Chapter

Botulinum Toxin for the Face

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Abstract

Botulinum toxin is a corner stone in the facial esthetics. It has been used for decades for various medical and esthetic indications. Botulinum toxin is a neurotoxin that interferes with the transmission at the neuromuscular/neurosecretory junctions by inhibiting the release of acetylcholine. An in depth knowledge of the functional anatomy of facial muscles is required to obtain the best results of the botulinum toxin injections. In this book chapter, a detailed practical guide for the FDA approved and the off label uses of botulinum toxin in the face is presented. The recently developed new indications are listed. The lengthy experience with botulinum toxin injections has proved safety and tolerability of the procedure; however, the probable complications, and steps for their prevention and management are highlighted.

Keywords: Botulinum toxin, facial esthetics, Crow's feet, anti-aging, forehead lines

Botulinum toxin (BTXN) is an exotoxin produced by the anaerobic, Gram positive, spore forming bacteria; *Clostridium botulinum*. There are seven serotypes A-G. A and B serotypes are the ones currently used commercially. The toxin is 150 kDa polypeptide, formed of heavy chain and light chain bound by heat sensitive disulfide bonds and noncovalent forces. The toxin may be formulated in a simple - free from proteins - form e.g. incobotulinum or complexed with proteins as hemagglutinin and "nontoxic molecule" to form onabotulinum toxin and abobotulinum toxin [1, 2]. It is essential to keep in mind that the different types of the toxin are not similar in their biological effects and potencies [1]. The currently available formulations are unique, so their doses are not interchangeable, and the dose response curves are probably not parallel [3].

1. Mechanism of action

It inhibits the release of acetylcholine (ACh) from nerve endings via cleavage of SNARE protein complex responsible for ACh release. Thus it affects the presynaptic nerve endings at the neuromuscular junction (NMJ) causing muscle paralysis (main site of action) [1], and the cholinergic postganglionic autonomic nerve fibers innervating the eccrine, salivary and tear exocrine glands (neurosecretory junction) [2, 4]. This inhibition is reversible within variable periods of time via the regeneration of synaptic junctions [1, 4].

Indications:

Despite being widely used for multiple indications, botulinum toxin's FDA approved indications are limited **Table 1**.

The indications of BTXN in the face is summarized in **Table 2**.

	Forehead lines/ Cosmetic	Other^
Onabotulinumtoxin (Botox)	Yes	Cervical dystonia, severe primary axillary hyperhidrosis, strabismus, blepharospasm
Abobotulinumtoxin (Dysport)	Yes	Cervical dystonia, blepharospasm
Incobotulinumtoxin (Xeomin)	Yes	Cervical dystonia, blepharospasm
Rimabotulinumtoxin #(Myobloc)	No	Cervical dystonia, blepharospasm

^*Upper limb spasticity, chronic migraine, overactive bladder and urinary incontinence.*

Table 1.
FDA approved indications of botulinum toxin.

Indications	Responsible muscles	Unites and Technique
Upper Face		
Glabella lines (**Figure 1**)	**Procerus** **Corrugator** supercilii Depressor supercilii Orbicularis oculi	**Procerus:** Intramuscular, single injection point, perpendicular to the skin, 2–4 U [3] **Corrugator:** Intramuscular 1–3 injection points at each side, First injection point 0.5–1 cm above the medial orbital rim, 2nd injection point 1 cm above and lateral to 1st injection point, 2–4 U/ point [3]
Lateral canthal lines (Crow's feet) (**Figure 2**)	**Orbicularis** oculi	Intradermal or SC injection of the lateral muscle fibers, 3 injection points 1–2 cm lateral to the orbital rim, 2–5 U/ point, total dose is 6–15 U [3, 5].
Forehead Lines[1] (**Figure 3**)	**Frontalis**	The target is to only soften, not to completely eliminate, forehead lines; the patient ideally can still elevate the eyebrows to a lesser extent than prior to treatment [1, 3, 6]. Intramuscular or intradermal (especially near eyebrow), 4–8 injection points in 1–2 rows, start injection with the upper lateral fibers to the mid forehead inferiorly (stop 2 cm above the brow), 2–4 U/point, total 8–25 U [6]. For narrow forehead less injection points and lower doses are used. To maintain neutral brow position and arch the corrugator supercilii, procerus and superiolateral fibers of orbicularis oculi are treated at the same time or a few days before frontalis injection [1, 3].
Bunny lines (Nasal oblique lines)	**Nasalis (upper fibers)**	Intramuscular, 2–3 injection points, 2 U/point [3].
Gummy smile[2]	**Levator labii superioris alaeque nasi**	Intramuscular (at the site of levator labii superioris alaeque nasi and zygomaticus minor convergence with the insertion of levator labii superioris, 1–2 injection points, 0.5–2 U/ point [3]
Lower Face		
Perioral rhytides (smokers' lines)	**Orbicularis oris**	BTXN injection is recommended for deep rhytides, superficial ones need either resurfacing or hyaluronic fillers Intradermal, 2–5 injection points, 0.5–1 U/ point [3, 6].
Marionette lines	**Depressor anguli oris**	Intramuscular, 1–2 points/ side, 2–3 U/ injection point. The main injection point is the posterior aspect of the depressor anguli oris muscle at the superior margin of the mandible, and at least 1 cm lateral to the oral commissure [3, 6].

