Supplement Article

The Practical Use of AbobotulinumtoxinA in Aesthetics

Michael A. C. Kane, MD; and Gary Monheit, MD

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Abstract

Botulinum toxin (BoNT) has been approved for aesthetic use since 2002. Since then, clinical studies and expert use have informed our understanding of how BoNT exerts its clinical effect and the practical use of this product across a number of aesthetic applications. This review discusses the clinical properties and characteristics of abobotulinumtoxinA, which patients are suitable for its use, and how it can be utilized to treat facial rhytides.

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Botulinum toxin (BoNT) has been in use since the 1970s.[1] Following its first use in strabismus,[2] and several difficult-to-treat neurological diseases,[3] BoNT has formed the foundation of minimally invasive aesthetic facial treatments. BoNT was initially used to smooth glabellar frown lines and its utility then expanded to include other facial areas.[4-8] BoNT is also used in combination with other minimally invasive agents and procedures.[9] In 1992, the first published aesthetic study on BoNT established that BoNT type A (BoNT-A) could be safely and effectively used to diminish the appearance of glabellar lines.[10] Large-scale, randomized controlled trials documenting the safety and efficacy of BoNT-A led to approval by the United States Food and Drug Administration (FDA) for cosmetic use in 2002.[11] BoNT-A is a safe and effective therapeutic treatment modality for several clinical conditions.[1] Three preparations of BoNT-A are commercially available and approved for use in the United States by the FDA—abobotulinumtoxinA (ABO; Dysport, Ipsen Biopharm Limited, Wrexham UK/Galderma LP, Fort Worth, TX), incobotulinumtoxinA (INCO; Xeomin, Merz, Frankfurt, Germany), and onabotulinumtoxinA (ONA; Botox, Allergan, Irvine, CA).[1] Each of these preparations is unique, as are the assays which determine their potency units, and consequently the units are not interchangeable.[12,13] Injection techniques and patterns have evolved, resulting in a more natural result and avoiding a "frozen" appearance, which relies not only on expert use but on an appreciation of the 3-dimensional structure of the face.[14] Practical recommendations for aesthetic use are available in addition to consensus papers and presentations at medical meetings;[15] these form the basis for the clinical recommendations in this paper.

The clinical effect of BoNT-A is a result of a highly specific, but reversible, blocking of presynaptic neurotransmitter (acetylcholine).[1,16] Toxin heavy chain-mediated binding to specific surface receptors on nerve endings, internalization

Dr Kane is a plastic surgeon in private practice in New York, NY. Dr Monheit is a Dermatologist, Departments of Dermatology and Ophthalmology, University of Alabama at Birmingham, Birmingham, AL.

Corresponding Author:
Dr Michael A. C. Kane, 115 East 67th Street, New York, NY 10065, USA.
E-mail: michaelkanemd@earthlink.net

of the toxin by receptor-mediated endocytosis, pH-related translocation of the toxin light chain to the cell cytosol, and cleavage of SNAP25 (25 kDa synaptosomal associated protein) lead to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction.[17] The recovery of neuronal activity has been attributed to 2 phenomena:[1,18] active axonal sprout development in response to growth factor secretion from denervated muscle that results in temporary reinnervation in the early recovery phase, and reestablished vesicular neurotransmitter release in the original nerve terminal in the later phase of recovery.

Although many current uses are considered "off-label," the widespread acceptance and favorable safety profile of botulinum toxins have made them some of the most common aesthetic treatments available.[19] A large-scale, retrospective, cross-sectional patient chart review (945 patients and 4103 treatment cycles) revealed that the majority of patients (81.5%; $n = 770$) received treatment in more than 1 area of the face.[20] The glabella was the most frequently treated area in 93.9% ($n = 887$) of patients, with treatment in the glabella, frontalis, and lateral periorbital region in 30.7% ($n = 290$); in the glabella and frontalis in 17.6% ($n = 166$); in the glabella and lateral periorbital areas in 15.6% ($n = 147$); and in the glabella alone in just 14.6% ($n = 138$) of patients.[20] Other areas of the face (16.8%), and non-facial locations (platysma, décolleté, axillary hyperhidrosis) are less frequently treated (3.0%) with botulinum toxins.[20]

ABOBOTULINUMTOXINA PROPERTIES AND CHARACTERISTICS

A summary of the properties and characteristics of ABO is presented in Table 1.[21-23]

