Therapeutic and cosmetic applications of Botulinum Toxin

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1.What is Botulinum Toxin

- Botulinum toxin (BNT) is a neurotoxin produced by a gram-positive anaerobic bacterium *Clostridium botulinum*.
- Infection by these bacteria results in a clinical condition called **botulism**.
- A hallmark of this potentially fatal disease is **flaccid paralysis** caused by interference with acetylcholine neurotransmitter release at presynaptic terminals.

2.Different Subtypes of Botulinum Toxin

- In order to be used as a drug the toxin has to be **isolated**,**purified** and **stabilized.**
- Seven serotypes , antigenic botulinum toxins exist labeled as types (**BNT-A, -B, -C, -D, -E, -F, and -G**) produced by different strains of Clostridium botulinum have been described.
- The human nervous system is susceptible to five toxin serotypes (**BNT-A, -B, -E, -F, -G**) and unaffected by 2 (BNT-C, -D).
- Although all toxins have different molecular targets, their action leads to the blockade of the cholinergic nerves.
- However, only the **two** are commercially available for clinical use in the United States (A and B) toxins.

3. Products of BNTs

- There are **several BNT-A** products and **one BNT-B** product on the market.

➢The BNT-A products differ in their **amount of protein** as well as in the **amount of albumin** added.

➢Several **BNT-A products** is marketed in some countries as:

- **Botox /Maxitox/Hutox.**
- **Dysport:** Is much diluted and spreads quickly when compared to botox.
- **Xeomin** (is more purified form, designed to deliver the toxin without any protein additive.)

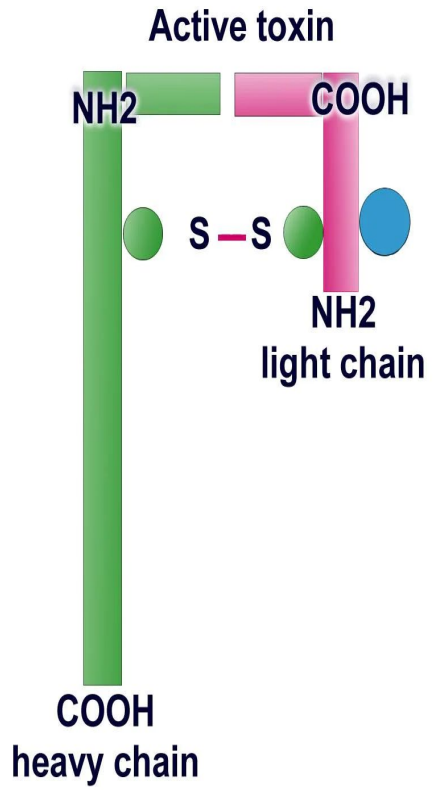
➢**NeuroBloc** (also marketed as Myobloc) is the only commercially available formulation of type -B.

- In aesthetic medicine, the type A toxin is predominately used for cosmetic treatment.
- Even though some trials have been published utilizing type B BNT.
- Type B-BNT (Myobloc) is predominately approved for clinical conditions.

1.3 Botulinum toxin structure

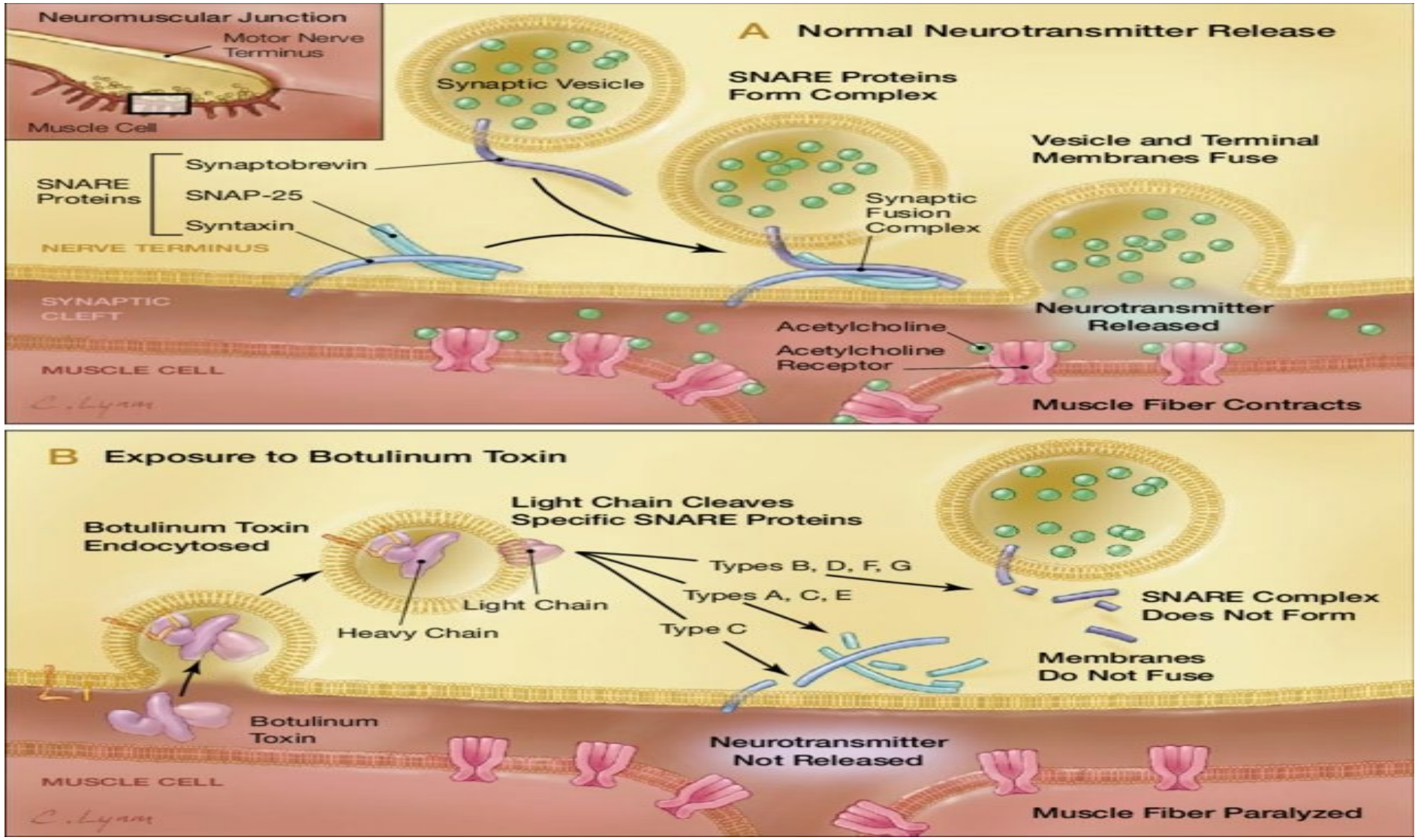
The light chain (~50 kD - amino acids 1-448) acts as a zinc (Zn^{2+}) endopeptidase similar to tetanus toxin with **proteolytic activity** located at the N-terminal end.

The heavy chain (~100 kD - amino acids 449-1280) provides **cholinergic specificity** and is responsible for binding the toxin to presynaptic receptors; it also promotes light-chain translocation across the endosomal membrane.



Proteolytic activity is located at the N-terminal end of the light chain of botulinum toxin type A.

1.4 Mechanism action of Botulinum toxin



Clinical and Cosmetic indications of Botulinum toxin

➢In brief botulinum toxin is used in treatment of :

- Muscle disorders such as cervical dystonia , blepharospasim.
- Pain disorders such as migraine, tension headache
- Autonomic disorders such as hyperhidrosis , Sialorrhea

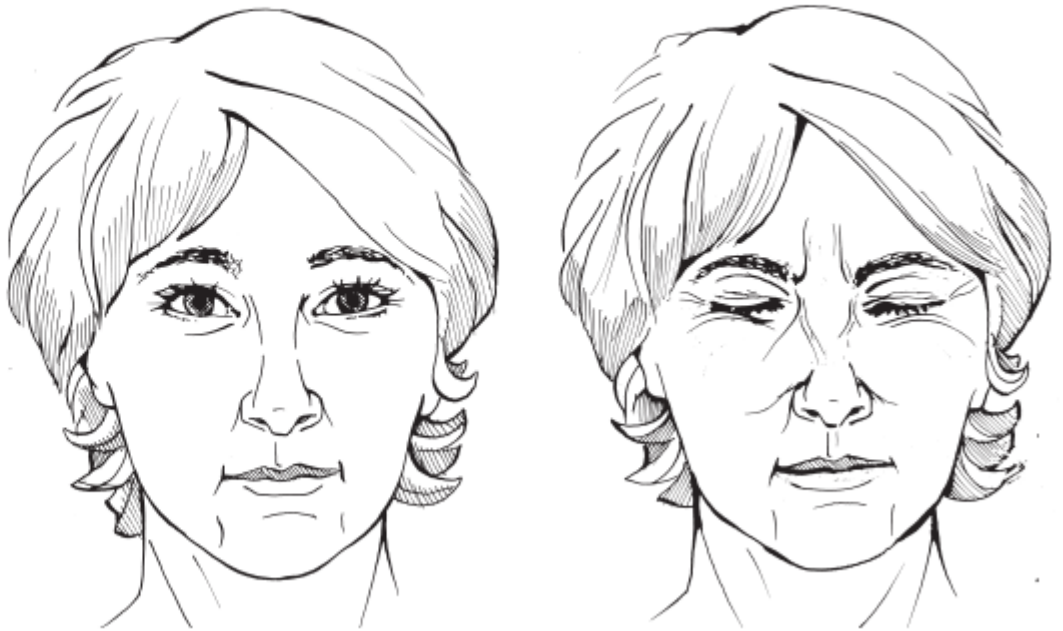
❑We will discuss its use in the management of common clinical conditions that the use of botulinum toxin in their management is FDA approve.