Indications	Responsible muscles	Unites and Technique
Mentalis overactivity	**Mentalis muscle**	Intramuscular, 1–4 injection points 3–5 U/ point.
Masseter overactivity (square jaw) / bruxism	**Masseter muscle**	Intramuscular, 1–6 injection points/ side, 5–15 U/injection. Average of 3 points are injected at the center of the masseter square at least 1.5 cm from the mandibular border [7], one superiorly and 2 inferior and laterally. Caucasians tends to need lower doses than Asians with longer periods of effect. The injection is to be directed at the posterolateral corner [6, 8, 9].
Platysmal bands	**Platysma**	Only for patients with obvious platysmal bands, and good cervical skin elasticity with no or minimal submental fat [6]. Intramuscular or deep intracutaneous, typically 2 bands are injected at a time with 3 points of injection in each band, 1–1.5 cm apart, 1–5 U/ injection point, total 15 U/ band and 30 U/ session [3, 6]. For horizontal neck folds: Superficial intradermal, 1–2 U/ point equidistantly in the folds.
Facial asymmetry Caused by Bell's palsy		The contralateral active side is injected using small doses (1–2 U) of Ona BTXN into muscles of the normally functioning side (the zygomaticus, risorius and orbicularis oris muscles) and 5–10 U into the masseter muscle [6, 10]. For post Bell's palsy synkinesis the paralyzed side is injected either as four periocular injections or into the affected muscles as orbicularis oculi, orbicularis oris and frontalis using the total dose of 10–40 units [10, 11].
Acne and Sebum production		Excess sebum production: Few reports of BTXN use as intradermal (1 cm apart forehead and check) or intramuscular injection (five fixed points in the forehead) in the forehead for management of excess sebum production 2 U/injection site [12]. Acne: one clinical trial has been registered using 1.5–3 U/ active lesions. The trial has been terminated with no published reports on the results [13]
Gustatory sweating (Frey syndrome)		Intracutaneous injections of 4 U /cm^2 [14]

Muscles written in bold *are the injected muscles. Facial musculature varies between males and females, with increased strength and bulk in men. Thus, higher doses and increased number of injection points are generally required in men in all regions of the face [5].*
[1]*Brow position is lowered with age "brow ptosis". Glabellar complex injection (20–40 U) lead to immediate lateral eyebrow elevation, followed by an entire brow lift that peaked 12 weeks post treatment. This effect is due to the toxin diffusion into the lower medial frontalis muscle fibers with subsequent increased tone in the upper and lateral frontalis fibers. Forehead lines is recommended to be done simultaneously with brow lift to maintain a neutral position for the eye brow [6].*
[2]*Exposure of ≥2 mm of the gingiva on smiling [8]. Done for younger patients with strong lip elevator complex [6].*
[3]*Youthful face is a heart shape with fullness in the upper part and tapering toward the mandible [1]. It is essential to exclude parotid gland hypertrophy either primary or secondary to pathology as Sjögren syndrome or bulimia nervosa or parotid gland mass using clinical assessment and CT imaging, or volume loss related masseteric prominence [3, 15].*

Table 2.
Botulinum toxin neuromuscular indications in the face.

2. Storage and reconstitution

The various BTXN products are supplied as lyophilized powder containing vials except for rimabotulinumtoxin which is supplied in a liquid form [1].

