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SPECIAL TOPIC
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Tailored Indications for Different Neurotoxins

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Background: Minimally invasive procedures have become increasingly popular because they require minimal downtime and are effective for achieving a more youthful appearance. All U.S. Food and Drug Administration–approved neurotoxins are indicated for achieving similar effects, even though they are different in regard to structure, manufacturing technique, and storage requirements. It is agreed upon that each neurotoxin is unique and therefore not interchangeable. The aim of the author is to provide an approach for choosing the optimal toxin in different indications regarding the area of treatment, the age and characteristics of the patient, potential risks, and ultimate goals.

Methods: As the country that the author practices carries onabotulinum (ONA), prabotulinum (PRA), and abobotulinum (ABO) toxin type-A, one of these three toxins was preferred for each category. ABO toxins were preferred in wide areas due to the broader action halo. Typical examples include hyperhidrosis treatment, wide forehead area, and calf slimming. In areas where very precise and targeted treatment is required, PRA and ONA toxins were preferred to limit potential side effects due to wider diffusion. First-time patients were typically treated with PRA toxins for a softer trial periods where as "repeat" patients were successfully treated with ABO toxins.

Results: No toxin is superior to the other in terms of producing effects. Yet, small differences in their properties can allow the plastic surgeon to cater to each patient's needs while yielding the most optimal results.

Conclusions: This study is meant to serve as a guideline for choosing the ideal toxin in different patient settings and indications. *(Plast Reconstr Surg Glob Open 2023; 11:e5404; doi: 10.1097/GOX.0000000000005404; Published online 27 November 2023.)*

INTRODUCTION

Minimally invasive procedures require minimal downtime and are highly effective in achieving a more attractive, rested, and youthful appearance. Among these nonsurgical alternatives, botulinum toxin type-A (BoNT-A) injections have taken the lead globally for over two decades. The American Society of Plastic Surgeons database has reported 4.4 million neurotoxin procedures in the United States in 2020 with the treatment being the highest-ranking aesthetic procedure among plastic surgeons since 1999.[1] The International Society of Plastic Surgery 2021 database has reported that neurotoxin treatments are the most frequently executed procedure among patients over the age of 18.[2] This comes as no surprise, as BoNT-A injections are effective in treating upper facial wrinkles, hyperhydrosis, and migraines, along with off-label indications including masseter hypertrophy, facial asymmetry, gummy smile deformity, peau d'orange of the chin, perioral asymmetry and descent of the corners of the mouth, platysmal bands, oculonasal synkinesis, and more.[3–5]

Currently, there are five different types of U.S. Food and Drug Administration (FDA)–approved BoNT-A in the US market.[6] These can be listed as onabotulinum (ONA) toxin type-A (Botox/Vistabel; Allergan Aesthetics, an AbbVie Company, Irvine, Calif.), abobotulinum (ABO) toxin type-A (Dysport/Azzalure; Ipsen, Paris, France/Galderma, Lausanne, Switzerland), incobotulinum (INCO) toxin type-A (Xeomin/Bocouture; NT 201; Merz Pharmaceuticals GmbH, Frankfurt, Germany), and prabotulinum (PRA) toxin type-A (Jeauveu/Nabota;

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Received for publication July 12, 2023; accepted September 26, 2023.

Presented at the American Society of Plastic Surgeons (ASPS) Global Partners Webinar Series on May 13, 2021, held virtually.

DOI: 10.1097/GOX.0000000000005404

Disclosure statements are at the end of this article, following the correspondence information.

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Evolus, Newport Beach, Calif./Daewoong Pharmaceutical Co., Seoul, Republic of Korea), with the most recent addition being daxibotulinum (DAXI) toxin type-A (DAXXIFY; Revence Therapeutics, Newark, Calif.) (Table 1).

Studies have reported differences among toxins regarding efficacy, effect initiation time, duration, side effect profile, and pharmacological properties, yet it is difficult to come across objective, comparative studies, as most research is sourced by manufacturing companies.[7–9] Nevertheless, it is agreed upon that each neurotoxin is unique and therefore not interchangeable.[10,11]

In general, conversion ratios between similar units of ONA, INCO, and PRA toxins have been accepted as 1:1.[12,13] A general ONA to ABO toxin conversion factor is suggested as 1:2.5 or 1:3.[14] It is also reported that ABO toxins reconstituted in equipotent, equivolemic solutions have a broader action halo, translating to activity occurring further out from the point of injection.[15–17] This is also true for more dilute reconstitutions, as this also increases the action halo, regardless of the toxin.[18] This is important while determining the range of the desired effect while taking into consideration the potential risk of side effects.