Table 1. Properties and Characteristics of AbobotulinumtoxinA[21-23]

Active substance	AbobotulinumtoxinA	
Presentation	Single-use, sterile vial for reconstitution intended for intramuscular injection	
Mode of action	SNAP25	
Units per vial (United States)	300 U (500 U vial is also available but reserved for therapeutic use only)*	
Reconstitution	0.9% NaCl without preservative per 300 Unit vial	Resulting Dose Units per 0.1 mL
	1.5	20
	2.5	12
	3.0	10
Excipients	Human serum albumin, lactose	
Storage before dilution	2-8°C	
Storage after dilution	24 hours/2-8°C	

NaCl, sodium chloride; SNAP25, 25 kDa synaptosomal associated protein. *Also 125 units Azzalure in the EU only.

A single-use sterile 300 U vial of ABO is reconstituted with 1.5 mL, 2.5 mL, or 3.0 mL of 0.9% sodium chloride (NaCl) injection USP without preservative.[21-23] However, experienced clinicians tend to be guided by each patient's individual facial anatomy, pattern of muscle activity, muscle mass, and treatment objectives rather than simply following preset templates for the dosages and injection sites of BoNT-A. The earlier agreed dose ratio between ABO and ONA in aesthetic clinical practice is 2:1 to 4:1 but is now more likely to be 2:1 to 2.5:1.[24-27]

Diffusion

Diffusion of BoNT-A always occurs. The product has to diffuse to hit the target receptors, but the extent and clinical importance of this process has been disputed.[16] Pickett has suggested that there has been confusion regarding the extent and clinical relevance of diffusion among the different BoNT-A preparations.[28] This can be attributed to incorrect extrapolations of information obtained from animal studies to the clinical setting, the inappropriate testing of products with different dose ratios, the incorrect suggestion that products with larger complex molecular size migrate less, and, in some cases, poor study design. It is therefore important to be clear on terminology. For example, spread is defined as the physical movement of toxin from the original site of injection (caused by factors such as volume of injection), whereas diffusion is defined as the dispersion of toxin (from a higher to a lower concentration) beyond the original site of injection (toward receptors). Spread is fast and active, but diffusion is slow and passive. Today, the effect of dose on diffusion is considered to be the key issue, and clear equivalence of results between different BoNT-A products has been obtained when the doses, not the units, are equal; the units of each product are specific to that product family and are not interchangeable between BoNT-A preparations.[27]

Physicians must have a working knowledge of the different serotypes, different doses used for each formulation of each serotype, and the adverse event profile of each product in order to ensure against spread- and diffusion-related adverse events.[16,29,30] A number of factors can influence comparative data on efficacy, diffusion, and spread, including properties intrinsic to the drug used, appropriate target selection, and the dilution, volume, and doses injected.[10,13,16,27] Careful injection of the toxin using the recommended dose exactly targeted to the right nerve endings of the muscle offers the best chance of producing a predictable and precise treatment effect.[16]

The adverse effects associated with BoNT are generally of 3 types: those related to expected effects of the neurotoxin (eg, excessive local muscle weakness), those related to clinical spread of the neurotoxin to nearby uninjected muscles, and those resulting from systemic distribution of the toxin.[29] Diffusion of BoNT beyond the target muscle is of clinical concern because of the potential for effects that result in muscle weakening away from the desired site.[29]

Neither molecular weight nor the presence of complexing proteins appear to affect diffusion and therefore are not related to any side-effects away from the desired side.[31]

PATIENT SUITABILITY

As with any medical procedure, informed consent should be obtained from the patient, and any medications that interfere with hemostasis should ideally be discontinued 7 to 10 days prior to the procedure in order to minimize bruising.[19] The clinician is responsible for understanding each patient's unique needs, goals, and expectations.[32] This responsibility has been emphasized in several consensus recommendations.[22,33-35]

Some patients may not be suitable candidates for specific aesthetic procedures, because of either medical or psychological factors.[21,36] This group includes patients who are psychologically unstable or who have unrealistic reasons and goals, those afflicted with a neuromuscular disorder (eg, myasthenia gravis, Lambert-Eaton myasthenic syndrome), and those taking certain medications that can interfere with neuromuscular transmission and amplify the effects of BoNT-A (eg, aminoglycosides, penicillamine, quinine, and calcium channel blockers). Specific contraindications include the presence of infection at the proposed site of injection, hypersensitivity to any ingredient in the formulation, and pregnancy.[21]

Patients should be informed that only dynamic rhytides are likely to improve, and that deep, static rhytides resulting from actinic damage or chronological aging may not see improvement.[36] To assess the treatment outcome, a follow-up appointment at about 3 to 6 weeks after the initial injection is recommended.[22]

PRACTICAL ASPECTS OF ABOBOTULINUMTOXINA AESTHETIC USE

General Injection Technique and Advice Postinjection

Injection technique tends to be personal and based on clinical experience. However, some useful guidance has been published and is presented below. A facial muscle map is presented in Figure 1.