- **Blepharospasm:** is a dystonia of the facial musculature that ranges in severity from an increased blink rate to disable contractions with pain and visual dysfunction.

Muscles possibly involved

Orbicularis oculi
Procerus
Frontalis
Corrugator

Blepharospasms

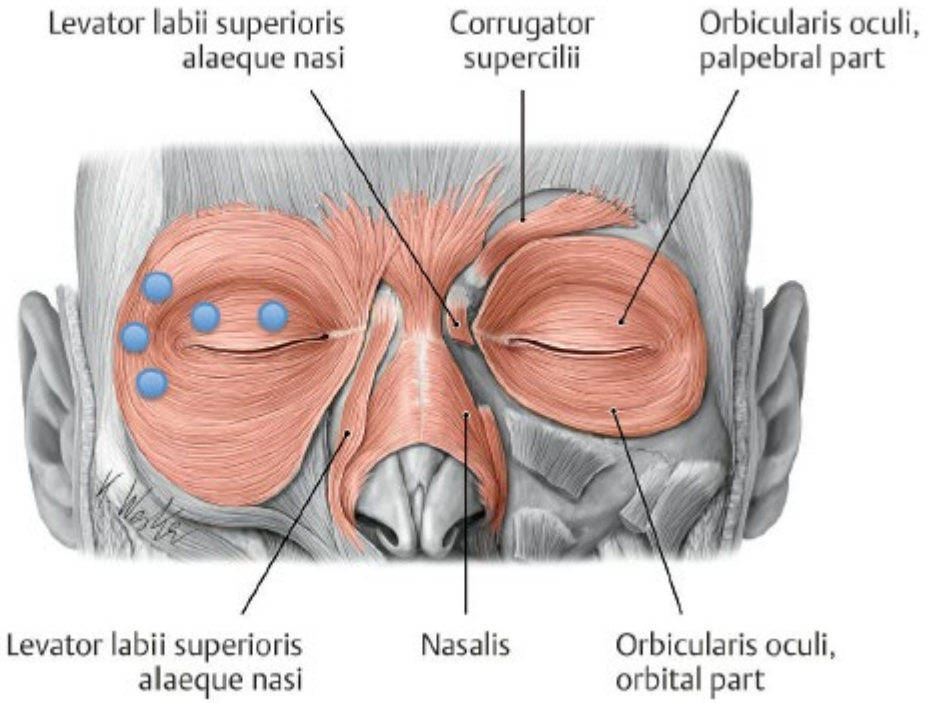


Pathophysiology

Not long ago, dystonia were thought to be manifestations of psychiatric disease. Today, they are understood to be complex neurologic disorders with abnormalities in sensory input, central processing, and motor output, interacting to produce the movement disorder

- **Blepharospasm** is uncommon, with an estimated prevalence of up to one case per 10,000 people. There is an increased female to male prevalence.
- Mean age of diagnosis is in the sixth decade of life.
- The condition usually begins with increased blink rate or spasms of the eyelids, forehead, or midfacial muscles.
- Patients often complain of eye irritation, pain, photophobia, or abnormal tearing, and may initially be diagnosed with various other ocular disorders.
- Spasms may be triggered by sensory stimulation such as wind, air pollutants, or bright light, and may be worse in stressful situations.

Botulinum neurotoxin (BoNT) injection has emerged as a treatment of choice for blepharospasm, and it is approved by the United States Food and Drug Administration (FDA) for this application.



Blepharospasms Dosing Ranges			
	Botox (BTX-A) units[1]	Myobloc (BTX-B) units[2]	Injection sites per muscle
Orbicularis oculi Pretarsal fibers	5 1–2.5/site	250–1,000	2–5
Procerus	2.5–5 2.5–7/site	250–500	1/side
Frontalis	10 2.5–7.5/site	500–750† 500–1,250*	2/side
Corrugator	5 3–7.5/site	250–750	1/side
Total dose	12.5–15	750–2,500 U/side	
Dilution	100 U/2–4 cc Dispensed in 1 cc syringes	Dilutions, see page xxvii	
Needle	30 G, 0.5 in		

Muscles possibly involved

Ipsilateral splenius capitis
Splenius cervicis
Inferior oblique longus capitis
Levator scapulae
Contralateral sternocleidomastoid

Cervical Dystonia – Torticollis 1/2

Cervical dystonia (CD) is the most common focal dystonia. It results in the sustained contraction of the cervical musculature, leading to abnormal posturing of the neck, head, and shoulder.

- The incidence of CD is 9 to 30 per 100,000 people in the United States, 2:1 female-to-male ratio.

In greater than 70% of cases, the disease begins between the fourth and sixth decades of life, with a **peak incidence in the fifth decade**.

- Symptoms typically worsen over the course of the first 5 years before stabilizing.
- Spontaneous remission is seen in 10 to 20% of individuals lasting days to years, although these are temporary and most patients eventually relapse.

Pathophysiology of idiopathic CD is not well understood, although it is generally thought to be an abnormality in central motor processing.

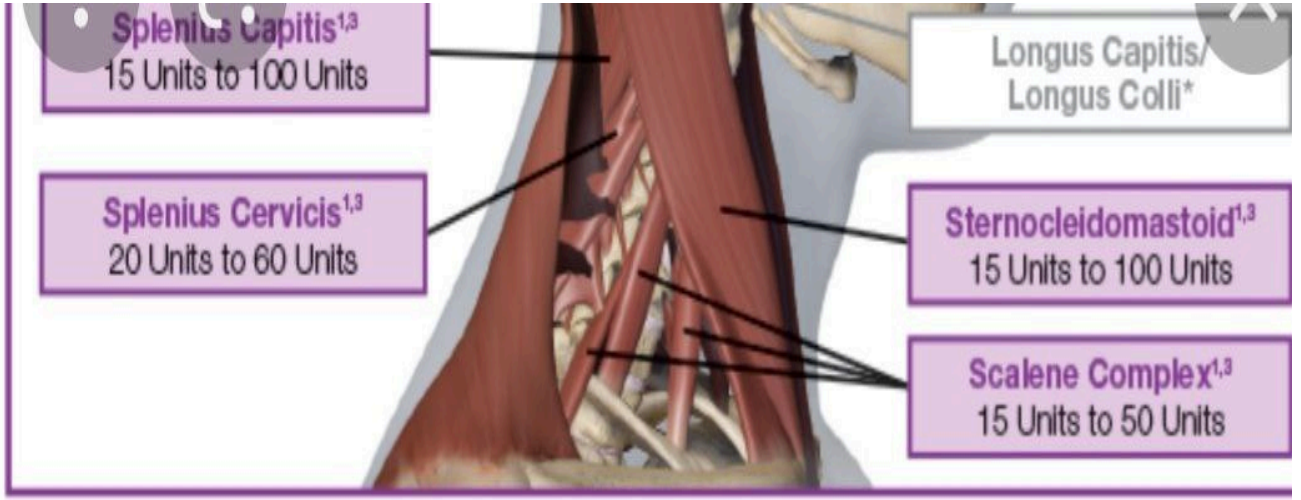
- There is a genetic component to the development of dystonia, but trauma and drug exposure can also be a precedent to focal dystonia

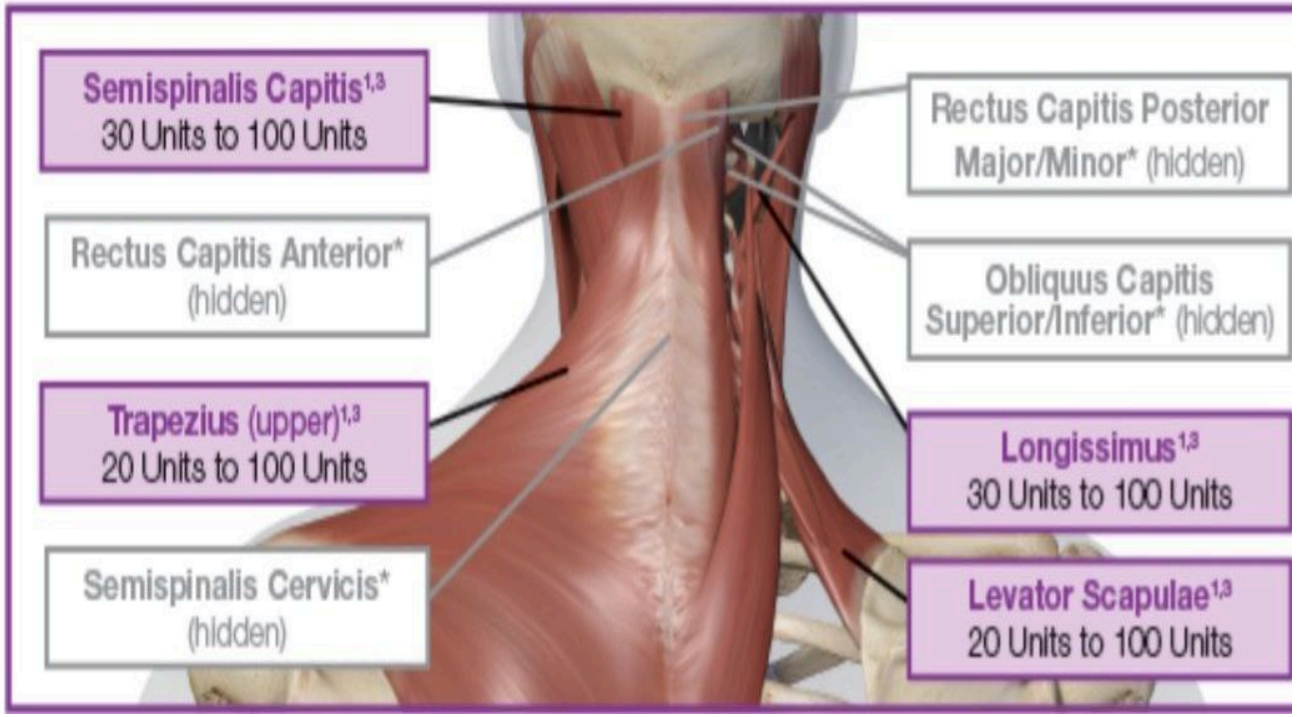
Management

- Medical such as Benztropine
  Benzodiazepines
  Baclofen
  Tetrabenazine
- Surgical denervation and myomectomy

Since 2000, the use of Botox or Myobloc has been a Food and Drug Administration (FDA)-approved indication for CD and has become the favored treatment for this condition. Botulinum neurotoxin in to muscles of the head and neck , cause weakness in the injected muscles, leading to atrophy and ameliorating the spasmodic contractions.

