



Botulinum toxin complications in registered and off-label aesthetic indications

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Abstract

Botulinum toxin A (BTXA) is one of the most popular nonsurgical cosmetic procedures worldwide. Overall, this procedure is associated with favorable complications profile. Nevertheless, any medical intervention carries inherent risks. This synopsis systematically reviews adverse effects of aesthetic BTXA for both approved and off-label indications. Based on published data, the approach for prevention and management is discussed.

KEYWORDS

botulinum toxin, complications

1 | INTRODUCTION

Awareness of the potential complications of aesthetic procedures helps to improve the outcomes. Botulinum toxin A (BTXA) injections procedure is considered safe and associated with a favorable complications profile.¹ Comprehensive reviews on adverse effects of BTXA, used for various approved and off-label indications, have been published more than 15 years ago, based on meticulous observations of a single injector.^{2,3} Since then, multiple studies, overviewing complications occurring during the use of BTXA for a single, usually approved or “to be approved” clinical indication, have been published.^{4–6} During the years, new aesthetic indications for BTXA use, have been developed. Currently, off-label indications of aesthetic BTXA are at least as popular as the registered ones.

This review provides a systematic synopsis of complications that might occur during BTXA use for most of the currently available aesthetic indications.

1.1 | Classification of complications

Adverse reactions in BTXA use can occur as a result of injection procedure, due to the biological effect of the product or idiosyncratically.

Reactions associated with the injection procedure include pain, bruising, and swelling at the injection sites.^{1–6}

The adverse effects due to the biological effect of the BTXA can be classified into functional and aesthetic (Tables 1 and 2). Functional complications affect general health or distort activity of muscles with functional importance. In aesthetic complications, either the esthetic goal of the treatment is not achieved or a new imbalance in the patient’s appearance is created.

Idiosyncratic reactions occur rarely and unpredictably in a small percentage of the patients and are not explained by the biological mechanism of the drug.

TABLE 1 Functional complications

Complication	References
Botulism	7,8,9,10
Headache	2,5,11,12
Eyelid ptosis	1-5,14-22
Diplopia	23
Dysphagia	24,25
Chewing weakness	26,27
Xerostomia	28,29
Dry eyes	4,30
"Floppy neck" syndrome	31

TABLE 2 Aesthetic complications

"Mephisto eyebrows"	2,38-41
Eyebrow ptosis (eyebrow heaviness)	2,42
Eyelid edema	43-45
Mouth asymmetry	2,46,47,28
Paradoxical bulging of the cheek during mastication	49,50

1.2 | Functional complications

BTXA injection site reactions, such as pain, edema, and bruising, are not uncommon. However, real allergic reactions to BTXA, supported by positive intradermal test, are only rarely reported.^{7,8} Few publications on granulomatous reactions at the BTXA injection sites exist. These granulomata can be of infectious origin or related to accidental inoculation by material eliciting a foreign body-like reaction, for example, from a BTXA diluent or lubricant material from the injection syringe.⁹⁻¹¹

Botulism is an extremely rare complication, caused either by the use of unlicensed botulinum toxins or overdosed injection.^{12,13} The use of counterfeit or unlicensed botulinum toxin products continues to be a worldwide concern.^{14,15} To avoid causing botulism by aesthetic BTXA injections, the product should be always obtained through the official representative or pharmacy. No internet purchase of the BTXA can be advised.

When treating adult patients for more than one indications, the maximum cumulative dose of Ona (BOTOX®) and Inco BTXA (Xeomin®) should not exceed 400 Units and for Abo BTXA (Dysport®) 30 units per kilogram body weight.

Headache- The underlying cause of postinjection headache is postulated to be injection-stimulated muscle spasm, and it occurs following glabella, forehead, and masseter injections.^{2,5,16} To avoid injecting to a contracted muscle, preinjection markings should be performed. The injections are delivered into completely relaxed muscles to decrease a risk of postinjection headache.

