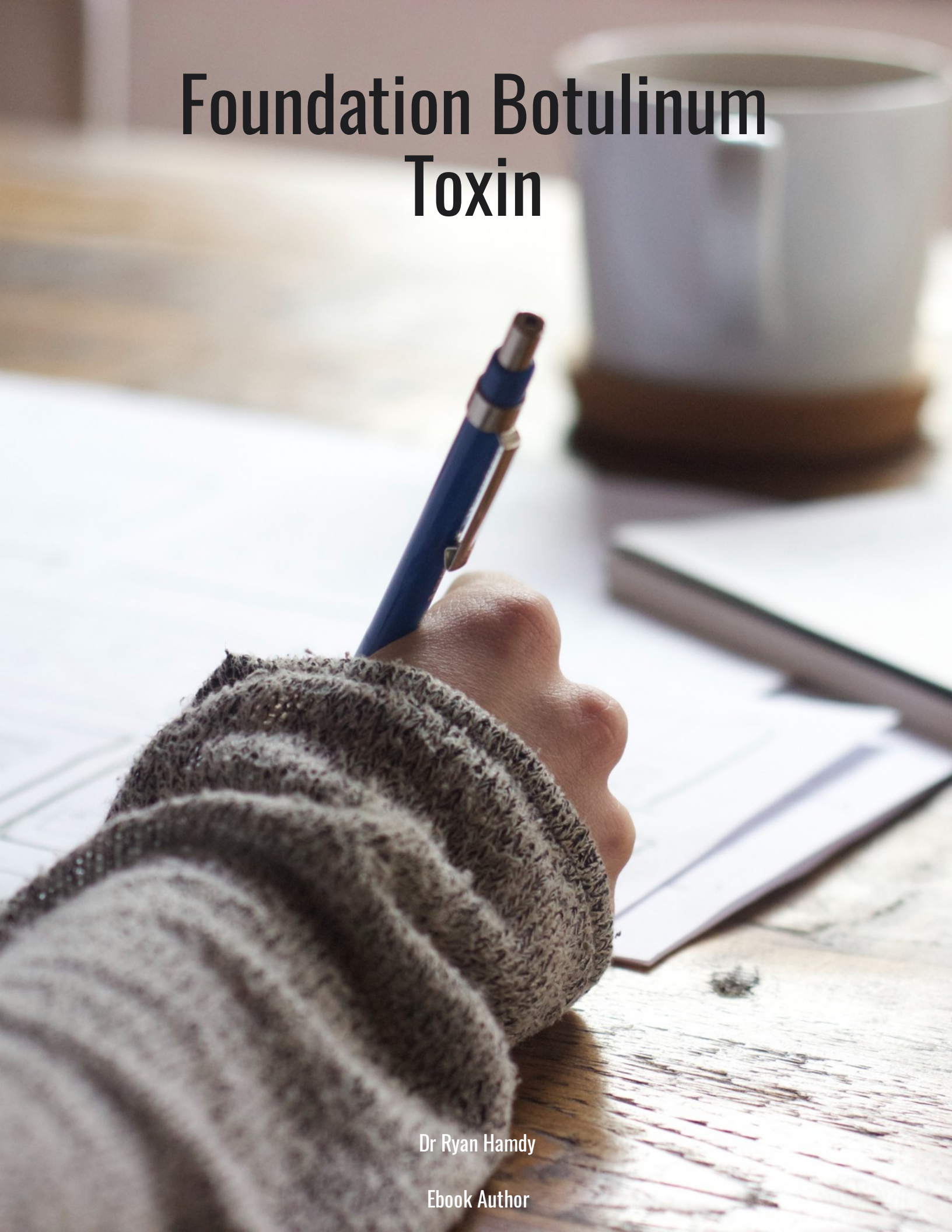
Foundation Botulinum Toxin



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Pharmacology

What is Botulinum Toxin?

Botulinum Toxin is a neurotoxic protein secreted anaerobically by the Bacterium **Clostridium Botulinum**, commonly found in the soil.

It is considered the most powerful neurotoxin ever discovered.