Cervical Dystonia—Torticollis 2/2 Dosing Ranges			
	Botox (BTX-A) units[1,2]	Myobloc (BTX-B) units[3]	Injection sites per muscle
Splenius capitis (ipsilateral)	75 (50–150)	1,000–5,000	2–4
Splenius cervicis	30 (20–60)	Limited data	2
Inferior oblique longus capitis	30[4]	Limited data	
Sternocleidomastoid (contralateral)	50 (15–75)	1,000–3,000	1–4
Levator scapula	50 (25–100)	1,000–4,000	1–3
Cervical dystonia		5,000–10,000	
Dilution	100 U/2–4 cc Dispensed in 1 cc syringes	Dilutions, see page xxvii	
EMG needle	27 G, 37 mm		





Migraine:

- Headaches account for 1 to 2% of all emergency room visits, with migraine making up nearly 40% of headache related visits.
- Nearly 18% of women and 6% of men are affected in the United States The disorder most commonly affects individuals between the **ages of 25 and 55.** Migraine is among the leading causes for missed days at work.

Migraine is a **paroxysmal headache disorder**, Headaches typically manifest with moderate to severe throbbing head pain lasting hours to days, in a hemicranial, frontotemporal distribution; however, bilateral and posterior cervical pain can occur.

- **The pathophysiology of migraine headache** is not completely understood. Experimental evidence suggests that at least three mechanisms are involved in the pathogenesis of the migraine headache: **extracranial arterial vasodilation**, **neurogenic inflammation**, and **decreased inhibition of central pain transmission**.

■ Treatment Approach

1-Abortive therapy for the acute attack (acute therapy) such as **NSIIAIDS** , **Opiates/barbiturates** ..

2- Preventive therapy to reduce the severity, frequency, and duration of future episodes such as ergots alkaloids(Ergotamine) .

Pharmacology of Botulinum Neurotoxin

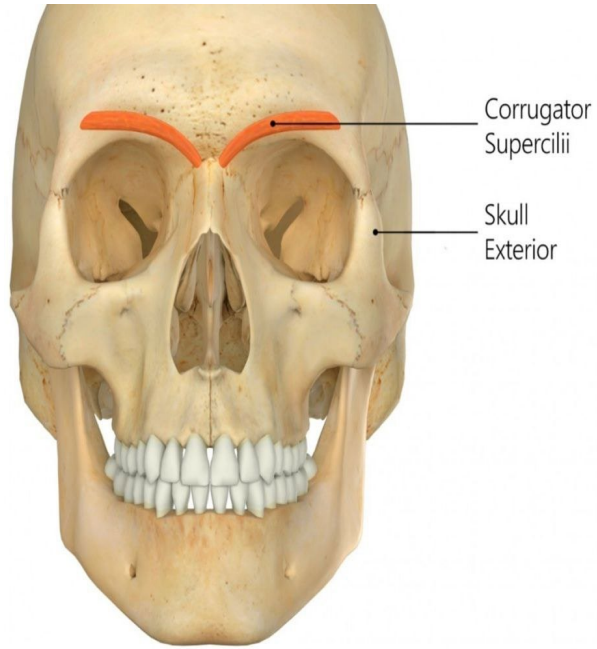
BoNT/A is a paralytic neurotoxin that inhibits acetylcholine (Ach) release at the neuromuscular junction.

BoNT/A's role as a useful agent for headache disorders was derived from anecdotal reports of patients being treating for hyperfunctional facial lines. Incidentally, these patients reported reductions in the frequency and severity of headache episodes and facial tension.

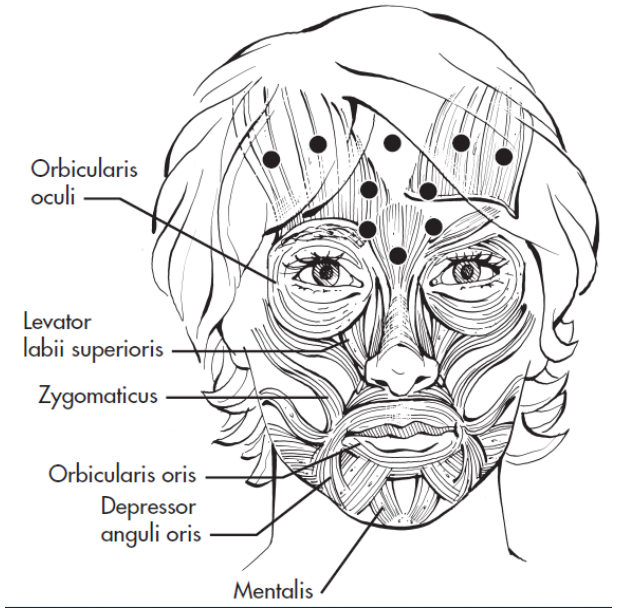
- It is unclear how BoNT/A relieves headache, but various possible mechanisms have been suggested. These include:

- direct effects at the neuromuscular junction and direct antiproprioceptive effects on nerves of the head and neck.
- Guyuron *et al* proposed that migraine may be triggered by cranial muscle contraction, particularly the **corrugator muscles,**which stimulate trigeminal nociceptors passing through the muscle.

- Recent evidence suggests that BoNT/A may also inhibit the release of various neuropeptides and neuromodulators such as **substance P**, **glutamate**, and **CGRP**, thereby blocking the transmission of afferent nociceptive signals to the central nervous system.



	Botox (BTX-A) units[1,2]	Myobloc (BTX-B) units[3]	Injection sites per muscle
Procerus	2.5–5.0/site	50–100† (125–500)*	1
Corrugator, medial	2.5–4.0/site	Limited data	1
Frontalis	2.5/site (4–6/side)	500–750 500–1,250[4,8]	8–12
Temporalis (each muscle)	2.5–5/site (4/side)	Limited data for specific muscles See data for regions below reference 3	4
Occipitalis	5–10/side		1
Splenius capitis	5–15/side		1–2
Masseter	5–15/side		1–2
Levator scapulae	10–25/side[6,7]		
Trapezius	5–15/side	625–1,000/side[4,5,8]	1–3
Semispinalis	5–10/side	Limited data for specific muscles	1
Sternocleidomastoid	10–20/side		2
Total dose	100–200	2,500–5,000	
Dilution	100 U/2–4 cc Dispensed in 1 cc syringes	Dilutions, see page xxvii.	
Needle	30 G, 0.5 in		



October 16, 2010 — The US Food and Drug Administration (FDA) has approved onabotulinumtoxinA (Botox; Allergan Inc) for headache prophylaxis in patients with adult chronic migraine who suffer headaches on 15 or more days per month, each lasting more than 4 hours.

Hyperhidrosis is a common condition characterized by abnormally excessive sweating that's not necessarily related to heat or exercise. sweating is required to regulate body temperature. It may be divided into **primary** and **secondary** forms.

- **Primary (idiopathic or essential) hyperhidrosis** is a focal disorder usually involving the palms, soles of feet, axillae, or face.
- The onset of primary hyperhidrosis is usually during adolescence, and 30 to 50% of affected individuals report a positive family history, which suggests a genetic component.
- Sweating episodes may be triggered by various factors including spicy foods, emotional stressors, and mental or physical activity, but do not occur during sleep. These episodes can cause significant social and occupational dysfunction, as well as psychological stress.

- **Secondary hyperhidrosis** is characterized by generalized perspiration and is usually related to excess adrenergic stimulation due to an underlying disease such as endocrine dysfunction (thyroid problems),neoplasia, or chronic infection, diabetes, low blood sugar, Nervous system disorders, medicine.

Topical medical therapies for hyperhidrosis are available, but the results are often unsatisfactory.

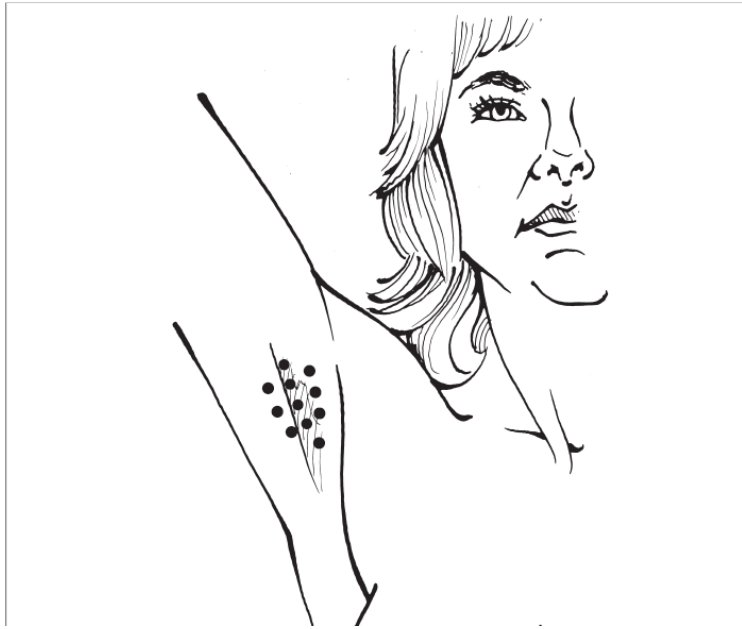
- Topical aluminum salts in a concentration of 20 to 25% are an effective first-line treatment, but localized burning, stinging, and irritation may limit their use.
- Iontophoresis is a second-line therapy that involves delivering ions through the skin using electrical current. Local irritation and the fact that it is time-consuming limit the use of this modality.