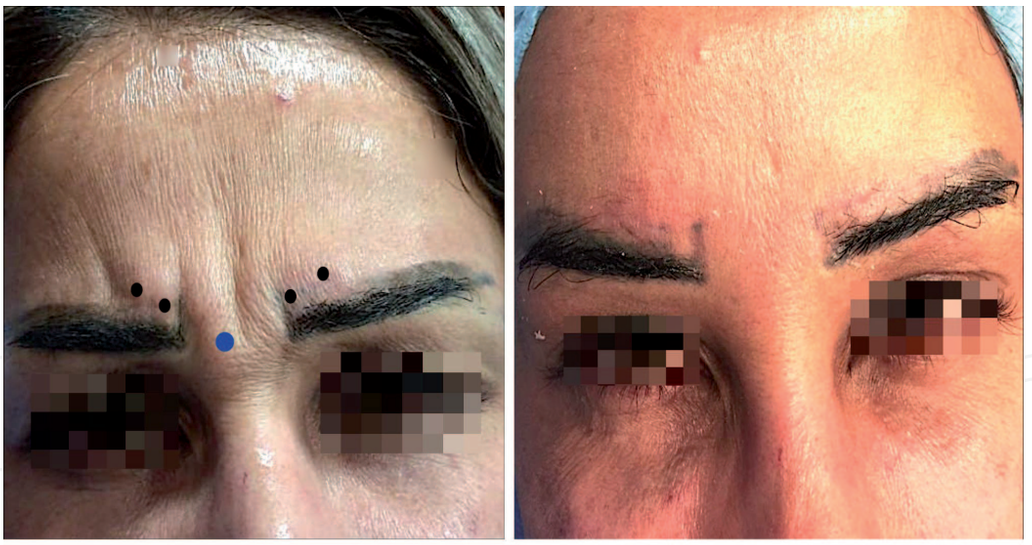

Figure 1.
Glabellar complex injection. (a) before: ***Procerus*** *(blue dot) single intramuscular perpendicular to the skin, 2–4 U,* ***corrugators*** **(***black dots***):** *2 intramuscular injection points 2–4 U/point; first injection point 0.5–1 cm above the medial orbital rim, 2nd injection point 1 cm above and lateral to 1st injection point. (b) after.*

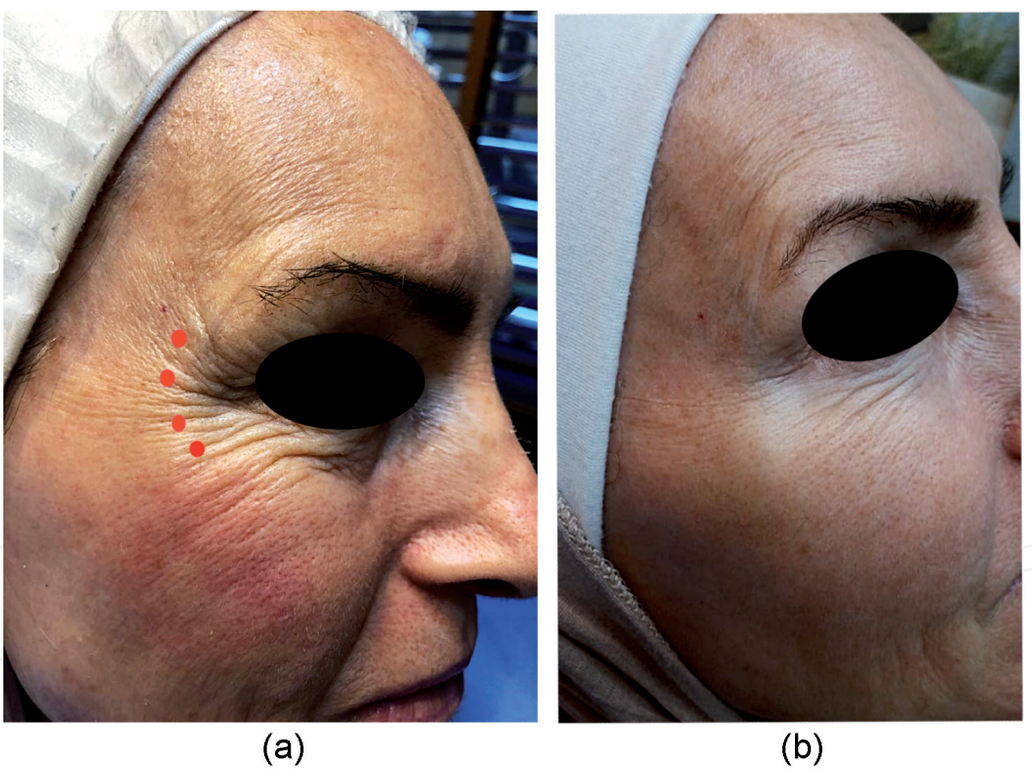

Figure 2.
Lateral Canthal lines injections. (a) before: 3 intradermal injection points 1–2 cm lateral to the orbital rim 2–5 U/ point. (b) After.