It causes Botulism, a rare but serious paralytic illness.

Symptoms were first described by Kerner, a German physician in 1817, as "sausage poisoning" from eating badly prepared meat products.

Symptoms include, diplopia, ptosis, reduced secretions, difficulty swallowing and speaking. Eventually widespread muscular paralysis and an inability to breathe.

What does Botulinum Toxin Do?

Botulinum Toxin acts as peripheral neuromuscular blocking agent.

How does it Act?

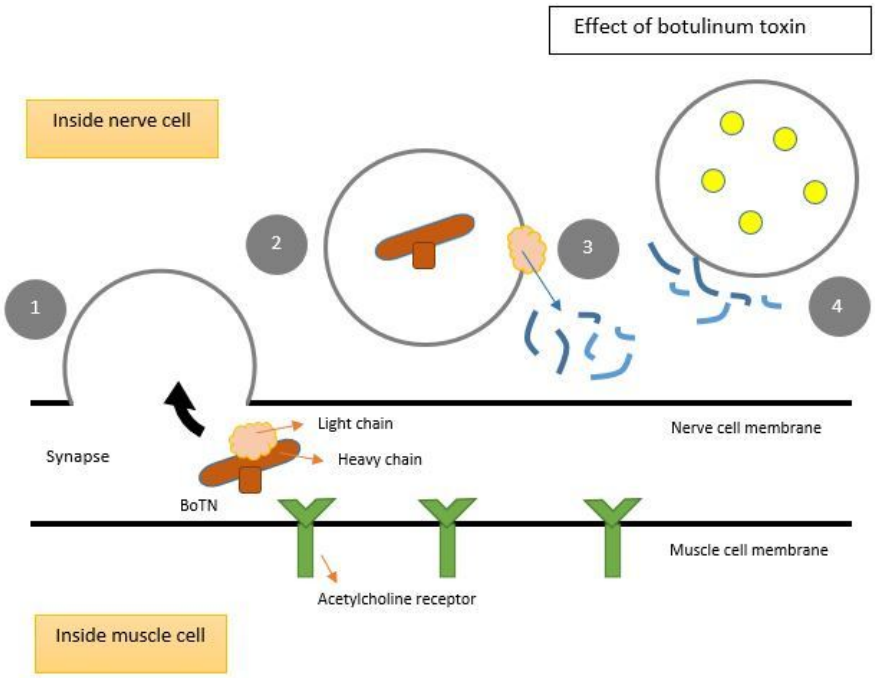
It acts by irreversibly binding to the presynaptic terminal of the neuromuscular junction preventing the release of the neurotransmitter **Acetylcholine,** thereby preventing muscle contraction.

There are 3 steps involved in this process.

1. Binding

2. Internalisation

3. Blocking



The Botulinum Molecule has a molecular weight of 150KD (kilodaltons). This is comprised of a **heavy chain** weighing 100KD and a **light chain** weighing 50KD.

Binding is the process that results in the Botulinum Toxin molecule attaching itself to receptors on the outer nerve cell membrane. The heavy chain is responsible for this process.