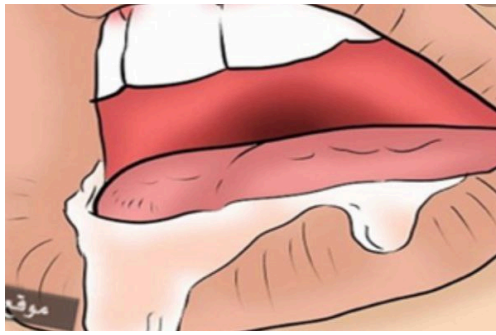
- Systemic drugs are primarily indicated in the treatment of secondary hyperhdrosis. Anticholinergic medications, including **glycopyrrolate**, **oxybutynin**, **propantheline bromide**, and **benztropine**, have been used with some success.
- Unfortunately, due to the relatively large doses that are required, a significant side-effect profile exists. Common side effects, including **dry mouth**, **blurred vision**, **tachycardia**, and **urinary retention**, limit the clinical efficacy of oral anticholinergic medication.
- Surgical treatments can be effective, but involve considerable risk. Endoscopic thoracic sympathectomy involves resection or ablation of the sympathetic ganglia.

- Because acetylcholine is **the primary neurotransmitter responsible for transmission at the cholinergic neurosecretory junction, Botulinum neurotoxin (BoNT) irreversibly blocks presynaptic acetylcholine release at the neuromuscular junction**, thus exerting its muscular paralysis effects.
- BoNT has also been shown to **be a safe and highly effective** method of abolishing focal sweating in idiopathic hyperhidrosis

In 2004, the U.S. Food & Drug Administration (FDA) approved BOTOX (**onabotulinumtoxinA**) for the treatment of severe primary axillary hyperhidrosis (excessive sweating of the underarms n in patients unable to obtain relief using antiperspirants hyperhidrosis-treatments/antiperspirants/antiperspirant.

Axillae Dosing Ranges			
	Botox (BTX-A) units	Myobloc (BTX-B) units	Injection sites
Axillae	50/axillae 5 U/site	2,500/axillae 250 U/site	2 cm apart/10 sites
Dilution	100 U/2 cc nonpreserved saline Dispensed in 1 cc syringes. = 2.5 U/0.1 cc	Undiluted: = 250 U/0.05 cc Diluted: 5,000 U +1 cc NS = 250 U/0.1 cc Dispensed in 1 cc syringes.	
Needle	30 G, 0.5 in		



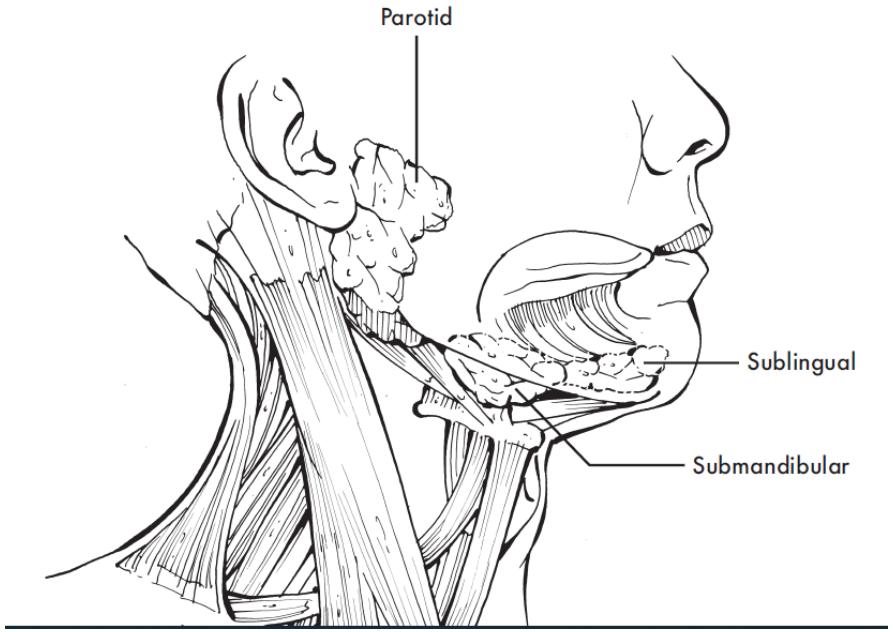


Sialorrhea: is drooling or hypersalivation beyond the lip margin.

- Sialorrhea are considered normal in infants, and it typically stops in the second year of life.
- Sialorrhea is considered pathologic when it presents in patients who are 4 years old or older.
- In a normal adult, approximately 1.5 L of saliva is produced daily.
- The six major salivary glands—the bilateral parotid, submandibular, and sublingual glands produce the rest. At baseline, approximately 70% of the total production comes from the submandibular and sublingual glands.
- Sialorrhea is a common problem in children with mental retardation and with cerebral palsy.
- And in adults usually with Parkinson's disease.

➢ **Anticholinergic medications** are effective in reducing drooling, but can be limited by side effects.

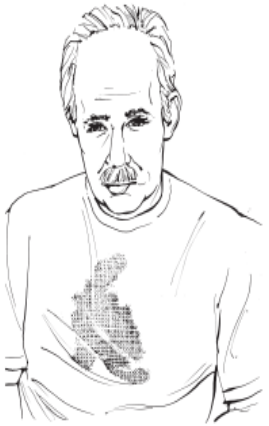
➢ .



Glands possibly involved

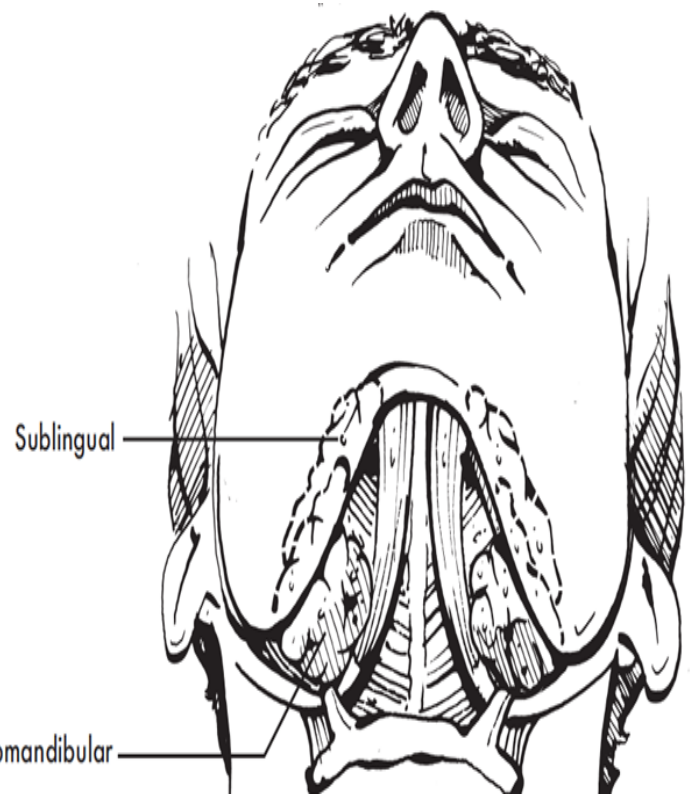
Parotid glands
Submandibular glands
Sublingual glands

Drooling/Sialorrhea



- **BoNT/A** injections into the **parotid** and **submandibular** glands are safe and effective, but repeat injections are necessary as the effect is temporary It not only blocks acetylcholine release at the neuromuscular synaptic end plate, but also blocks **cholinergic parasympathetic secretomotor fibers of the salivary glands**.

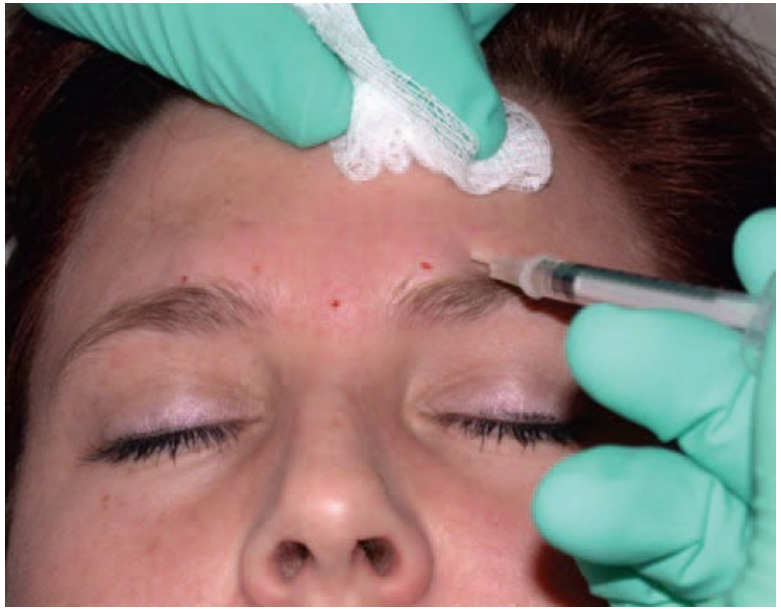
Drooling/Sialorrhea Dosing Ranges			
	Botox (BTX-A) units[1]	Myobloc (BTX-B) units[2]	Injection sites per gland
Parotid glands	15–40/gland	500–1,000/ gland* 1,000/gland	2
Submandibular glands +/– ultrasound guidance	10–15/gland	250/gland	1
Dilution	100 U/1–2 cc Dispensed in 1 cc syringes	Dilutions, see page xxvii	
Needle	30 G, 0.5 in		