These toxins are indicated for achieving similar effects, even though they may demonstrate differences in regard to structure, manufacturing technique, and storage requirements.[19] Although each newly emerging toxin comes with its novel advantages, it is without a doubt that some advantages may also bring potential drawbacks in certain scenarios. Although each toxin can be safely utilized for each indication in the hands of the expert injector, different toxins in different anatomical sites and patients can yield more optimal effects.

The author's purpose is to provide an algorithmic approach for choosing the optimal toxin for different indications regarding the area of treatment, the properties of the patient, potential risks, and ultimate goals.

MAIN CATEGORIES FOR OPTIMAL TOXIN SELECTION

The main factors that affect the choice of BoNT-A can be categorized into three main groups (Fig. 1). Although there are five FDA-approved toxins available, the country where the author practices carries ONA, PRA, and ABO toxins; therefore, one of the three toxins has been recommended.

Takeaways

Question: Can differences among botulinum toxin type-A products be utilized to achieve the most optimal result for different indications?

Findings: All U.S. Food and Drug Administration–approved neurotoxins are indicated for achieving similar effects even though they exhibit differences. Understanding these differences can be beneficial for achieving optimal results for different indications grouped under anatomical areas, the characteristics of the patient, and expectations.

Meaning: No toxin is superior to the other in terms of producing effects. Yet, small differences in the properties of these toxins can allow the plastic surgeon to cater to each patient's needs while yielding the most optimal results.

Factors affecting the choice of optimal BoNT-A are as follows:

1. Anatomy and properties of the injection site
2. Patient age, gender, and characteristics
3. Expectations

ANATOMY AND PROPERTIES OF THE INJECTION SITE

Considering the vast number of indications that present with BoNT-A treatments, potential injection sites can differ dramatically in terms of anatomy, such as the proximity of neighboring muscles and surface area of treatment. In this section, optimal choices for BoNT-A will be discussed according to different anatomical areas with specific characteristics.

Hyperhidrosis

Hyperhidrosis treatment is among the BoNT-A indications with high rates of patient satisfaction.[20] The most frequently treated areas are the axilla, the palm of the hands, the sole of the feet, and the forehead, all of which require

Table 1. FDA-approved BoNT-A Products: Summary of Properties

	ONA Toxin	ABO Toxin	PRA Toxin	INCO Toxin	DAXI Toxin
Molecular weight (kDa)	900	500-900	900	150	150
Stabilization	Vacuum-dried	Lyophilization	Vacuum-dried	Lyophilization	Lyophilization
Contains accessory proteins	Yes	Yes	Yes	No	No
Contains has	Yes	Yes	Yes	Yes	No
Composition other	Sodium chloride	Lactose	Sodium chloride	Sucrose	PS20, sugar, buffer, excipient peptide (RTP004)
Can be stored at room temperature unreconstituted	No	No	No	Yes	Yes
Shelf-life once reconstituted (h)	36	24	24	36	72
On-label aesthetic indications	Glabellar lines; lateral canthal lines; forehead lines	Glabellar lines	Glabellar lines	Glabellar lines	Glabellar lines