Occasionally, intractable and prolonged headache is reported after injection of BTXA for aesthetic indications and is considered as an idiosyncratic phenomenon.¹⁷

Eyelid ptosis can occur during glabellar areas treatment.^{1-5,18} The reported incidence of eyelid ptosis in controlled studies is 0.8–3.4%.^{19,20} Most of the BTXA-induced eyelid ptosis cases are unilateral and mild and do not imply severe functional limitation. It is crucial to assess and photograph eyelid position before BTXA injection, since uni- or bilateral ptosis is a frequent finding in a mature population.²¹ The definition of eyelid ptosis is based on measurement of margin reflex distance (MRD), which is the vertical distance between the pupillary light reflex (corresponding to the center of the pupil) and the upper eyelid margin. Eyelid ptosis is defined as MRD distance below 2.5 mm or an asymmetry of more than 1 mm between the two eyes.²²

The anatomical basis of BTXA-induced eyelid ptosis is diffusion of BTXA to levator palpebrae superioris muscle.²³ This muscle is located deeper and lower to the recommended lateral corrugator muscle injection site. Spread of the toxin can result from inappropriate dosage, high injected volume, too deep or too lower located injection site, excessive post-treatment manipulation of the injected area, or individual anatomical variation.

To prevent eyelid ptosis, the injection to lateral corrugator site is performed superficially with only the tip of the needle penetrating the skin.

If eyelid ptosis occurs, stimulation of superior tarsal muscle (Mueller's muscle) might be helpful. Mueller's muscle is a small non-acetyl choline-mediated muscle, participating in the upper eyelid opening. Stimulation of Mueller's muscle is possible by using ophthalmic drops containing selective alpha-adrenergic agonists, such as apraclonidine 0.5% or naphazoline. The effect is transient, and repetitive use is needed until the ptosis resolves.^{24,25}

Few reports indicate that eyelid ptosis may respond to oral 60 mg pyridostigmine three times daily.²⁶

Another option to treat BTXA-induced eyelid ptosis is to attempt to decrease the sphincteric activity by injecting the pretarsal portion of orbicularis oculi muscle.²⁷

Diplopia is caused by extraocular muscle weakness induced by diffusion or spread of BTXA to the muscles, responsible for the movement of the eyeball.²⁸ This can happen due to poor injection technique, misplacement of the injections, or defective orbital septum, allowing diffusion of the product.

To avoid diffusion of BTXA to extraocular muscles, the injections should be made with the needle tip oriented away from the orbit and located at least 1 cm away from the lateral orbital rim. If developed, diplopia can last a number of weeks. Since double vision generates significant difficulties to perform daily tasks, it can be addressed by temporary occlusion of the affected eye.

Dysphagia is caused by off-label injection of BTXA to platysma to improve lower face definition and contour. During the pharyngeal phase of swallowing, a bolus transition from oral cavity to esophagus occurs using the thyrohyoid and suprahyoid muscles.²⁹ These muscles are anatomically located deeply to the central platysmal fibers. Improper injection technique and large dosage are considered to be the risk factors of deeper neighboring muscles weakness.

If dysphagia occurs, off-label administration of pyridostigmine, a reversible acetylcholinesterase inhibitor, has been suggested as an option to alleviate the symptoms.³⁰

Chewing weakness - This complication is associated with the off-label use of Botox to treat masseter hypertrophy. It is reported in a wide range of frequency (0.9%-63.6%), starting 1-4 weeks after Botox injection and returning to preinjection levels in around 12 weeks.^{31,32}

For optimization and safety of treatment, before the injection, the masseter is palpated and marked while a patient is clenching the teeth. A line is drawn from the angle of the mouth to the tragus. All the injections are performed under this line to avoid affecting other muscles.

If a patient complains on chewing difficulties, soft food diet is recommended until the problem resolves.

Xerostomia- Dry mouth is reported following off-label Botox injection for masseter hypertrophy. Parotid gland, which partially overlies the masseter muscle in its lateral portion, is innervated by acetylcholine and can be affected by Botox.