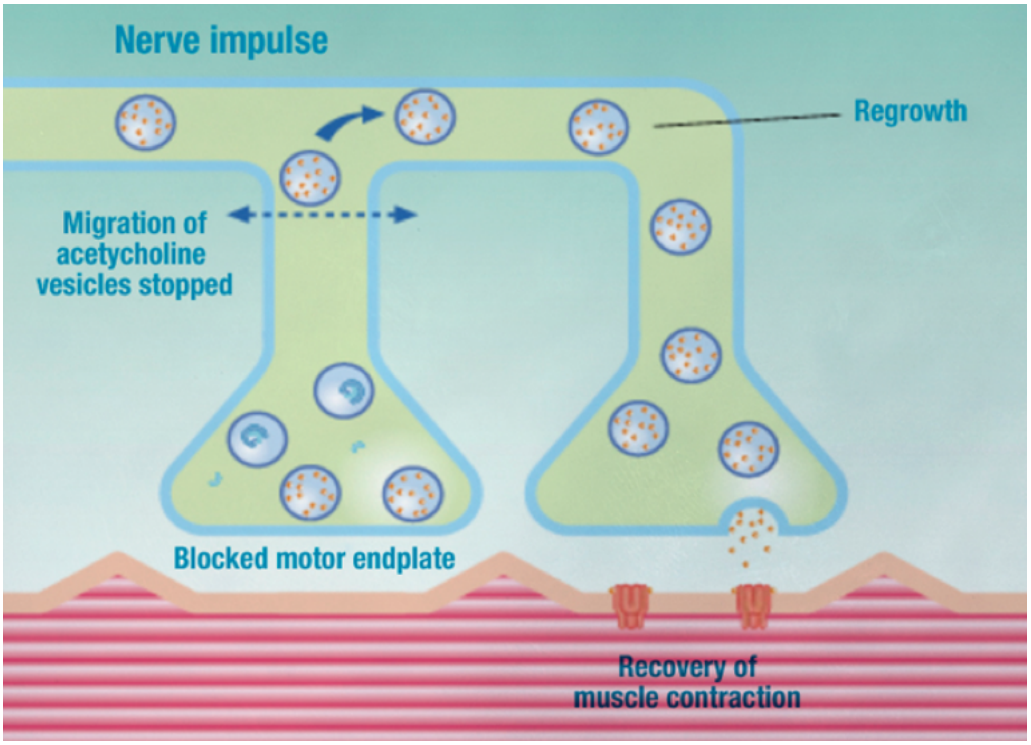
Internalisation is the process by which the Botulinum Toxin molecule is taken into the nerve end cell and encapsulated. The light chain subsequently sheers from the main molecule and is released into the nerve cell.

Blocking is the process whereby the Botulinum Toxin light chain damages the Snare Complex resulting in an inability of the acetylcholine vesicles to bind to the inner wall of the nerve cell membrane thereby preventing release of neurotransmitter to the muscle cell. The Snare Complex is a collection of proteins which act as a release receptor allowing acetylcholine vesicles to bind and release their contents.

What happens to the nerve once blocked?

In response to nerve paralysis, new synapses with adjacent muscle fibres begin to develop.

This gradually restores neuromuscular transmission and muscle function, explaining the temporary nature of Botulinum Toxin paralysis.



Function of the original synapse eventually returns and as a result the new sprouts disappear.

What are Botulinum Toxin Serotypes?

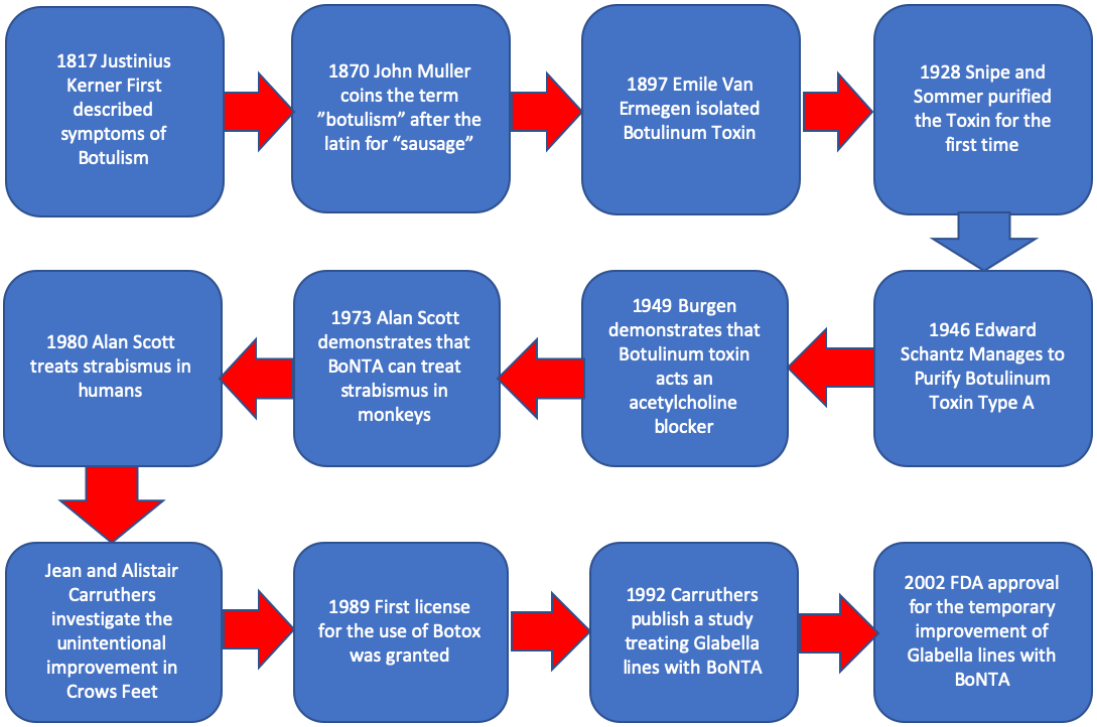
A serotype is a serologically distinguishable strain within a single species or microorganism.