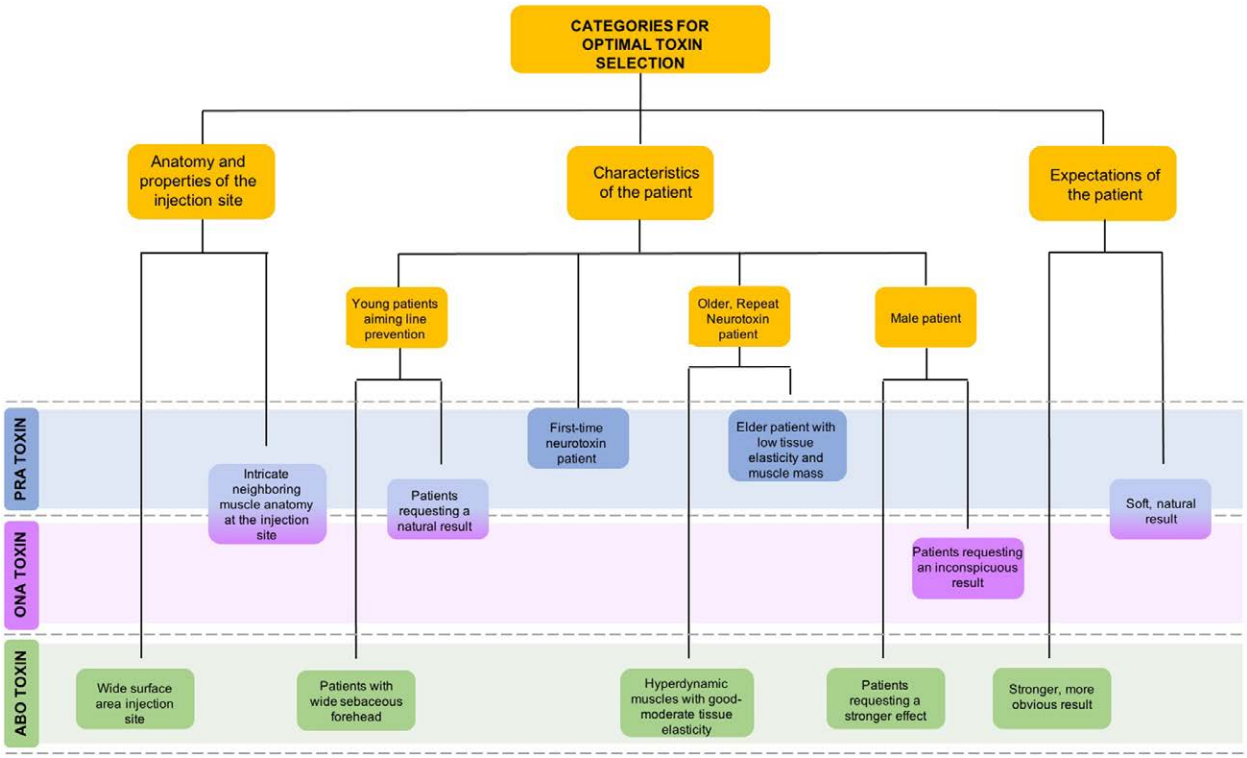

Fig. 1. Flowchart depicting optimal choices for ideal toxin selection in different indications.

application over a wide surface area and a homogenous widespread effect.[21] This is why ABO toxin is very practical and yields very successful results. The injection is done intradermally to target sweat glands. An area where ABO toxins can have a higher risk of potential side effects is the palmar region due to the close proximity of the thenar and hypothenar musculature which can pose a risk for palmar atrophy.[22] Although the effect is transient, it may cause discomfort for individuals required to grasp pencils and write, such as students. Although more injections and potentially more toxins may be required, palmar hyperhidrosis may therefore be best treated with ONA or PRA toxin to reduce this risk. It is also worth mentioning that reconstituting any toxin with higher dilution can also yield similar side effects as this also increases the diffusion of the toxin to neighboring muscles.

Masseter Hypertrophy/Bruxism

Botulinum toxin injections in the masseter have also become increasingly popular not only for the treatment of bruxism but also for lower face slimming. The masseter is a large muscle therefore treatment requires higher units of toxin compared to other facial muscles (Fig. 2). Approximately 20–30 units of ONA/INCO/PRA toxin administered in three to four injection sites is required per muscle to achieve the desired result.[23] Care must be taken to inject centrally in the muscle to prevent potential effects into the neighboring muscles such as the risorius. Although treatment can be fairly controlled with this protocol, the adverse situation where these muscles are affected can cause asymmetry during smiling and speech, which can bring about a high level of discomfort.[24] Considering the high dose of BoNT-A that is required, the author mainly prefers ONA or PRA toxin for this indication as the diffusion of the toxin from the three to four points will be narrower, albeit the higher number of units.

Perioral Applications

Muscles of the perioral region that are frequently targeted are the orbicularis oris, levator labii superioris alaeque nasii, depressor anguli oris, and the mentalis. These muscles are fine, delicate muscles that overlap each other, creating a complex anatomy with treatment indications more suitable for experienced injectors.[25] When injecting in the perioral musculature, the depth and the exact points of injection are crucial determinants of successful treatment.[26] As very precise treatment is warranted, ONA and PRA toxins are the toxins of choice (Fig. 3). The units to be injected differ from muscle to muscle and on average can be two to four units for the orbicularis oris, three to four units for the depressor anguli oris for treating the marionette and frown lines, two to four units for the levator labii superioris alaeque nasii for treating the gummy smile, and five to 10 units in total for the mentalis for alleviating the orange peel appearance of the chin.