The reported incidence of xerostomia is 6.3%-13.3%.^{30,33} The recovery takes 3-4 weeks. Pilocarpine hydrochloride tablets, which increase salivary flow, are suggested as a treatment option in patients with severe mouth dryness following Botox injection to masseter.³⁴

Dry eyes can be associated with periorbital injection of Botox. The reported frequency of this adverse effect varies extensively.^{4,35}

Normal eye lubrication is dependent, among other factors, on contraction of the orbicularis oculi muscle. With each blink, tears are pushed and dispersed across the eye. If blinking mechanism or closure of the eye is affected, dryness occurs. In addition, lacrimal gland activity is mediated by acetylcholine. Diffusion of Botox into the lacrimal gland (located above the lateral canthus and medially to the orbital rim) may negatively affect tear secretion.

To avoid this complication, patients over 50 should be specifically asked regarding eye dryness prior to periorbital Botox injections. In addition, periorbital injections should be performed 1 cm lateral to the orbital rim to avoid diffusion of Botox to the lacrimal gland.

"Floppy neck syndrome"- Difficulty at attempt raising the head from supine position can be caused by overdosing in neck injection or by affecting fibers of sternocleidomastoid muscle. The incidence of this complication is up to 1%.³⁶ As psychological support is the only treatment to be offered, preventing this complication using correct doses and precise placement of the injections is crucial.³ In addition, only upper parts of the platysma are preferentially injected.

2 | AESTHETIC COMPLICATIONS

Aesthetic complications occur if either the aesthetic goal of the treatment is not achieved or a new imbalance in the patient's appearance is created due the treatment.

Insufficient effect or worsening of pre-existing wrinkles- In spite of a few clinical cases published, the risk of clinical resistance to Botox in aesthetic use is very low.^{37,38} The development of positive neutralizing antibodies occurred only in 11/2240 of study subjects. However, only four subjects appeared to loss clinical response and six subjects had negative antibodies assays at study exit.³³ Therefore, insufficient cosmetic effect, as judged by remaining ability to contract treated muscles, indicates in most cases inadequate dose or wrong injection pattern, rather than resistance to the Botox.^{39,40}

Occasionally, patients express disappointment from the treatment results in the glabellar area due to residual nondynamic wrinkles. Deep glabellar wrinkles may require a combination of both Botox and a filler.

Sometimes patients complain on worsening of wrinkles in areas close or related to a treated area. It is caused by hyperactivity and overcompensation of untreated muscles.⁴¹

Asymmetry- Pre-existing asymmetries draw sometimes patient's attention for the first time only after the treatment. A patient should be informed regarding any asymmetry noted before the injection. An effort should be done to correct pre-existing asymmetries by modification of the injection scheme and doses according to the specific patient's anatomy.⁴²

"Mephisto eyebrows"-In spite of being well recognized in the aesthetic practice, only few publications specifically mention this adverse effect.^{2,43,44} Eyebrows in which the lateral end (the tail) is positioned exaggeratedly higher than the medial part (the head) are called "Mephisto eyebrows," due to their resemblance to the Mephistopheles' (demon in Faust) image.

Disharmonic shape of the brow can be caused either by hyper-elevation of brow tail or by dropping of the brow head. If, when treating forehead wrinkles, lateral fibers of the frontalis are not addressed, they over-pull the brow tail at brow elevation (Figure 1).⁴⁵ More frequently, "pseudo Mephisto eyebrows" are seen following glabella complex injection, due to the ptosis of the eyebrow head (Figure 2A,B).⁴⁶ Glabellar complex includes eyebrow depressors: corrugator, procerus, and medial fibers of orbicularis oculi muscles. Frontalis muscle, which is a brow elevator, overlays the corrugator and parts of orbicularis oculi muscles. Superficial and highly located injection of the corrugator affects frontalis together with brow depressors. As a result, lifting capacity of the frontalis in the central forehead is lost and the head of the eyebrow droops. To avoid "pseudo Mephisto eyebrows" while injecting glabellar complex, medial injection should be performed deeply to the eyebrow depressors plane and lateral injection superficially and very close to the brow.