8 Botulinum Toxin serotypes have been identified all with distinct structures. **A-H.**

The A serotype is the most powerful and is most commonly used in facial aesthetics

We will refer to Botulinum Toxin molecule as **BoNTA** from now on. **Botulinum Neurotoxin Type A.**

Historical Time Line



Other interesting Historical Landmarks

1989 FDA approval for Botox™ for the treatment of strabismus, blepharospasm and hemifacial spasm.

2002 FDA approval for Botox™ for the temporary improvement of Glabella lines.

2010 FDA approval for Botox™ for the management of migraine and upper limb spasticity.

2013 Botox™ receives FDA approval for the cosmetic treatment of Crows Feet.

2017 Botox™ receives FDA approval for the cosmetic treatment of Forehead lines.

In addition to Botox Xeomin (Bocouture) is licensed for the treatment of all 3 upper face areas.

Dysport™ (Azzalure™) is licensed for the treatment of Glablla lines and Crows Feet only.

Dysport™ was developed as a joint collaboration between clinicians and the Applied Microbiology Research Facility at Porton Down in Salisbury UK. It acquired a licence in 1990 to treat dystonia. Hence the name.

Dystonia and **Port**on Down-**DYSPORT.**

Brands

The most commonly used brands include Botox™, Azzalure™, Dysport™, Bocouture™ and Xeomin™.

All are derived from the same strain of **BoNTA.**

Botox™

Onabotulinum Toxin A. It's a 900 KD BoNTA molecule. Produced by Allergan™.

100 BU per vial. Also contains 0.5mg Human Albumin and 0.9mg Sodium Chloride.

Vacuum dried. Must be refrigerated prior to use, and once reconstituted, at 2-8˚.

Botox™ is licensed for use in all 3 upper face areas- glabella, forehead and lateral canthal lines.

Vistabel™ is also Onabotulinum Toxin A produced by Allergan™ but in a 50 BU vial.

Azzalure™

Abobotulinum Toxin A. It's a 500-900 KD BoNTA molecule. Produced by Ipsen™ and commercialised by Galderma™.

125 Speywood Units (SU) per vial. Also contains Human Albumin and Lactose.

Lyophilised (freeze dried) and stored as a powder. Must be refrigerated prior to use, and once reconstituted, at 2-8˚.

Azzalure™ is only licensed for use in the glabella and lateral canthal lines.

Dysport™ is also Abobotulinum Toxin A produced by Ipsen™.

It is available in 300 SU or 500 SU vials. It is also stored at 2-8˚.

Bocouture™

Incobotulinum Toxin A. It's a 150 KD BoNTA molecule. Produced by Merz Pharma Group™.

50 Bocouture Units per vial. Also contains 0.5mg Human Albumin and 2mg of Sucrose.

Bocouture is available in a 100 Bocouture unit vial.

Free from complexing proteins. Complexing proteins are thought to protect the free Neurotoxin molecule from the gastrointestinal tract and aid stability.