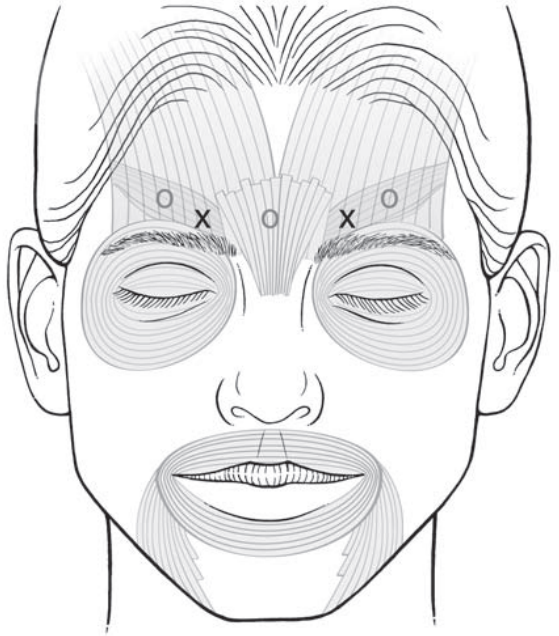


Injection Technique	
Parotid	Posterior to the palpated masseter muscle and anterior to the external ear[2]
Submandibular	Anterior and medial to the genu of the mandible[2]

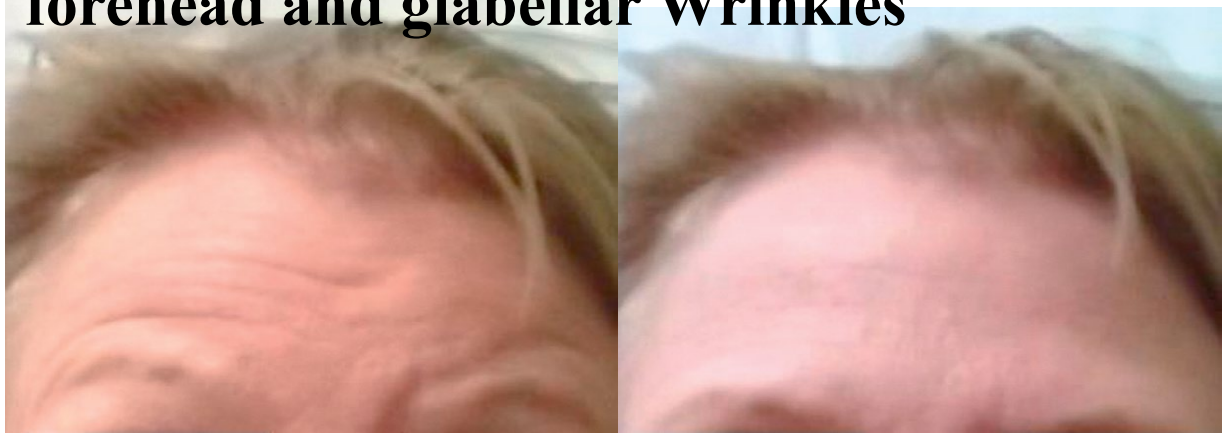
The first area to be successfully treated with botulinum toxin for cosmetic purposes and FDA approved was the glabellar region (Glabellar frown lines). Total dose 15-20 units of Botox

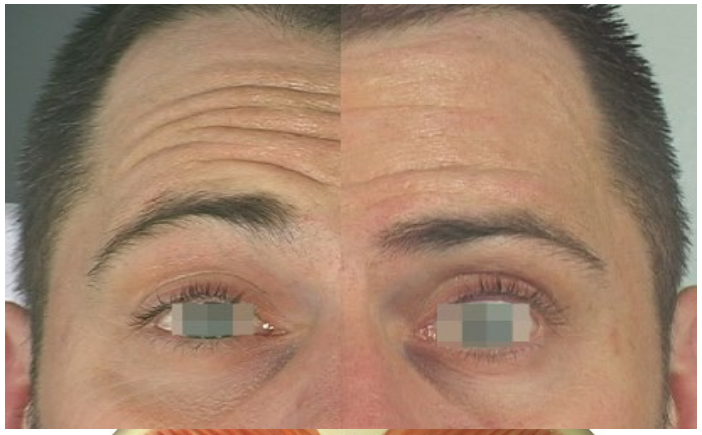
Injections in the glabellar region should be performed with the needle directed slightly caudad and away from the orbit to avoid inadvertent spread of the botulinum toxin behind the septum, which may weaken the extraocular muscles or levator palpebrae superioris and inadvertently induce **diplopia and/or ptosis**.

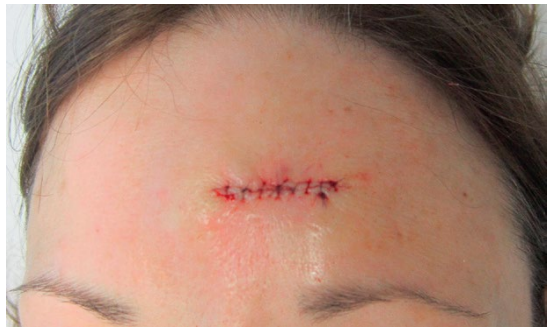


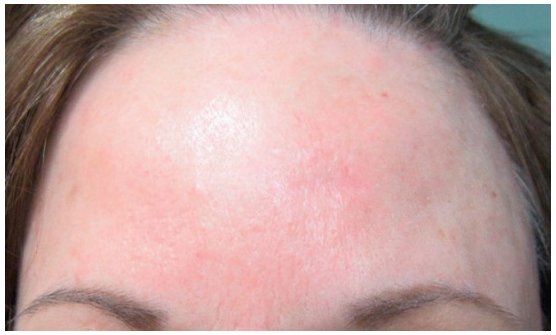


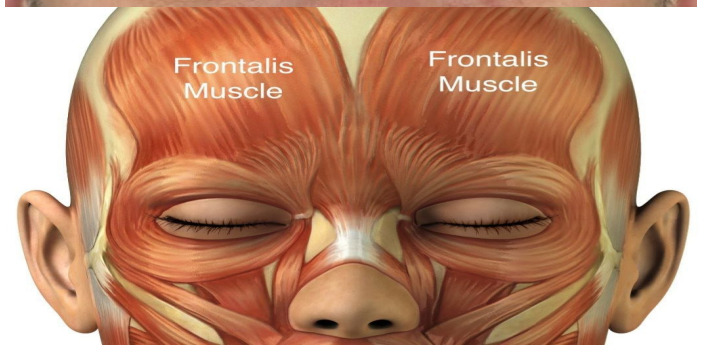
Botulinum toxin can be safely utilized to **treat horizontal forehead lines** .The **frontalis muscle** is very responsive to treatment and therefore low doses of toxin should be utilized initially (**10-15 units**). Botulinum toxin (given around the time of suturing) has also been shown to be **effective for minimizing the appearance of scars** due to surgical and traumatic wounds. The aim of the treatment is to **decrease the forehead and glabellar Wrinkles**



