipe for success, because each injector treats patient slightly differently, but only some get great results.

AGENTS ON THE HORIZON

DaxibotulinumtoxinA (Revance Therapeutics, Inc) is currently in clinical development for aesthetic (glabellar lines) as well as therapeutic indications.[43-45] Phase 3 clinical trials demonstrate safety and efficacy lasting 6 months or more for moderate to severe glabellar lines.[43,44] This agent contains no human serum albumin or other human- or animal-derived components but has a proprietary stabilizing excipient peptide (RTP004) that is cationic and binds to the BoNT-A molecule. DaxibotulinumtoxinA is much different than any of the other available neurotoxins. The panelists related that additional experience with daxibotulinumtoxinA is needed to determine how it will translate to off-label use with regard to dosing, diffusion, longevity, and other effects. It will likely be another agent that reveals the separation between really good injectors and those with less skill.

EB-001 (Bonti, Inc.), an investigational BoNT serotype E, has the distinct profile of faster onset of action (about 24 hours) and shorter duration of effect (14-30 days) than commercial BoNT-As.[46] It has been tested in phase 2a studies for glabellar lines,[46,47] for scar reduction after Mohs surgery,[48] and for reducing postsurgical musculoskeletal pain.[49,50] The fast onset may benefit patients who desire a rapid treatment for facial rhytides before unexpected social or professional events. The limited duration of effect may be a positive attribute for toxin-naïve patients considering treatment but who are unwilling to make a longer-term commitment,[46] but is unlikely to be favored by existing patients.

CONCLUSIONS

The advancing science and applications of BoNT-A highlight the importance for aesthetic physicians to keep up to date regarding ongoing developments in the field. Due to their differences, no single agent works for all injectors and in all patients. All physicians, regardless of specialty, should continually examine the agents and techniques they use and make an effort to investigate and embrace novel developments that can improve patient outcomes and quality of life. Detailed anatomical knowledge, along with these advances, will allow practitioners to achieve optimal results. With the recent addition of a fourth BoNT-A product into the US market, the panel encourages aesthetic physicians to become familiar with using all 4 BoNT-A products to be able to use them alone or in combination based on comfort, experience, and outcomes with each product.

REFERENCES

1. Fagien S, Carruthers JD. A comprehensive review of patient-reported satisfaction with botulinum toxin type A for aesthetic procedures. *Plast Reconstr Surg.* 2008;122(6):1915-25.
2. American Society of Aesthetic Plastic Surgery. 2018 Cosmetic (Aesthetic) Surgery National Data Bank Statistics. Available from: https://www.surgery.org/sites/default/files/ASAPS-Stats2018.pdf. Accessed December 27, 2019.
3. Ibrahim O, Keller EC, Arndt KA. Update on botulinum neurotoxin use in aesthetic dermatology. *Semin Cutan Med Surg.* 2014;33(4):152-6.
4. Gart MS, Gutowski KA. Overview of botulinum toxins for aesthetic use. *Clin Plast Surg.* 2016;43(3):459-71.
5. Sundaram H, Signorini M, Liew S, et al. Botulinum toxin type A—evidence-based review, emerging concepts, and consensus recommendations for aesthetic use, including updates on complications. *Plast Reconstr Surg.* 2016;137(3):518-29.
6. Fardouly J, Vartanian LR. Social media and body image concerns: current research and future directions. *Curr Opin Psychol.* 2016;9:1-5.
7. Perrin A, Kumar M. About three-in-ten U.S. adults say they are 'almost constantly' online. Pew Research Center July 25, 2019. Available at: http://www.pewresearch.org/fact-tank/2019/07/25/americans-going-online-almost-constantly/. Accessed December 27, 2019.
8. Sherber NS. The millennial mindset. *J Drugs Dermatol.* 2018;17(12):1340-2.
9. US Census Bureau. Millennials Outnumber Baby Boomers and Are Far More Diverse, Census Bureau Reports. June 25, 2015. Available at: https://www.census.gov/newsroom/press-releases/2015/cb15-113.html. Accessed December 27, 2019.
10. Hilton L. Aesthetic medicine: marketing by generation. *Dermatology Times.* January 7, 2019. Available at: https://www.dermatologytimes.com/practice-management/aesthetic-medicine-marketing-generation. Accessed December 27, 2019.