To reconstitute the powdered BTXN, a non- preserved saline, preserved (bacteriostatic) saline or lidocaine can be used as a diluent agent, the laters are associated with less pain on injection [1, 4].

The reconstituted vial can be used for up to 4 weeks safely if kept frozen at –20°C or refrigerated at 4°C [1, 4].

A single vial can be used for multiple patients, as long as there is safe and sterile reconstitution and injection techniques are followed [1, 16].

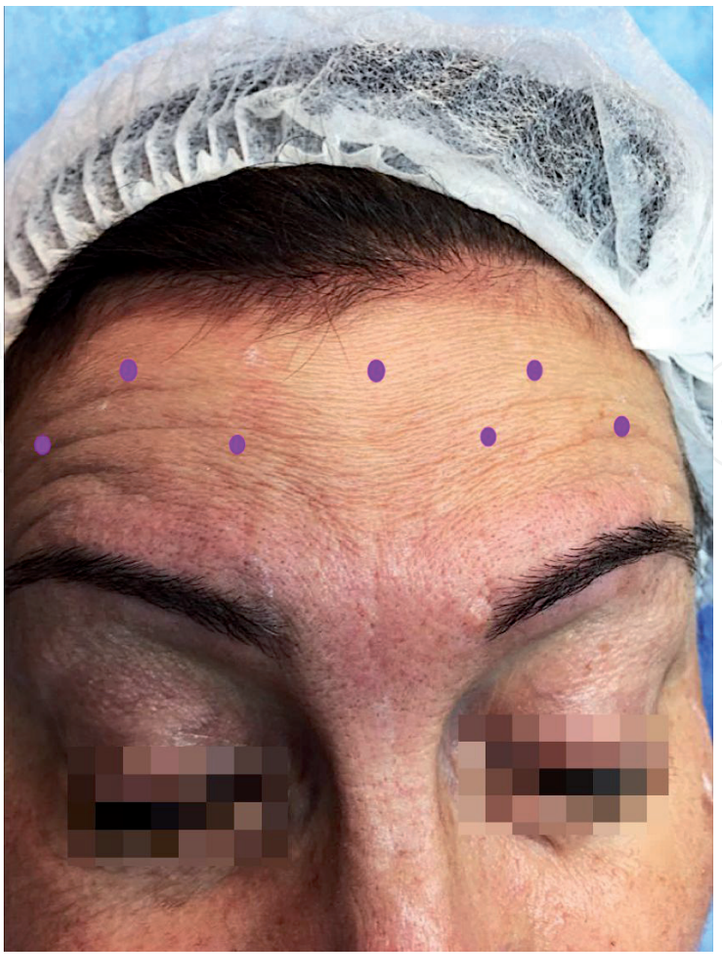

Figure 3.
Forehead lines injection. 4–8 intramuscular - intradermal near eyebrow - injection points in 2 rows, starting with the upper lateral fibers (stop 2 cm above the brow), 2–4 U/point.

There are variable methods for BTXN reconstitution. 100 U vial of onabotulinum A is commonly reconstituted in 2 cc of the diluent, which means there is 5 U/0.1 cc. 500 U of abobotulinum toxin A is diluted in 2.5 cc of the diluent so that there is 20 U/0.1 cc [7].

3. Clinical considerations

3.1 Pretreatment assessment

The key to successful intervention is tailoring the treatment plan to every patient's need and combining different procedures to achieve best outcome [3]. Combination with hyaluronic acid fillers is increasingly utilized to optimize outcomes. The combined treatment with fillers can be considered for all regions, including the upper face [16].

For esthetic indications, the current trend accepted by both patients and physicians is to use BTXN in the least effective dose, injection points, and at longer intervals to achieve muscle activity modulation rather than muscle paralysis [3].

Assessment of the muscles should be performed at rest and at maximum muscle contraction [5].

Muscular and bony landmarks are to be used to identify the injection points [3].

It is recommended to discuss with the patients the black box warning and to document consent [8].