Calf Slimming

Although lower leg slimming is popular in Asia, there is an international increase in demand for non-surgical calf slimming. The treatment is much like masseter injections in that the main goal is to minimize

Fig. 2. BoNT-A for masseter hypertrophy. A, 36-year-old female patient with masseter hypertrophy and bruxism. B, Preinjection oblique view. C, Treated with a total of 25 units of PRA toxin with three injection points, 6-week result after injection demonstrating a slimming effect in the lower face. D, Postinjection oblique view.

muscle bulge by creating transient muscular atrophy. The muscles that are treated are the medial and lateral heads of the gastrocnemius muscles, and treatment can be tailored according to the distribution of muscular bulk.[27] Nevertheless, both heads of the muscle require a significant amount of toxin, which can be quite expensive. Therefore, ABO toxin is the preferred toxin, as the amount of toxin is higher per vial, and injections result in homogenous wide distribution, which is deemed necessary for an effective result. The average dosage for ABO toxin in the gastrocnemius muscle is 250–350 units.[28] The treatment is quite safe, and the injection points are marked when the patient rises on their toes, and the muscle is further flexed to determine the bulkiest points. Five to 10 injection points are marked, and injections are carried out intramuscularly with a minimum of 13-mm-length needles to penetrate through the skin. In cases where skin and subcutaneous tissue are very thick, it may be wiser to not go through with this technique, as toxins may not yield optimal results. If treatment is still pursued under these circumstances, ultrasound-guided measurements can be helpful for determining the depth of the muscles in such cases.[29]

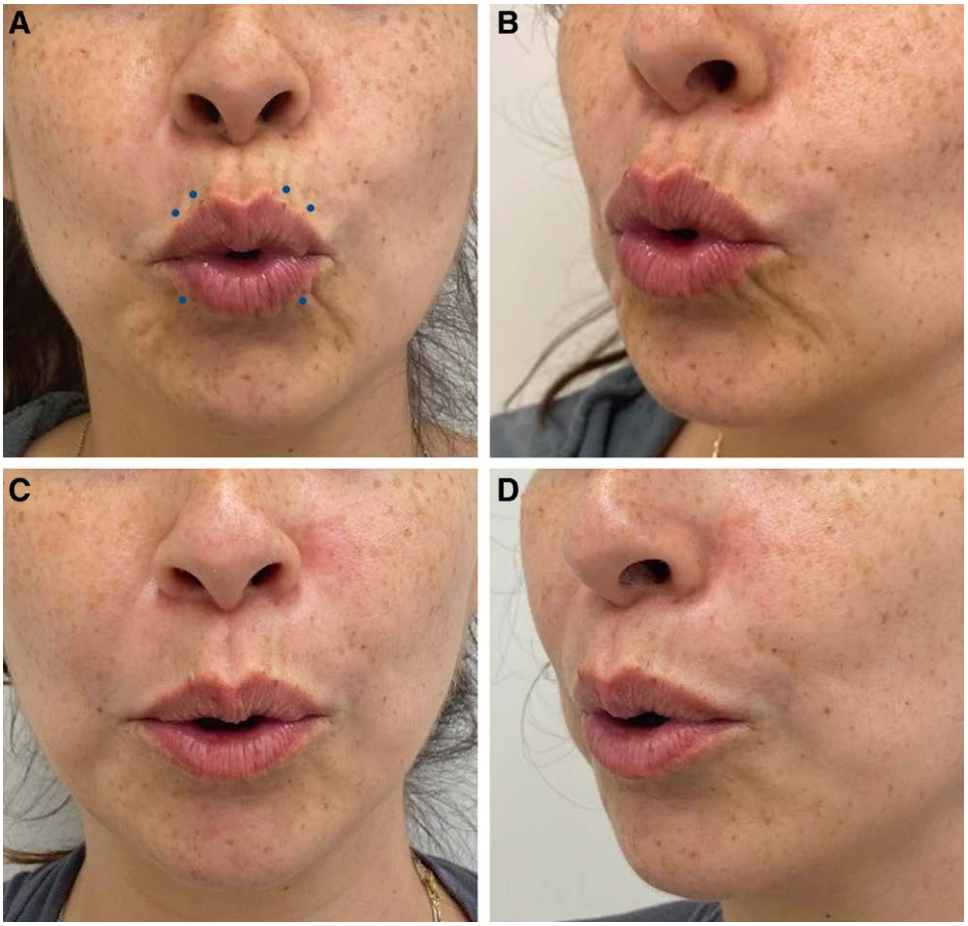

Fig. 3. BoNT-A for perioral applications. A, 38-year-old female patient with barcode lines of the upper and lower lip, frontal view. Injection points have been marked with blue dots. B, Preinjection oblique view. C, Treated with a total of 12 units of ONA toxin with six injection points (four points: upper lip, two points: lower lip), 4-week result after injection demonstrating a natural improvement with symmetrical oral competency, frontal view. D, Postinjection oblique view.