11. Bonati LM, Fabi SG. Treating the young aesthetic patient: evidence-based recommendations. *J Drugs Dermatol.* 2017;16(6 Suppl):S81-3.
12. Narurkar V, Shamban A, Sissins P, et Stonehouse A, Gallagher C. Facial treatment preferences in aesthetically aware women. *Dermatol Surg.* 2015;41(Suppl 1):S153-60.
13. American Society of Plastic Surgeons. 2018 Plastic Surgery Statistics Report. Available from: https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf. Accessed December 27, 2019.
14. Sundaram H, Liew S, Signorini M, et al. Global aesthetics consensus: hyaluronic acid fillers and botulinum toxin type a-recommendations for combined treatment and optimizing outcomes in diverse patient populations. *Plast Reconstr Surg.* 2016;137(5):1410-23.
15. Dover JS, Monheit G, Greener M, Pickett A. Botulinum toxin in aesthetic medicine: myths and realities. *Dermatol Surg.* 2018;44(2):249-60.
16. 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(9):1506-15.
17. Lupo MP. Tox outside the box: off-label aesthetic uses of botulinum toxin. *J Drugs Dermatol.* 2016;15(9):1151-7.
18. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. *Toxins (Basel).* 2016;8(3).
19. Wilson AJ, Chang B, Taglienti AJ, et al. A quantitative analysis of onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA: a randomized, double-blind, prospective clinical trial of comparative dynamic strain reduction. *Plast Reconstr Surg.* 2016;137(5):1424-33.
20. Jeuveau [highlights of prescribing information] Santa Barbara, CA: Evolus; 2/2019.
21. Botox Cosmetic [highlights of prescribing information] Irvine, CA: Allergan, Inc.; 10/2017.
22. Xeomin [highlights of prescribing Information] Raleigh, NC: Merz Pharmaceuticals, LLC; 7/2018.
23. Dysport [highlights of prescribing information] Fort Worth, TX: Galderma Laboratories, L.P.; 1/2019.
24. Samizadeh S, De Boulle K. Botulinum neurotoxin formulations: overcoming the confusion. *Clin Cosmet Investig Dermatol.* 2018;11:273-87.
25. Brin MF, James C, Maltman J. Botulinum toxin type A products are not interchangeable: a review of the evidence. *Biologics.* 2014;8:227-41.
26. Lorenc ZP, Kenkel JM, Fagien S, et al. Consensus panel's assessment and recommendations on the use of 3 botulinum toxin type A products in facial aesthetics. *Aesthet Surg J.* 2013;33(1 Suppl):35S-40S.
27. Maas C, Kane AC, Bucay VW, et al. Current aesthetic use of abobotulinumtoxinA in clinical practice: an evidence-based consensus review. *Aesthet Surg J.* 2012;32(1 Suppl):8S-29S.
28. Wollina U, Konrad H. Managing adverse events associated with botulinum toxin type A: a focus on cosmetic procedures. *Am J Clin Dermatol.* 2005;6(3):141-50.
29. Gart MS, Gutowski KA. Aesthetic uses of neuromodulators: current uses and future directions. *Plast Reconstr Surg.* 2015;136(5 Suppl):62S-71S.
30. Beer KR, Shamban AT, Avelar RI, Gross JE, Jonker A. Efficacy and safety of prabotulinumtoxinA for the treatment of glabellar lines in adult subjects: results from 2 identical phase III studies. *Dermatol Surg.* 2019;45(11):1381-93.
31. Wieder JM, Moy RL. Understanding botulinum toxin. Surgical anatomy of the frown, forehead, and periocular region. *Dermatol Surg.* 1998;24(11):1172-4.
32. Shamban A. Customized approach to facial enhancement. *Facial Plast Surg Clin North Am.* 2015;23(4):471-7.
33. Carruthers A, Carruthers J. Cosmetic uses of botulinum A exotoxin. *Adv Dermatol.* 1997;12:325-47.