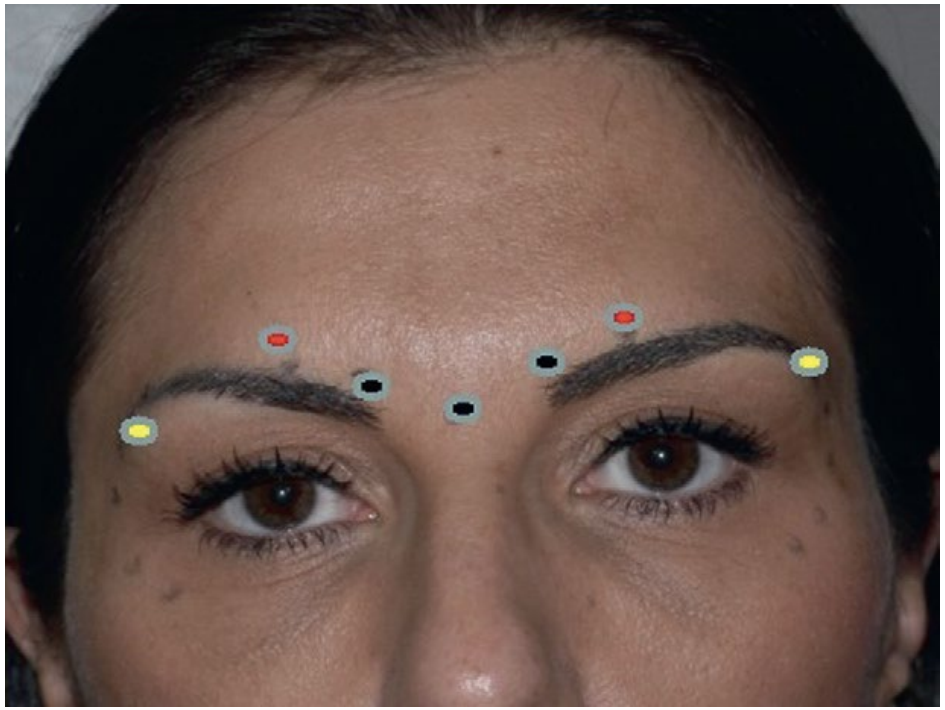


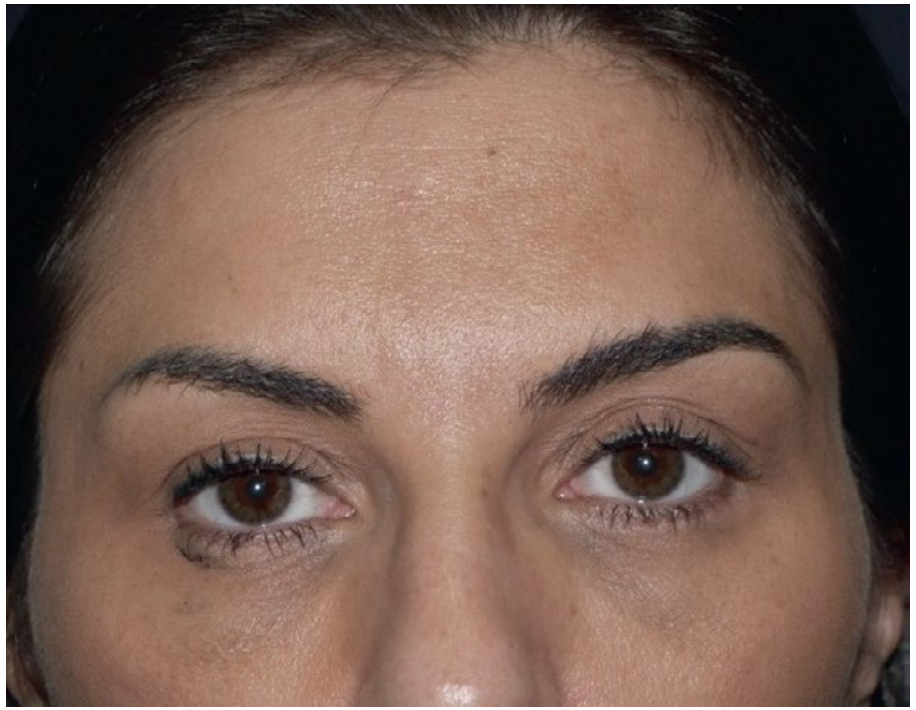




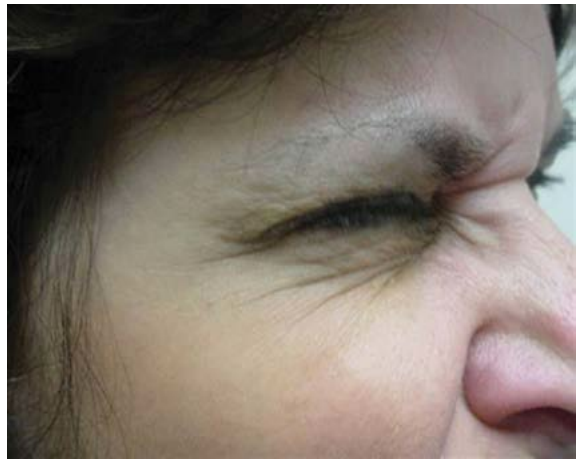


Eyebrow height and shape play a key role in attractiveness, emotional expression, and perceived youthfulness; the ideal brow for an individual depends on many factors, Enhancement of brow height and contour following treatment with botulinum toxin is well documented. **Eyebrow asymmetry is a common problem and asymmetric treatment with botulinum toxin may offer a simple, non-surgical method of correction**

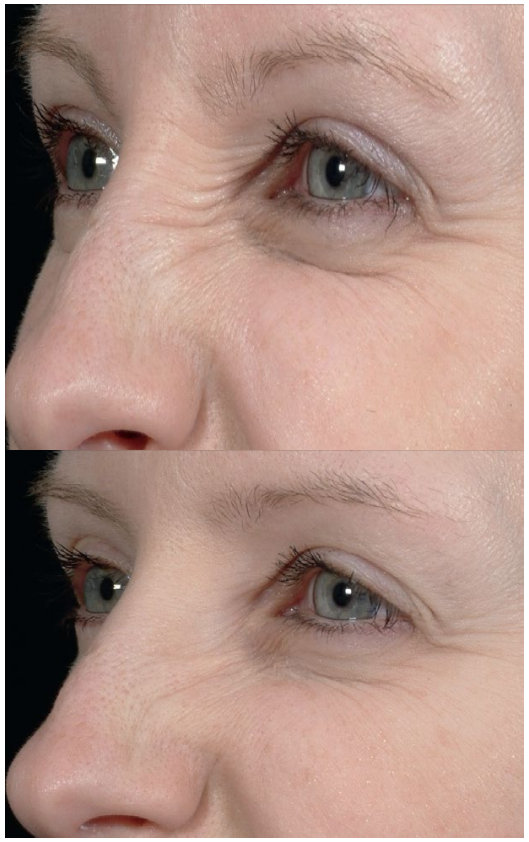


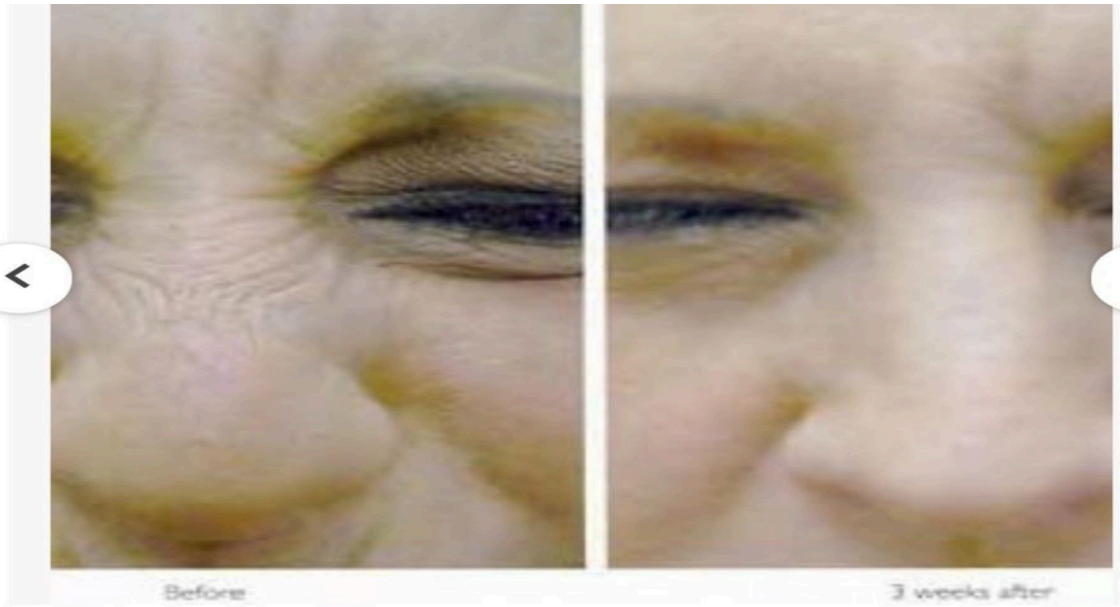


Treatment of **crow's feet** with botulinum toxin is safe and effective, with predictable cosmetic results .Superficial injections into the dermis, combined with frequent needle changes, may reduce injection discomfort, ecchymoses.



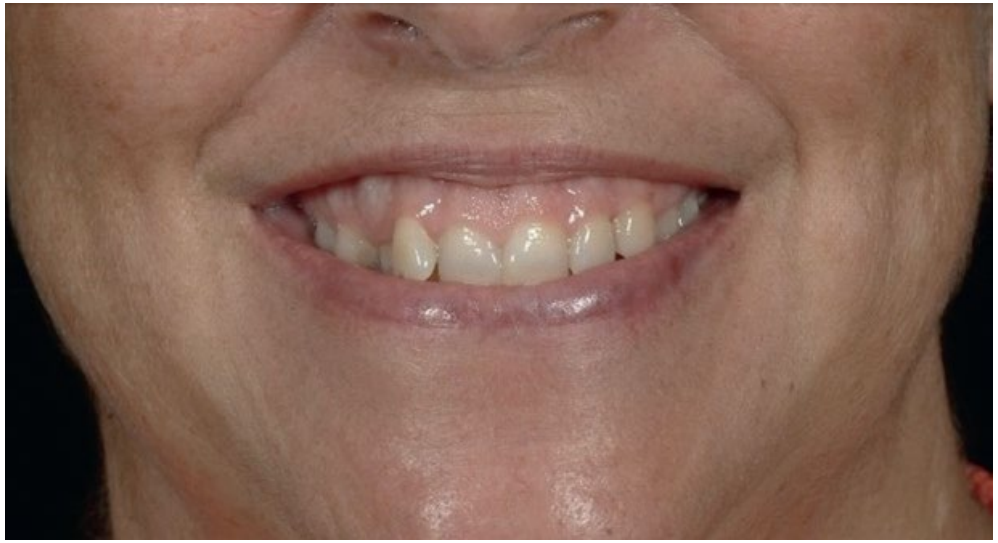
Bunny' lines or nasal sidewall '**scrunch' lines** are angled, horizontal rhytides that traverse the nasal bridge. While not necessarily associated with aging, many patients find them distressing as they convey the **impression of distaste.**