PATIENT AGE, GENDER, AND CHARACTERISTICS

Another domain of factors worth noting is patient characteristics, including gender, age, and treatment history. The author describes the categories under which many patients fall:

a. First-time neurotoxin patients
b. Young patients
c. Mid-older age regular toxin patients
d. Male patients

First-time Neurotoxin Patients (the Neurotoxin-naive Patient)

Patients who are undergoing BoNT treatments for the first time comprise a special subgroup within the patient range. These patients are generally quite anxious and unable to explain what they truly want in terms of results. They are usually young but may also be older patients. It is important to address their experience as a "warm-up" or "trial" by creating a softer, natural result so that they can determine their thoughts on neurotoxin treatments without having a dramatic difference, and their fear of stigmatized appearances is unjustified. To achieve a softer and less apparent look, PRA toxin is the toxin of choice in this subset of patients, as the action halo is tighter, which often results in precision and natural results (Fig. 4). These patients must be followed up, as any further treatments can then be planned and assessed according to these initial reactions.

Young Patients (Preventative Toxin Applications)

The young patient who has established a BoNT routine is set apart from the first-time patient in regard to several different aspects. Contrary to first-timers, young patients usually have a clear mindset about their expectations (Fig. 5). The treatment is generally undertaken in pursuit of delaying the formation of deeper lines. Some patients may want a dynamic result that allows movement, mainly in the forehead. This milder version of BoNT treatment, which is often referred to as "baby botox" requires the injector to use fewer units. The narrower effect halo of PRA and ONA toxins can be a better option for this subgroup. Patients seeking a very