34. Kane MA, Cox SE, Jones D, Lei X, Gallagher CJ. Heterogeneity of crow's feet lines patterns in clinical trial subjects. *Dermatol Surg.* 2015;41(4):447-56.
35. Carruthers A, Bruce S, de Coninck A, Connolly S, et al. Efficacy and safety of onabotulinumtoxinA for the treatment of crow's feet lines: a multicenter, randomized, controlled trial. *Dermatol Surg.* 2014;40:1181-90.
36. Moers-Carpi M, Carruthers J, Fagien S, Lupo M, et al. Efficacy and safety of onabotulinumtoxinA for treating crow's feet lines alone or in combination with glabellar lines: a multicenter, randomized, controlled trial. *Dermatol Surg.* 2015;41:102-12.
37. Dressler D, Saberi FA, Barbosa ER. Botulinum toxin: mechanism of action. *Arq Neuropsiquiatr.* 2005;63(1):180-5.
38. Carruthers A, Carruthers J, Monheit GD, Davis PG, Tardie G. Multicenter, randomized, parallel-group study of the safety and effectiveness of onabotulinumtoxinA and hyaluronic acid dermal fillers (24-mg/mL smooth, cohesive gel) alone and in combination for lower facial rejuvenation. *Dermatol Surg.* 2010;36(Suppl 4):2121-34.
39. 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(1 Suppl):S7-S22.
40. Benedetto AV. What's new in cosmetic dermatology. *Dermatol Clin.* 2019;37(1):117-28.
41. Matarasso A, Matarasso SL, Brandt FS, Bellman B. Botulinum A exotoxin for the management of platysma bands. *Plast Reconstr Surg.* 1999;103(2):645-52.
42. Carruthers JD, 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(5 Suppl):5S–30S.
43. Carruthers JD, Fagien S, Joseph JH, et al. DaxibotulinumtoxinA in the treatment of glabellar lines: results from each of two multicenter, randomized, double-blind, placebo-controlled, phase 3 studies (SAKURA 1 and SAKURA 2). *Plast Reconstr Surg.* 2020;145(1):45-58.
44. Bertucci V, Solish N, Kaufman-Janette J, et al. DaxibotulinumtoxinA for Injection has a prolonged duration of response in the treatment of glabellar lines: Pooled data from two multicenter, randomized, double-blind, placebo-controlled, phase 3 studies (SAKURA 1 and SAKURA 2). *J Am Acad Dermatol.* [Epub ahead of print]. 2019 Nov 15.
45. Jankovic J, Truong D, Patel AT, et al. Injectable daxibotulinumtoxinA in cervical dystonia: a phase 2 dose escalation multicenter study. *Mov Discord Clin Pract.* 2018;5(3):273-82.
46. Yoelin SG, Dhawan SS, Vitarella D, Ahmad W, Hasan F, Abushakra S. Safety and efficacy of EB-001, a novel type E botulinum toxin, in subjects with glabellar frown lines: results of a phase 2, randomized, placebo-controlled, ascending-dose study. *Plast Reconstr Surg.* 2018;142(6):847e-55e.
47. NCT02939326. Evaluate safety and efficacy of a single treatment cycle of EB-001 in subjects with glabellar frown lines. Last updated February 15, 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT02939326. Accessed December 27, 2019.
48. NCT03346902. Study of EB-001 in facial scar reduction. Last updated January 8, 2019. Accessed November 22, 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03346902. Accessed December 27, 2019.
49. NCT03193593. Study to evaluate EB-001 in reducing musculoskeletal pain. Last updated January 25, 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03193593. Accessed December 27, 2019.
50. NCT03429556. Study to evaluate botulinum neurotoxin serotype E (EB-001) in reducing musculoskeletal pain in abdominoplasty. Last updated February 15, 2019. Available at: https://clinicaltrials.gov/ct2/show/results/NCT03429556. Accessed December 27, 2019.

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