3.2 Pretreatment preparation

1. Removal of makeup

2. Thorough skin cleansing using 70% alcohol before, during, and after injection

3. Topical anesthesia can be used to minimize the pain.

4. Sterile injection technique using 1 ml 30 gauge needle.

3.3 Post treatment instructions and care

1. Ask the patient to frown and smile repeatedly for 30 minutes following injection to minimize the diffusion outside the injected muscles.

2. Avoid massaging the treated areas within 3 hours after injection to minimize diffusion to other non-injected muscles

3. For upper face, avoid bending over or strenuous physical activity (controversial), lying down or sleeping for 3 hours following the injections.

Contraindication [8, 17]:

1. Infection at site of injection.

2. Known hypersensitivity reaction to any of the ingredients (toxin or human albumin).

3. Preexisting inflammatory skin condition at site of injection e.g. acne, contact dermatitis, atopic dermatitis and psoriasis.

4. Pregnancy (reports of premature delivery no causal relationship was proven) or lactation, it is categorized as C drug

5. Neuromuscular disease or patients with preexisting difficulties in swallowing or breathing e.g. myathenia gravis, amyotrophic lateral sclerosis and myopathies. Those patients are more predisposed for marked muscle weakness, dysphagia or respiratory compromise the toxin unmasked subclinical disease in some patients, however BTXN injection was used successfully in others.

6. Co-administration with drugs interfering with neuromuscular activity as aminoglycosides, lincosamides, cholinesterase inhibitors, curare-like depolarizing blockers, succinylcholine, magnesium sulfate, calcium channel blockers, quinidine, and polymyxin.

7. Anti coagulant therapy or bleeding disorders.

4. Complications

Neurotoxins treatments are proven to be remarkably safe. All the reported adverse events are related to injection techniques, dosage, or volume of injection. Allergic reactions are very rarely encountered.

General	
	How to avoid
Pain	Topical anesthetics, lidocaine for vial reconstitution, small gauge (30–32) needles and ice packs.
Edema/ Erythema	Ice packs application immediately before and after injection.
Ecchymosis	Avoid the superficial vasculature (proper lightening and stretch the skin for better visualization) Patient counseling regarding the need to stop NSAIDs, aspirin or anticoagulant therapy prior to injection for ≤1 week.
Headache	Those at risk can receive prophylaxis acetaminophen.
Neutralizing antibodies	They block the pharmacologic activity of the treatment affecting 0.3–6% of patients, its incidence is much higher in patients receiving toxin treatments for medical indications. BTXN-B products are more immunogenic than BTXN-A. It is controversial whether there is cross reactivity across different serotypes of the toxin, however it is worth trying to shift the patient to another serotype e.g. from BTXN-A to BTXN-B as a solution for neutralizing antibodies.
Procedure specific	
Glabellar complex	**Eyelid ptosis** due to toxin diffusion through the orbital septum, paralyzing the levator palpebrae superioris muscle, specially when injecting the mid pupillary line 1 cm above the bony supraorbital rim to obtain horizontal brow. Avoided by the lateral corrugator muscle subdermal injection and do not inject within a 1-cm distance above the superior orbital rim. It is treated with α-adrenergic eye drops, such as apraclonidine or phenylephrine eye drops.
Frontalis	• **Brow ptosis** due to overtreatment of the frontalis muscle. Avoided by keeping the lower most injection points 1.5 cm above the brow. • Excessive lateral brow elevation **"Quizzical" brows** due to central fibers treatment, while the lateral fibers inadequately treated causing lateral brow elevation.
Crow's feet	• **Ectropion**, **diplopia**, or **lateral lower eyelid drooping** due to injection of the lateral rectus muscle so avoid deep intramuscular injection within 1 cm from the lateral bony orbit • **Upper lip ptosis** due to injection into zygomaticus muscle. This can be avoided by not injecting during smiling and do not follow the lines inferiorly.
Masseter hypertrophy	• Salivary gland enlargement • **Smile limitation** and/or **asymmetry** which is avoided by injecting into the square-shaped safe area that is bounded by a line joining the oral commissure to the ipsilateral earlobe superiorly, the mandibular border inferiorly and the anterior and posterior borders of the muscle identified while patient grinds on his/her teeth.
Platysma	**Dysphagia, hoarseness**, **weakness** of the flexors of the neck, **dry mouth**. This is avoided by keeping the injection units ≤50 U

Conflict of interest

None.

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