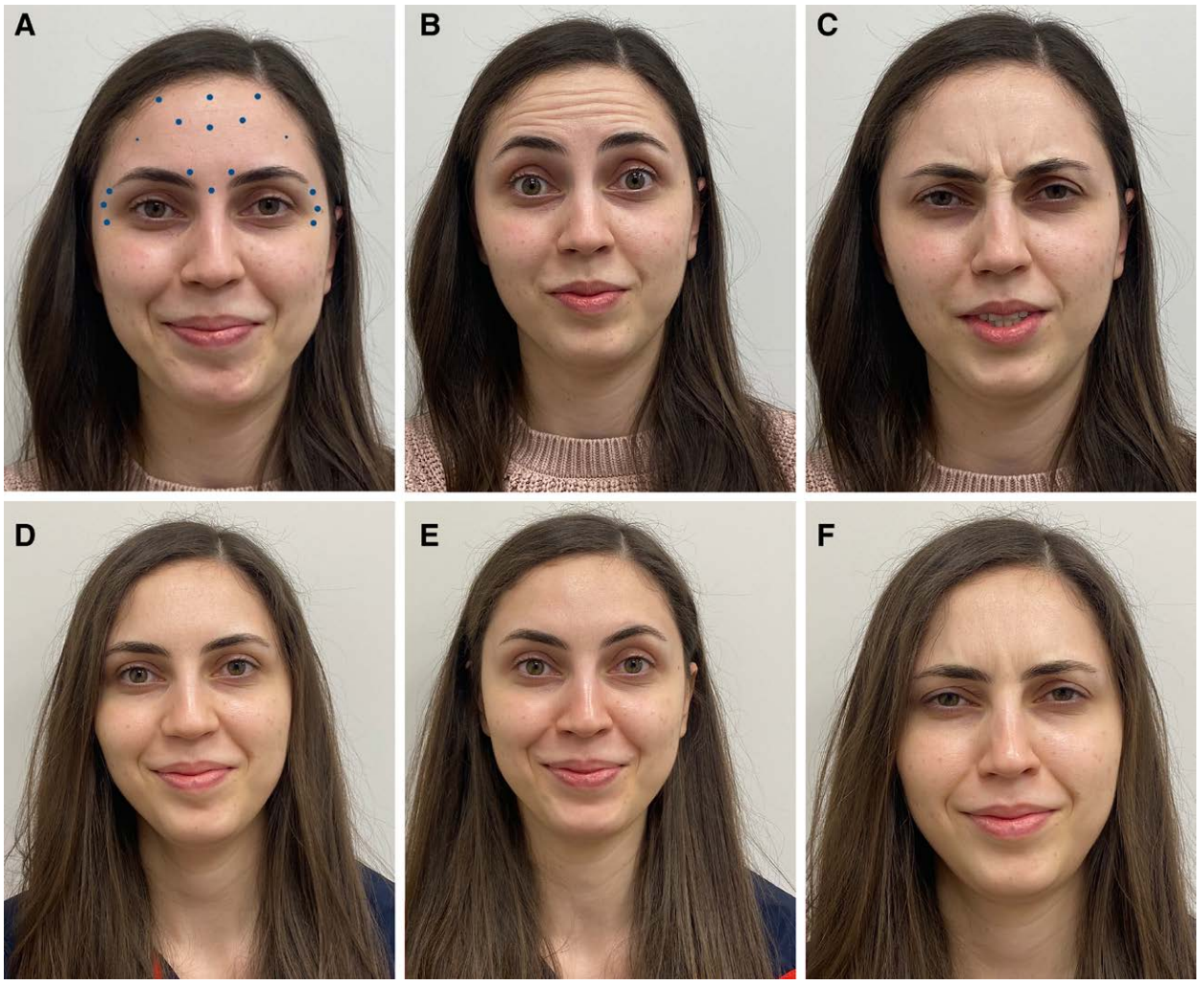

Fig. 4. BoNT-A injections for the neurotoxin-naïve patient. A, 25-year-old female "first-time" patient, preinjection at rest. Injection points have been marked with blue dots. B, Forced contracted forehead. C, Forced contracted glabella. D, Treated with a total of 35 units of PRA toxin, 4 weeks postinjection at rest. E, Postinjection contracted forehead. F, Postinjection contracted glabella.

homogenous result with less movement and subsequent elevated brows require higher doses and wider effect halos. The width of the forehead plays an important role in the decision-making process. Patients with vertically short foreheads should be approached cautiously in this indication, as an exaggerated treatment can weigh down the brows and result in a tired, ptotic appearance. These patients can also be better candidates for PRA and ONA toxins, whereas, on the contrary, patients with wider foreheads can benefit from the more global effect of ABO toxin. Patients with acne or hyperhidrosis of the forehead can also benefit tremendously from all BoNT treatments with ABO toxin having an upper hand due to its widespread effect and longevity.

Mid-older Age Regular Toxin Patient (the Repeat Patient)

Patients over the age of 45 who undergo routine BoNT treatments also require special attention. These patients have set expectations on treatment goals and wish to continue with these effects as years pass. Ongoing treatments allow for BoNT to still yield satisfaction yet some factors undoubtedly change with aging. Wrinkles can become moderate to severe and the loss of skin elasticity, volume loss, and tissue sagging become more apparent. Patients must be guided on other interventions that can be required to achieve better results when their usual routines may start to fall short.

Facial mimic muscles can become hyperdynamic, requiring higher units to achieve similar outcomes while also decreasing the longevity of BoNT. A personal preference for ABO toxin in these patients can increase satisfaction and be quite helpful in overcoming both problems, as the effect is stronger and therefore has a longer duration. [**See figure, Supplemental Digital Content 1**, which displays (A) a 55-year-old female patient with dullness of the skin and visible crows feet at rest. Injection points have been marked with blue dots. B, Crows feet treated with 25 units of ABO toxin per side, 6 weeks postinjection, **http://links.lww.com/PRSGO/C858**.]