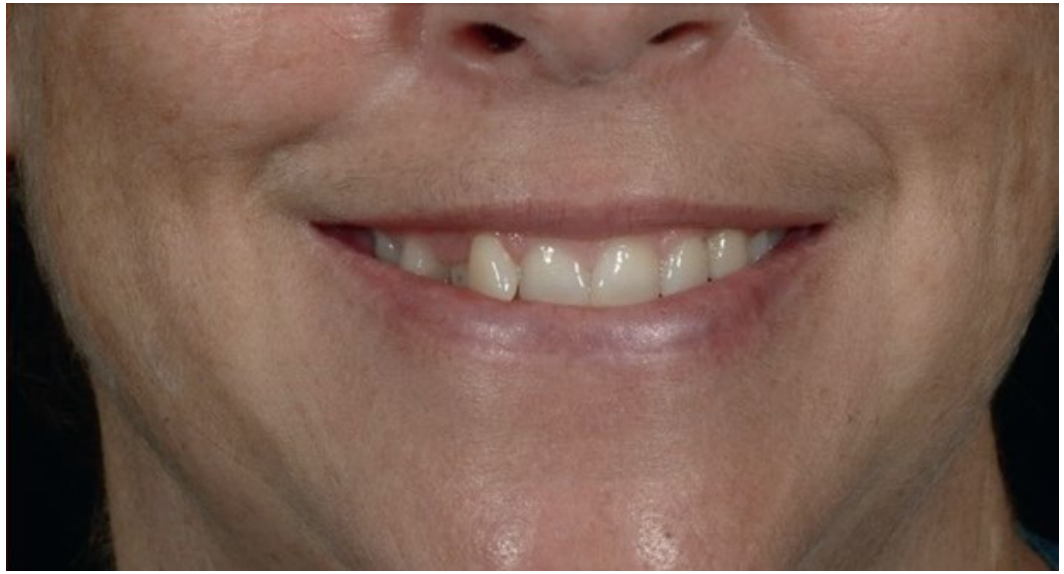




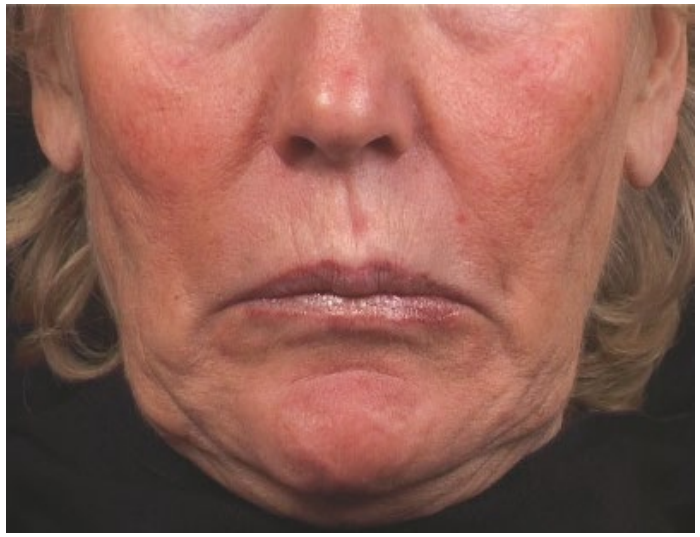
3b This 49-year-old patient is shown frowning before and 3 weeks after a treatment with BOTOX ®. Note the diminished nasoglabellar 'bunny lines'

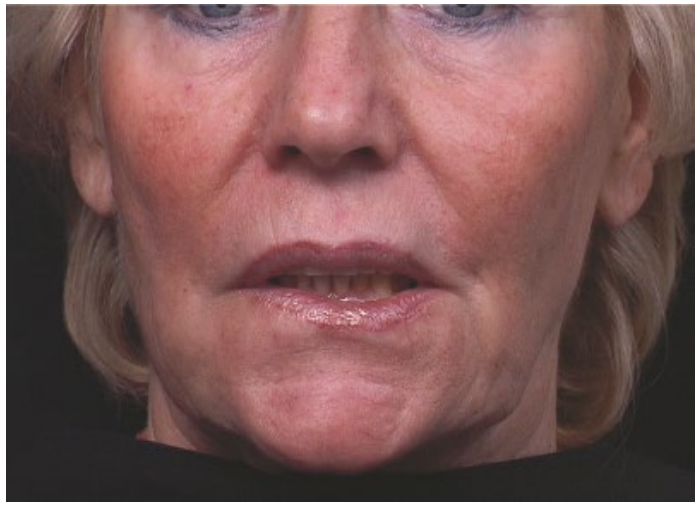
Gummy smile, also known as excessive gingival display, is **a smile that shows an excessive amount of gum under the upper lip**. It is a common unaesthetic clinical condition, which can be caused by an **abnormal dental eruption** (delayed passive eruption), hyperfunction of the upper lip elevator muscle (in this case it can be treated by botox)

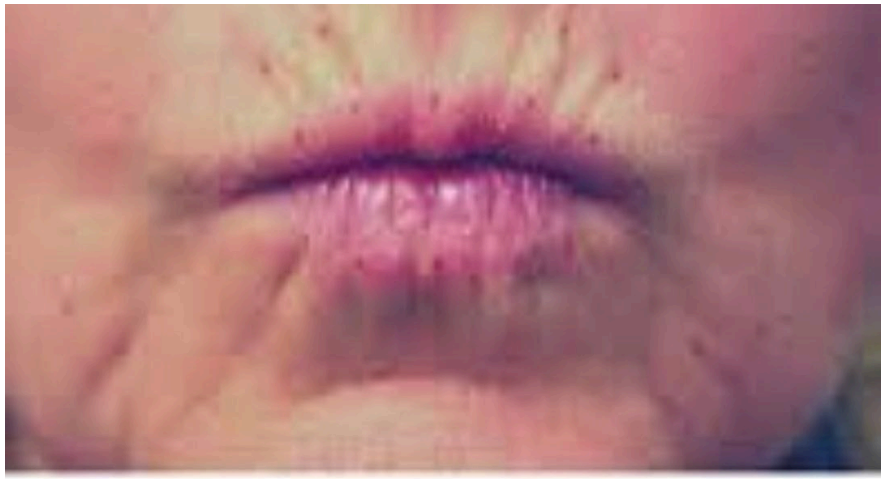


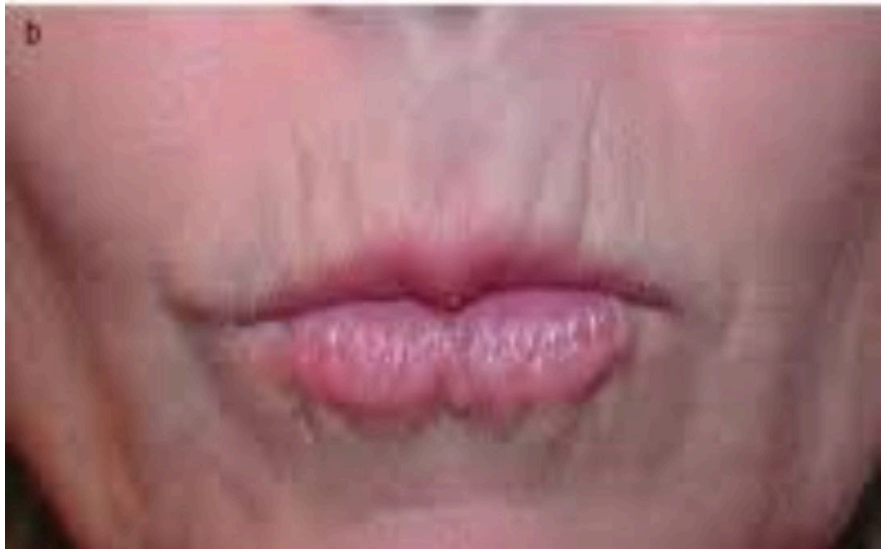


Aging of the perioral and chin regions is characterized by radial perioral wrinkles (so-called smokers' lines or lipstick lines)

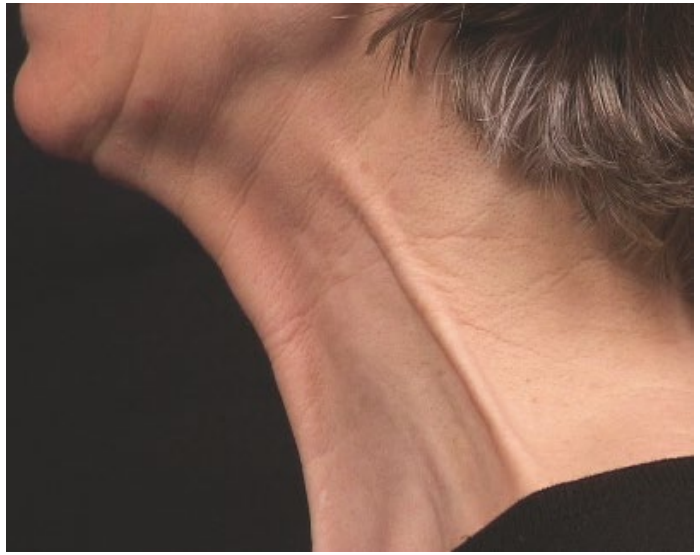


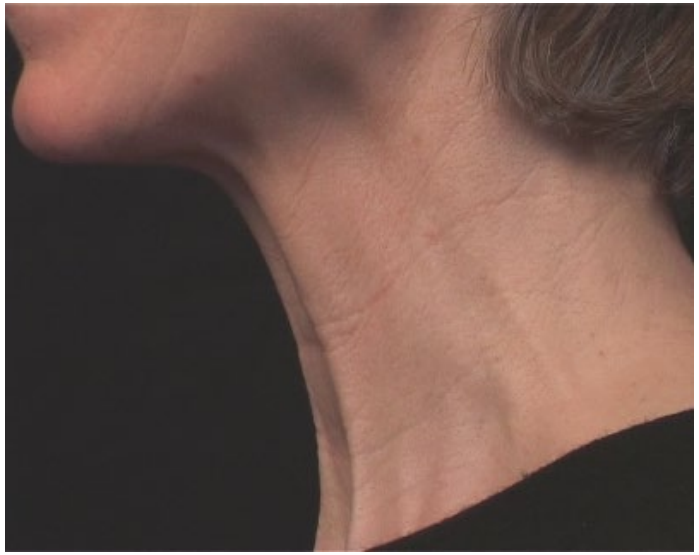


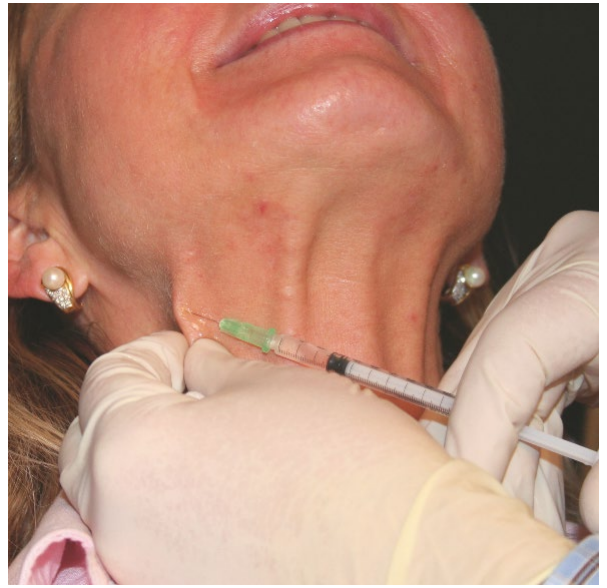




The aim of treatment with BNT-A in the neck area is a reduction of the **vertical bands that appear when the patient contracts the platysma** . Furthermore, lateral cheek lines can be improved when reducing the strength of the platysmal bands. Injection of platysmal bands: should be superficial **very superficial injection**.