For injection, patients should be seated and reclined approximately 60 to 90 degrees, with the chair height such that the patient's head is at shoulder level with the injector.[34] This allows the patient to relax and lie back, and stabilizes their head for injection. In most cases, injections should be done perpendicular to the skin and intramuscularly.[36] However, each patient will require individualized injection patterns.[36]

All patients have slight facial asymmetry at baseline, which should be recorded and accounted for when deciding where to inject and also how much product to inject.[36]

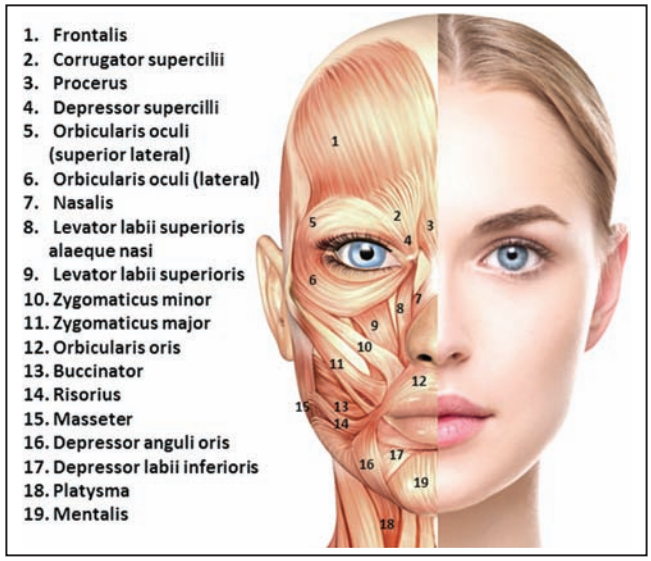

Figure 1. Facial muscle map (to be used merely as guidance for novice injectors).

To evaluate treatment outcomes, "before" photographs can be used as a comparison.[22,36,37]

A 3 cc syringe is frequently used to introduce the diluent using a large bore needle (16-25 gauge), while minimizing bubbling and agitation by gentle rotation of the vial.[38] For patient injection, an insulin syringe (BD Ultrafine II 0.3 cc; Becton, Dickinson and Company, Franklin Lakes NJ) with a short 30 gauge needle is usually employed.[38] Patients are advised not to lie down, do exercise, or massage the treated area during the first 4 hours after the procedure.[39,40]

Common Upper Face Areas

In the upper face, BoNT-A is most commonly used to eliminate or diminish glabellar rhytides (procerus and corrugator muscles), forehead rhytides (frontalis muscle), and periorbital rhytides or crow's feet (lateral orbicularis oculi muscle).[1] In all cases, extreme caution should be taken with injections within the orbital rim (Figure 2).[19]

For glabellar rhytides, ABO has been successfully administered in 3 to 5 deep intramuscular and perpendicular injections in a V-shaped pattern 0.5 to 1 cm from the upper orbital rim and internal to the midpupillary lines.[22,23]

For forehead rhytides, treatment is highly variable because of the anatomic variability of the frontalis muscle and characteristics of each patient's animation patterns.[19,42,43] ABO is usually administered in 4 to 10 superficial intramuscular and perpendicular injections in a horizontal or V-shaped pattern under the hairline (Figure 2).[19,22,41]

For periorbital rhytides, ABO is usually administered in 2 to 6 superficial intradermal injections placed 1 cm lateral to the orbital rim at 3 sites overlying the lateral fibers of the orbicularis oculi muscle, avoiding injecting the zygomaticus