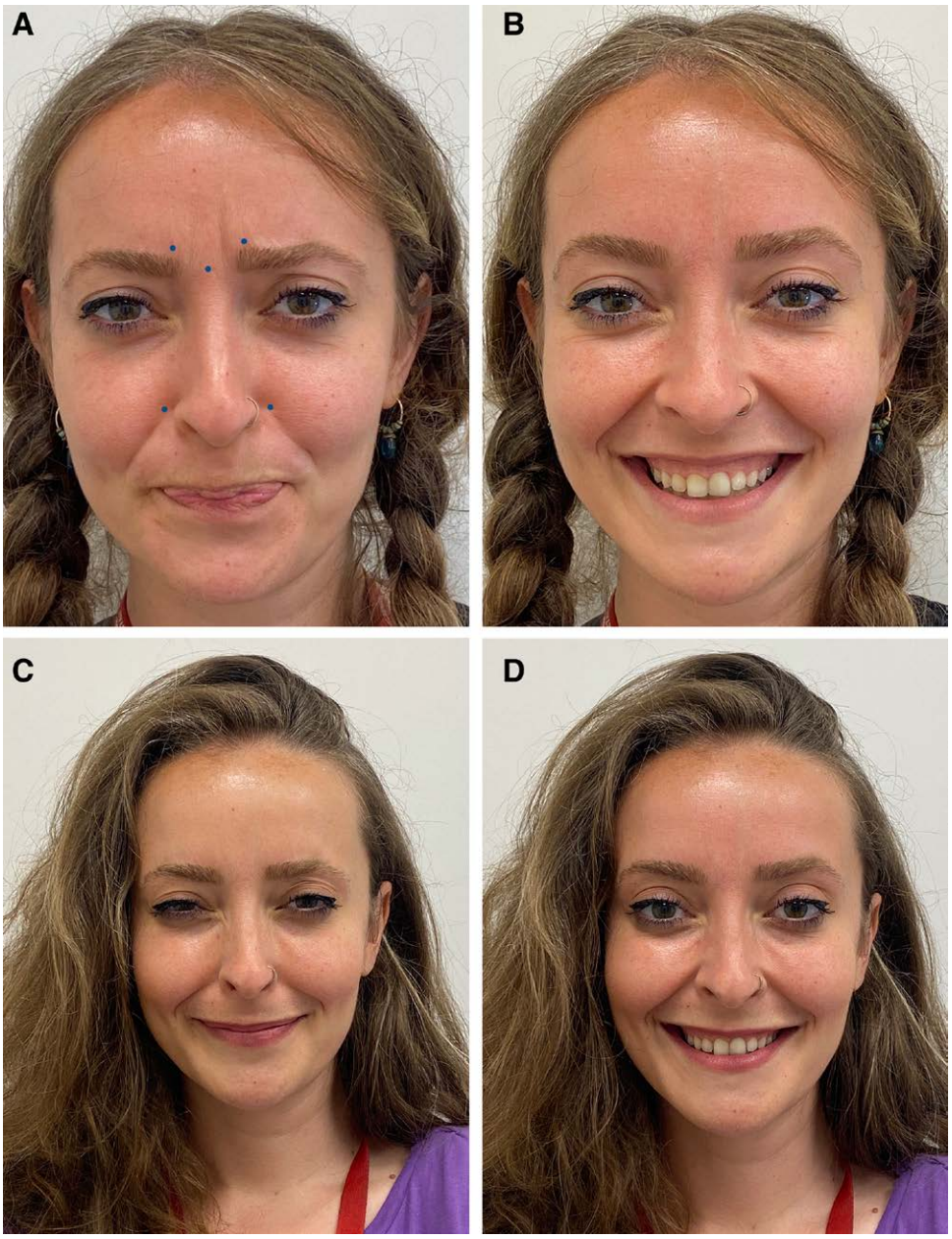

Fig. 5. Routine BoNT-A injections for a young patient. A, 30-year-old female patient with mild glabellar lines. Injection points have been marked with blue dots. B, Gummy smile deformity with forced smile. C, Glabella treated with 12 units of ONA toxin for a soft yet mobile result, 4 weeks postinjection. D, Gummy smile treated with two units of ONA toxin per side.

Yet, care must be taken to remember that loss of elasticity and muscle mass in much older patients can make toxin spread relatively easier, resulting in unwanted effects. A small amount of neuromodulator in the forehead of an older patient may induce significant brow ptosis due to the combined effect of inelastic skin, skin excess, and a weak frontalis muscle. This population can benefit from the precision of PRA toxin. It is also worth mentioning that many patients have compensatory lateral frontalis hyperactivity to elevate heavy eyebrows and injecting BoNT in the lateral forehead can cause brow ptosis (Table 2). Therefore a very detailed assessment must be conducted before injecting to determine such risk points and approach them cautiously during treatment.

Male Patients

Male patients usually have higher muscle bulk; therefore, higher units may be required to achieve complete chemodenervation and can benefit from the ABO halo. However, it must be taken into account that some men prefer to have continuous activity for a more inconspicuous effect, so a detailed evaluation is mandatory before

Table 2. Possible Side Effects of BoNT-A in the Face Due to Overdosage and Underdosage

	Overdosage
Upper face/midface	Ptosis of the eyebrow Ptosis of the eyelid Asymmetry Lower lid retraction Smile disruption/asymmetry Weakness in chewing Lip ptosis
Lower face	Smile disruption/asymmetry Oral motor insufficiency Impaired dental show Exaggerated jowling Dysphagia (during neck treatment)
	Underdosage
Upper face/midface	Insufficient chemodenervation Early loss of toxin effect Mephisto deformity of the brow (during lateral frontalis treatment) Unyielded expectations
Lower face	Insufficient chemodenervation Unyielded expectations

choosing the optimal toxin. [**See figure, Supplemental Digital Content 2**, which displays (A) a 34-year-old male patient with prominent dynamic forehead lines with contraction. Injection points have been marked with blue dots. (B) Frontalis treated with 42 units of ABO toxin, 7 weeks postinjection, **http://links.lww.com/PRSGO/C859**.]