BOTOX® Cosmetic Aftercare

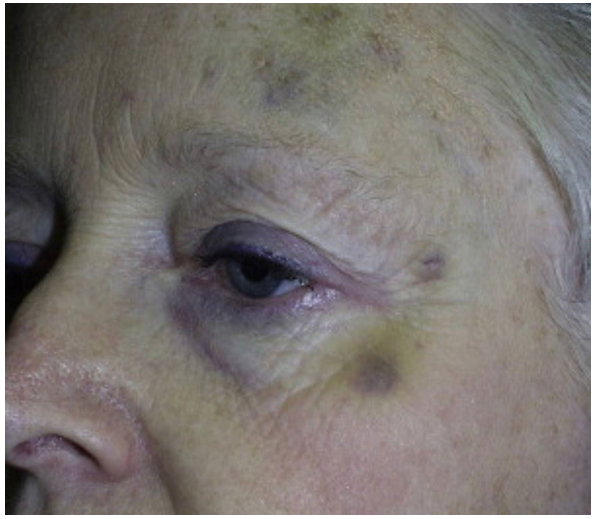
- Don't rub or massage your face.
- Avoid strenuous exercise.
- Keep your head upright.
- Avoid hot tubs and saunas.
- Limit alcohol consumption.
- Avoid blood-thinning medications.
- **Enjoy your rejuvenated look!**

Contraindications to BOTOX® Cosmetic injections

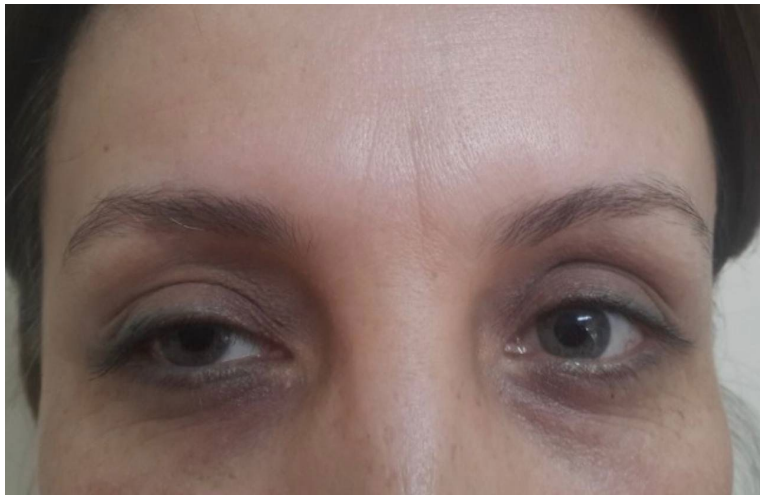
Patients should not be treated or treated with extreme caution who are:

- Psychologically unstable or who have questionable motives and unrealistic expectations
- Dependent on intact facial movements and expressions for their livelihood (e.g. **actors**, **singers**, **musicians** and other media personalities)
- Afflicted with a neuromuscular disorder (e.g. myasthenia gravis, Eaton-Lambert syndrome)
- Allergic to any of the components of BTX-A or BTX-B (i.e. BTX, human albumin, Saline.)
- Taking certain medications that can interfere with neuromuscular impulse transmission and potentiate the effects of BTX (e.g. aminoglycosides, penicillamine, quinine, and calcium blockers)
- Pregnant or lactating (BTXs are classified as pregnancy category C drugs)

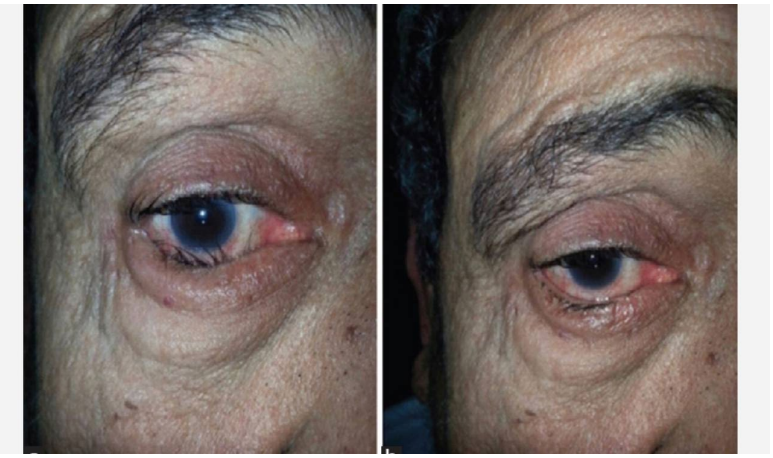
Ecchymosis



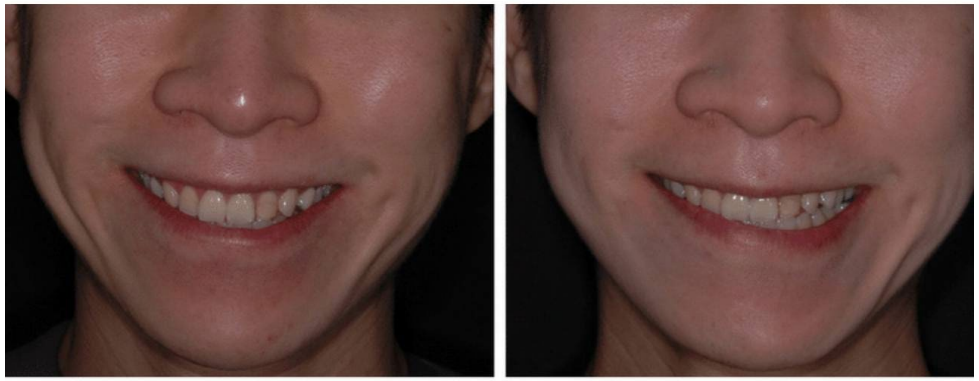
Upper Eyelid ptosis



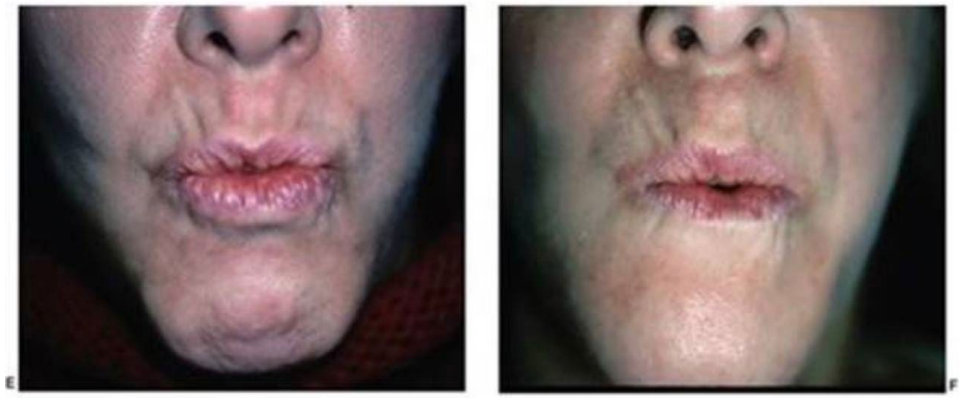
Lower eyelid ectropian



Facial asymmetry



Oral incomptenece



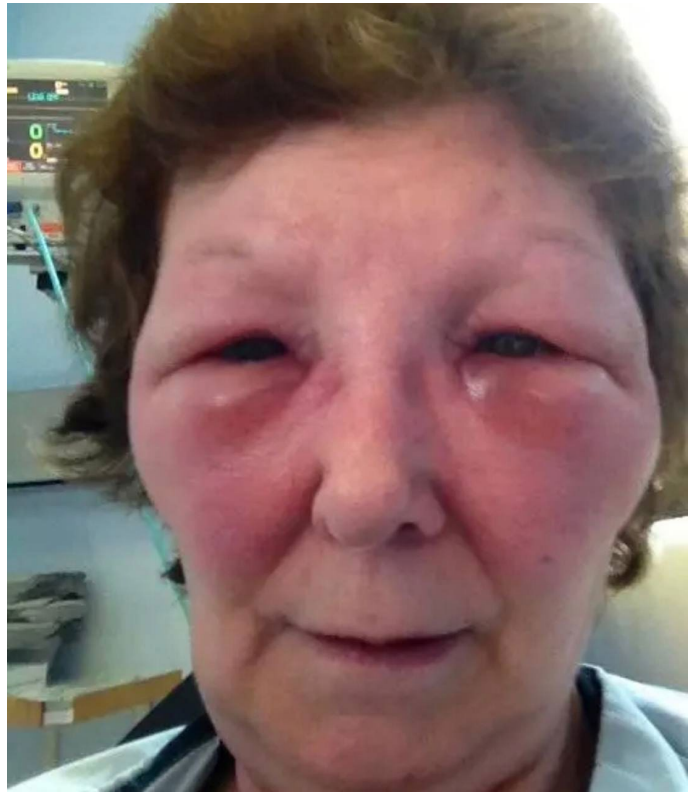
Other rare complications

- Diplopia
- Diminished tearing and xeropthalmia with or without keratitis
- Dysphagia

Immediate hypersensitivity reactions

- Dysarthria

  Urticaria
- Dyspnea
- Soft tissue edema
- Anaphylaxis
- **Allergy reaction to Botox injections is possible**.



THANK YOU

Any Question

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