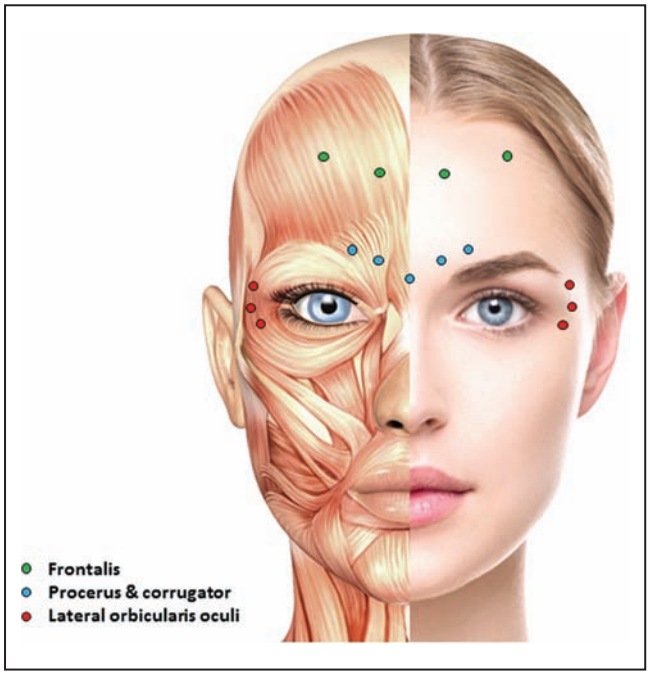

Figure 2. Common upper face injection areas (to be used merely as guidance for novice injectors).

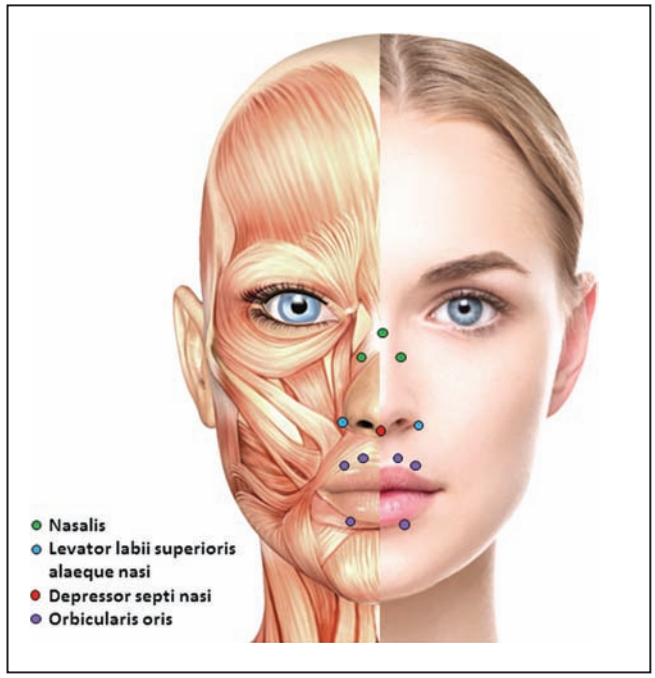

Figure 3. Common midface injection areas (to be used merely as guidance for novice injectors).

muscle (Figure 3).[22,32,44] In a comparison of 1 and 3 injection points, efficacy was shown to be equivalent.[45]

A summary of the total doses for each region of the upper face is provided in Table 2.[22,23,33,35,42,46-48]

Most adverse effects of aesthetic applications of BoNT-A are mild and transient.[1,20,22] The majority of adverse effects in the upper face include bruising, edema, headache, nasopharyngitis, or pain at the injection site, and possibly flu-like symptoms.[1,20,38] More serious adverse effects in the upper face include blepharoptosis (2.5%), brow ptosis (3%), and eye sensory disorders (3%) from extraocular muscle weakness, all of which tend to spontaneously resolve.[1,20] The reported incidence of ptosis in clinical trials is low, and variability may be caused by the percentage of patients with this condition on entry.[49] The risk of ptosis can be identified before injection by careful examination of the upper lid for separation or weakness of the levator palpebrae muscle (true ptosis), identification of lid ptosis, and evaluation of the range of lid excursion while manually depressing the frontalis to assess frontalis compensation.[49] Evaluation of patients before application of ABO should mitigate the risk of new ptosis events.[49]