The only way to correct eyebrows position in both scenarios is by carefully injecting high lateral frontalis fibers to lower eyebrow tail. In most cases, elevation of eyebrow head is impossible.

Eyebrow ptosis (eyebrow heaviness)- Frontalis muscle is the only elevator of the eyebrows. Elder people use their frontalis muscle to elevate sagging supraorbital tissues to improve vision. Even if not noted clinically, over-injection of the forehead causes unpleasant heaviness of the eyebrows. The exact prevalence of this complication is not known.

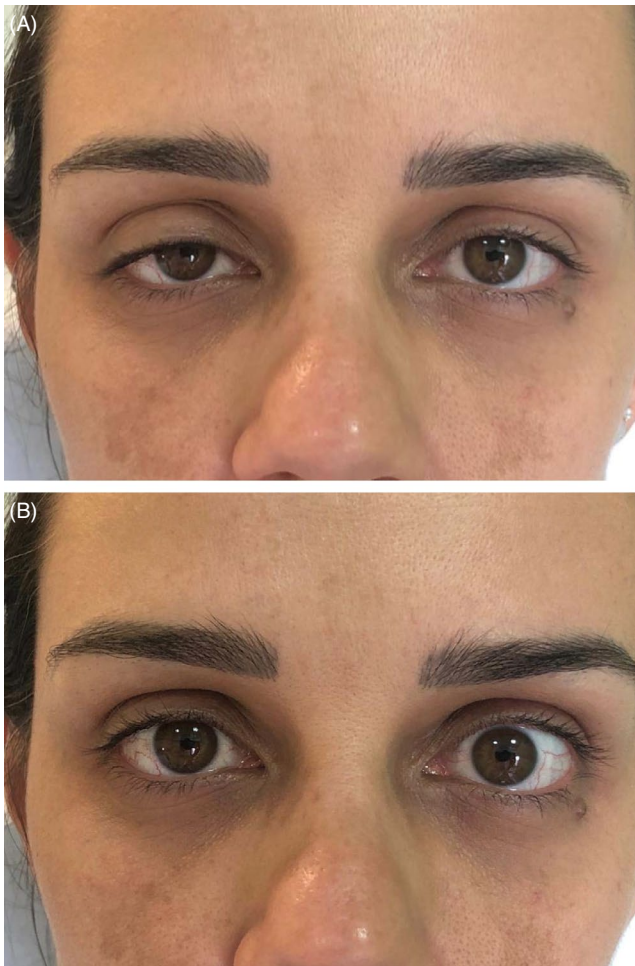


FIGURE 1 A, Left eyelid ptosis B, Immediate response to iopidine eyedrops. These ophthalmic drops with adrenergic activity can stimulate superior tarsal muscle (Mueller's muscle). Eyelid ptosis may respond to oral 60 mg pyridostigmine three times daily or by injecting the pretarsal portion of orbicularis oculi muscle to decrease its sphincteric activity

Patients have to be cautiously preselected for forehead injections. Frontalis should be under-dosed, and BTXA should not be injected closer than at least 2 cm to the eyebrows.^{2,47}

Once happened, eyebrows ptosis lasts about 3-4 weeks. Exercising the muscle by trying to elevate the eyebrows against pressure applied by a hand laid on a forehead may shorten period of inconvenience.

Eyelid edema- This complication is reported in 0.04%-1.4% of patients, with higher incidence in Asians, while injecting periorbital wrinkles.^{48,49} The suggested mechanism might be related to venous or lymphatic stasis due to decreased muscle tone, which lessens the interstitial fluid return against gravity.⁵⁰

Before the injection, patients at risk should be specifically asked regarding lower eyelid edema in the mornings. In borderline cases, the dose of BTXA is decreased and no injection inferior-medially to the lateral orbital rim border is performed.