PATIENT EXPECTATIONS

The last category and maybe one of the most important factors to consider while planning the optimal BoNT treatment for a patient is their expectations. Some patients want to have very natural results, even if it translates to a shorter duration. At this point, using lower doses and opting for PRA or ONA toxin can be more suitable. On the contrary, if patients want to have obvious results that last longer, utilizing higher units with ABO toxin can be better.[30] It is also important to reveal any unrealistic expectations that patients may have, as these have to be clarified, and treatment may need to be canceled if there is disconcordance with what is expected versus what can be achieved.[31]

DISCUSSION

The cosmetic utilization of BoNT-A is mainly guided by principles shared by all BoNT-A products along with specific properties that make each toxin unique. Awareness regarding the innovation and science behind different agents, along with the underlying anatomy, enables the injector to cater to patients' needs with a variety of treatment options.[32] Individualized assessment, personalized appropriate dosing, selection of the exact injection site, and clinical follow-up are critical to achieving optimal results.[33]

An expert panel recently published on the changes in patient population, similarities of and differences between the FDA-approved BoNT-A agents, evolving use of BoNT-A throughout the face, and how the approval of a new BoNT-A can affect clinical practice.[34] They reported that BoNT-A agents fall on a spectrum with regard to field of effect, with ABO toxin having a wider field of effect, and PRA toxin having a tight, precise field of effect compared to ONA toxin. This finding was in line with the author's personal experience, and the majority of indications were based on the similar effect of the halo spectrum. The report also mentioned that increased diffusion was not a detriment unless the toxin was injected midpupillary right on the brow, or in the perioral region. The study ultimately concluded that 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. The author agrees with the critical areas where diffusion may cause problems but also goes on to add other areas, including the masseter, the palm, and in certain cases that have been discussed, the forehead. The injector must not forget that different advantages offered by each toxin can also yield a limitation that should be taken into consideration when choosing the optimal toxin for specific indications.

The latest addition to the FDA-approved toxins list is the DAXI toxin. A current study reports a consistent duration of efficacy following DAXI treatment of cervical dystonia and glabellar lines.[35] This can be very powerful not only for patients functionally dependent on BoNT-A for therapeutic indications but also for patients with established notions of realistic expectations. The emergence of a new BoNT-A can ultimately provide doctors the opportunity to re-evaluate anatomic considerations and the evolving patient population. Getting experience with all FDA-approved agents steers the injector away from executing a "cookie cutter" treatment, which may be seen more frequently when only a single brand of toxin is used for all indications and patient types.

Although this article serves as an expert opinion on optimal choices of toxin for different patient and indication subgroups, it is meant to be a guide for injectors as they take into consideration not only the unique properties of toxins but also their individual patients. Experience will always be a key factor in optimizing toxin treatments, and each injector will ultimately tailor their treatment plans not only according to toxin choice but other factors as well, such as concentration and injection depth. It is important to emphasize that each of these toxins is effective at producing satisfactory results even though they may demonstrate structural differences. This is why adequate training remains a key factor, as the injector must have in-depth anatomical knowledge regarding three-dimensional musculature, the different facial layers as they pertain to injection depth, and also correct techniques. Choosing the optimal toxin can be compared to choosing the optimal soft tissue filler for different anatomical areas, ethnicities, genders, and expectations. A "one size fits all" mentality cannot produce the best result for every patient in every area. Although each toxin can be safely utilized for each indication in the hands of the expert injector, adjusting toxin usage in different anatomical sites, patient groups, and patient expectations can yield more optimal effects by creating a tailored neurotoxin treatment plan.

CONCLUSIONS

Why is producing the best possible result so important when merely satisfactory results can be achieved much more easily? Because building the foundation for trust between doctor and patient begins with primary encounters which, considering the frequency of treatments, are often times toxin injections. This initial relationship can become much stronger when patients are able to have their expectations met with minimal side effects. Such patients later upgrade to further treatments and surgery and also become reference points. This is what the author implies through the saying "it all starts with a drop of neurotoxin" because many patients primarily recruited from toxins form an established trust towards their physician for years to come.

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DISCLOSURES

Dr Sezgin is an international key opinion leader for Teoxane. She has previously spoken for Dysport and Nabota at scientific events held in Turkey.

PATIENT CONSENT

Patients provided written consent for the use of their images.

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