Common Lower Face Areas

The use of BoNT-A for lower face areas requires more skill and lower doses than the upper face because of the potential for adverse effects involving the mouth.[38] BoNT-A is used to treat perioral lip rhytides (orbicularis oris, depressor anguli oris, and mentalis muscles) (Figures 3 and 4).[1,22,33-35] There is no consensus on whether or not injection should be limited to the upper lip or include the entire area of the muscle.[19] Injections in the perioral region are generally given in small amounts, for example, 1 to 3 U per point, 4 to 12 U ABO total, within 5 mm of the vermilion border, at least 1.5 cm from the corners of the mouth.[1,33,35] These are usually superficial intramuscular injections administered perpendicular to the skin at a maximum of 6 points around the lip; 2 to 4 points in the upper lip, 2 points in the lower lip.[33,35] A recent study using a total of 15 U ABO in the perioral region showed that excessive weakness is a common adverse event at high doses, present in 75.0% of patients treated with this dose, but was less prevalent (26.3%) in those patients injected with a lower dose (10 U ABO).[47] The oral commissures (depressor anguli oris muscles) can also be treated with BoNT-A, with 1 injection given on each side directly into the depressor anguli oris muscle overlying the mandibular body (Figure 4).[1,13,24-26] Injections in the midline, directly into the mental fold, or in close proximity to the mouth should be avoided.[50]

A summary of the total doses for each region of the lower face is provided in Table 2.[1,22,33,35,46,48]

Treatment-related adverse events in the lower face have been reported in about 7% of patients, all of which spontaneously resolve.[20] The risk of dysarthria and oral incompetence should be discussed with the patient prior to administration in the lower face.[50]

Other Areas

Lowered nasal tip can occur with aging due to contraction of the depressor septi nasi muscle (Figure 3).[46] This can be

Table 2. Total Doses of AbobotulinumtoxinA for Treatment of the Upper and Lower Face[1,17,22,23,33,35,44,46-48]

Indication	Total dose of abobotulinumtoxinA, U
Glabellar lines	30-80
Forehead rhytides	20-60
Periorbital rhytides	20-60
Perioral lip lines	2.5-15
Marionette lines	4-25

treated with a single-site injection just below the nose tip in the columella.[46]

Nasalis fanning rhytides (also referred to as bunny lines) occur as a result of contraction of the transverse portion of the nasalis muscle as well as the lower medial orbicularis muscle (Figure 3).[32,38] These can be treated with a single midline injection high on the nasal dorsum or 2 injections on the lateral aspect of the nasal wall above the nasofacial groove.[19,32,36] Injection sites are generally kept high on the nose and superficial in order to avoid excessive paralysis of the deeper and more inferior levator labii superioris and levator labii alaeque nasi, which are important elevators of the upper lip (Figure 3). Excessive chemodenervation of these muscles may lead to upper lip ptosis.[19]

Nasolabial folds can result in a "gummy smile," where all incisors and some of the gingivae show when smiling. Based on data available in the literature, the levator labii superioris alaeque nasi (llsan) muscle should be considered as the key component for treatment.[39,51-53] with other targets including the levator labii superioris, the zygomaticus major, and the zygomaticus minor. The injection techniques depend on the format of the condition, with 4 types being identified. Treatment has been well described in the literature (Figures 1 and 3).[36,39,50,52]

Labio-mental rhytides (also referred to as marionette lines) are a result of drooping mouth corners partially due to contraction of the depressor anguli oris muscle, which can give the face a sad expression.[33] These have been successfully treated by bilateral injections into the corners of the mouth (depressor anguli oris) above the mandibular angle of the nasolabial groove (Figure 4).[54]

An asymmetric smile can be caused by spasm of the ipsilateral depressor labii inferioris muscle of the lower lip or segmental weakness of the levator labii superioris muscle.[32,55] The number of injection points and total dose should be decided on an individual patient basis.[32]

A dimpled chin is caused by the contraction of the mentalis muscle, and regional loss of collagen and subcutaneous fat.[54] This has been successfully treated with 2 injection points into the mentalis muscle, close to the mandibular bone to avoid asymmetry or lower lip ptosis.[1,32,33]