Mouth asymmetry - Mouth asymmetry can occur as a result of BTXA treatment for various clinical indications, such as crow's feet,



FIGURE 2 A, "Mephisto" eyebrows b. after correction. This condition is caused by unaddressed activity of the lateral fibers of the frontalis muscle, over-pooling brows tail, while treating forehead wrinkles. To correct eyebrows position, careful injection of high lateral frontalis fibers is performed to lower eyebrow tail. In most cases, elevation of eyebrow head is impossible.

upper lip wrinkles, dimpled chin, masseter hypertrophy, and depressed lip corners. Mouth asymmetry developing as a complication can become evident at rest, in smile or during animation.

a) Asymmetry in smile can result as a complication of crow's feet treatment. Zygomatic major muscle is a mouth corner elevator. It is attached to zygomatic bone down to the point of its greatest prominence. If injection to orbicularis oculi muscle is performed below this point, zygomatic major muscle is affected. As a result, the absence of mouth corner elevation becomes evident at smile (Figure 3).

To avoid this complication, periorbital BTXA injections should be always placed above the "cheekbones."² Longer periorbital wrinkles are corrected by a filler rather than BTXA.

b) Mouth asymmetry during animation can result from injection of BTXA to depressor anguli oris (DAO). Anatomically, DAO overlaps medially the depressor labii inferioris muscle (DLI), which normally pushes the lower lip up. Imprecise injection to DAO, which affects DLI in one side, causes mouth asymmetry, especially during animation (Figure 4).⁵¹



FIGURE 3 A, Before B, after glabellar complex injection creating “Pseudo Mephisto” eyebrows. This condition is caused by ptosis of the brow head with compensatory eyebrow tail elevation after the injection. To correct eyebrows position, high lateral frontalis fibers are injected to lower eyebrow tail



FIGURE 4 Asymmetry of smile. This condition is caused by BTXA effect on left Zygomatic major muscle while treating crows' feet. To avoid this complication, periorbital BTXA injections should be always placed above the “cheekbones”

To avoid this complication, injection to DAO is performed superficially, 8-10 mm lateral and 8-15 mm down to the mouth corner with a needle tip facing laterally.⁵²



FIGURE 5 Mouth asymmetry during animation. This condition is caused by BTXA effect on right Depressor Labii Inferioris while injecting Depressor Anguli Oris muscle. To avoid this complication, injection to DAO is performed superficially, lateral and down to the mouth corner with a needle tip facing laterally

c) Mouth asymmetry during animation can result also from BTXA injection to mentalis. Anatomically, mentalis overlaps superiorly and laterally both DLI and orbicularis oris muscles. Injecting too close to the lower lip or too lateral from the chin center may affect these muscles function, causing asymmetry on animation (Figure 5).²

To avoid this complication, injections should be placed 0.5-1 cm above the lower margin of the chin and not closer than 1.5 cm from the lower lip.

d) Overactivity of orbicularis oris muscle causes upper lip wrinkles, evident especially during animation, talking, and whistling/kissing. To avoid any asymmetry, treatment of perioral lines should be carried out by injecting BTXA in minimal and meticulously precise and even doses in both sides of the lip.

e) The asymmetric smile can result from injection to masseter if unilateral BTXA diffusion into the risorius muscle occurs. Risorius muscle participates in smile by pulling mouth corners laterally. To avoid incidental risorius injury, it has been suggested to inject half a dose of the BTXA deeply to the most prominent part of the contracted masseter, and the rest at its inferior border.⁵³

Paradoxical bulging of the cheek during mastication - It is an occasional side effect of BTXA injection for masseter hypertrophy.⁵⁴ It occurs 2-4 weeks after the injection in 0.49%-18.8% of patients and usually recovers within 10 days. A cause of paradoxical bulging is the compensatory effect of the untreated superficial masseter muscle fibers.⁵⁵ In case of bulging, additional superficial injection should be considered to correct the phenomenon.

3 | SUMMARY

Overall, BTXA has safe complication profile. Almost all the potential complications are avoidable, treatable, and transient. To decrease complication risk, a clinician has to have knowledge on relevant facial

anatomy, including ethnic and individual variability, BTOX recommended dosages and injection schemes. In case a complication happens, in most cases it is possible to decrease its severity and visibility until spontaneous resolution occurs.


CONFLICT OF INTEREST

None.

CONSENT

Consent obtained from all participants.

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