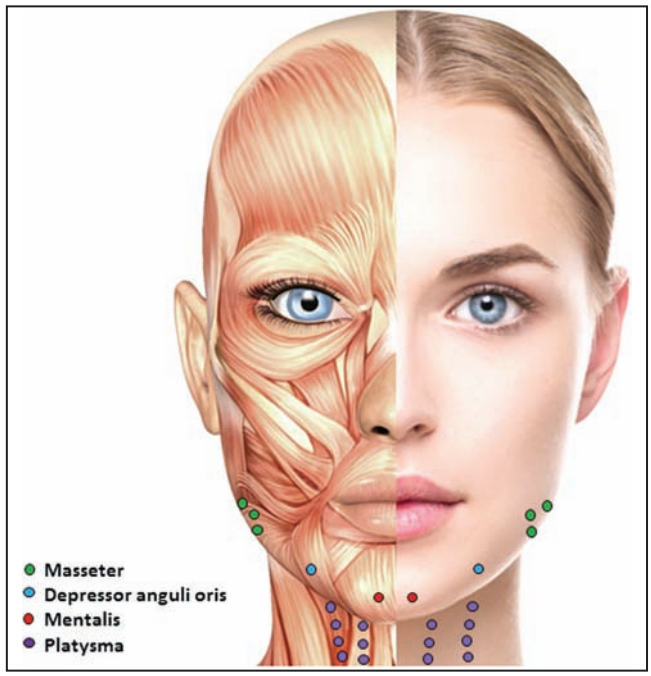

Figure 4. Common lower face injection areas (to be used merely as guidance for novice injectors).

Doses should generally be injected deep into the target muscle because of the reasonable amount of fat that exists in the chin area.[36] ABO can be given at 2 injection sites in a paramedian position (5 mm lateral to the midline) overlying the inferior mandibular border.[36]

In patients being treated for a dimpled chin, clinicians should avoid injecting too far laterally into the depressor anguli oris muscle or too far superiorly into the orbicularis oris muscle, as this can lead to oral incompetence and a drooping mouth.[36]

Masseter hypertrophy (enlargement) has also been extensively treated with BoNT-A injections despite being an off-label indication.[56] Injection into the masseter muscle to alter the shape of the jawline is a popular application in patients of Eastern Asian descent.[1] ABO can be used on each side, and is usually administered at 1 to 3 injection sites (Figure 4).[1,56] Interestingly, there appears to be significant variation in the dosing of patients depending on their ethnicity; a study in Asian patients reported using 100 to 140 U per side, whereas in Caucasians, a lower dose of 30 U per side is more commonly reported.[33]

Mastication difficulty, muscle pain, dysarthria, and awkwardness with smiling have been reported in patients treated for masseter hypertrophy.[1,56]

In the neck, BoNT-A may be used to treat platysmal bands, particularly in older patients who are not good candidates for surgery, in those who do not want surgery, or in younger patients who are not candidates for cervicofacial rhytidectomies.[57,58] Ideal patients for this indication should

Table 3. Total Doses of AbobotulinumtoxinA for Treatment of Other Areas[1,22,32,33,35,36,46-48,50,56]

Indication	Total dose of abobotulinumtoxinA, U
Nasal tip	5-10
Bunny lines	10-20
Gummy smile	5-15
Asymmetric smile	Individually assessed
Dimpled chin	10-20
Masseter hypertrophy	30-90
Platysmal bands	30-100

have thin skin in the neck (little or no fat) and good skin elasticity.[33] Patients should forcefully contract their necks by clenching their teeth. Each band can then be grasped individually, and held firmly between the thumb and index fingers.[36] Direct injections into the bands are administered at 4 to 12 sites at 1 to 2 cm intervals from the jaw line to at least the middle of the bands, up to a maximum dose of 50 U per side.[19,33,35,41] It is recommended that these injections are superficially intramuscular with the needle held at 30° to avoid deep injection, particularly in the anterior area.[33-35]

Injection into the strap muscles when treating platysmal bands must be avoided as dysphagia, dysphonia, and neck weakness may occur.[50]

A summary of the total doses for other areas of the face and neck is provided in Table 3.[1,22,32,33,35,36,46-48,50,56]

This paper highlights the wide dose ranges currently being used in clinical practice (Tables 2 and 3). A key factor influencing dose is the provision of individualized therapy; depending on gender, muscle mass and strength, wrinkle severity, elasticity, areas to be treated, and the desired degree and duration of effect.[22,23,33,35,48,50] There also appears to be a tendency to use conservative dosing in areas that are either deemed higher risk or where there are limited dose-finding studies available, with a preference to conduct further treatments at a later date if required.[22,35,50] Recently there has also been a trend for reducing dosing in certain areas of the face (for example the forehead) reflecting the current patient preference for a more natural look.[46]

CONCLUSION

ABO is used to treat a range of facial rhytides. Its effective and safe use requires a comprehensive understanding of facial anatomy, practical experience regarding which patients are suitable for treatment, as well as appropriate injection technique, location, and dosage for the areas being treated.

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