Lyophilised and stored as a powder. Bocouture™ **can** be stored at room temperature, but must be refrigerated, after reconstitution, at 2-8˚.

Bocouture™ is licensed for use in all 3 upper face areas-glabella, forehead and lateral canthal lines.

Xeomin™ is also Incobotulinum Toxin A produced by Merz Pharma Group™.

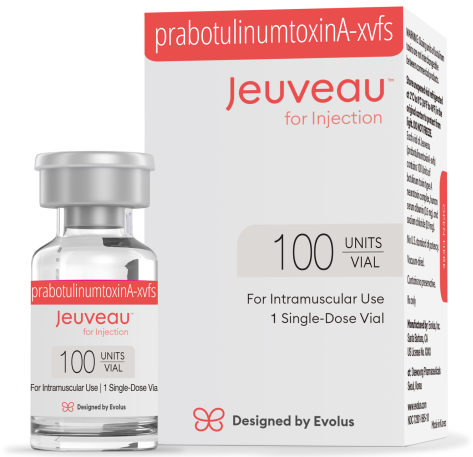
It is available in 50 and 100 Xeomin Unit vials.

Note Bocouture™ and Xeomin™ are identical.

Other FDA approved Neurotoxins.

Myobloc™. This is Rimabotulinum Toxin B. Currently approved for cervical dystonia. Very limited use cosmetically due to poor duration and discomfort of injection.

Jeuveau™. This is Prabotulinum Toxin A produced by Evolus Inc ™. It's a 900 KD BoNTA. It has received FDA approval for the treatment of Frown lines. It comes in a 100 Jeuveau Unit vial and dosing is said to be on a 1:1 ratio with Botox™. Jeuveau™ was available for use in the US in 2019.



Please Note.

The Dosing Units are **NOT** interchangeable.

Although independent studies have suggested a ratio of;

Botox™ **(1BU)** : Bocouture™ **(1 Bouture Unit)** : Azzalure™ **(2.5 SU).**

Also, all Neurotoxins are defined as **medicines** and as such need to be prescribed by a Doctor, Dentist or Nurse with prescribing privileges.

Preparation

What consumables will you Need?

1. Sterile dressing pack with sterile swabs.

2. Gloves.

3. Cleansing solution.e.g. Chlorhexidine, Clinisept.

4. 1ml or 2.5ml syringes to add diluent.

5. 21 or 23 G needle to add diluent.

6. Cap-off device to remove metal collar from vial. This allows the rubber bung to be removed.

7. 0.3ml, 0.5ml and 1.0ml Insulin syringes with 30G-32G needles. To administer dosing.

8. Removable marker pencil to mark injection points.

9. Bacteriostatic Saline to act as a diluent and Toxin of choice.

Reconstitution

This is done in clinical practice with **Bacteriostatic Saline**. All inserts will advise using non-preserved saline. However, it appears that using Bacteriostatic saline results in significantly less discomfort for the patient.

Botox™ 100 BU

Recommended dilution is with 2.5mls. of Bacteriostatic Saline.

The resulting concentration is **4 BU per 0.05mls**. of solution.

Allow the vacuum to pull the Bacteriostatic Saline into the vial. Do not agitate but gently roll the vial to ensure full dissolution of product.

Azzalure™ 125 SU

Recommended dilution is with 0.63mls. of Bacteriostatic Saline.

The resulting concentration is **10 SU per 0.05mls**. of solution.

Allow the vacuum to pull the Bacteriostatic Saline into the vial. Do not agitate but gently roll the vial to ensure full dissolution of product.

Bocouture™ 50 U

Recommended dilution is with 1.25mls. of Bacteriostatic Saline.

The resulting concentration is **4 Bocouture Units per 0.05mls**. of solution.

Allow the vacuum to pull the Bacteriostatic Saline into the vial. Do not agitate but gently roll the vial to ensure full dissolution of product.

Preparing to Inject

After reconstitution The BoNTA solution can be withdrawn from the vial with either a 0.3ml, 0.5ml or 1.0ml Insulin syringe depending on your dosing. Remove metal collar and remove rubber bung prior to withdrawal.

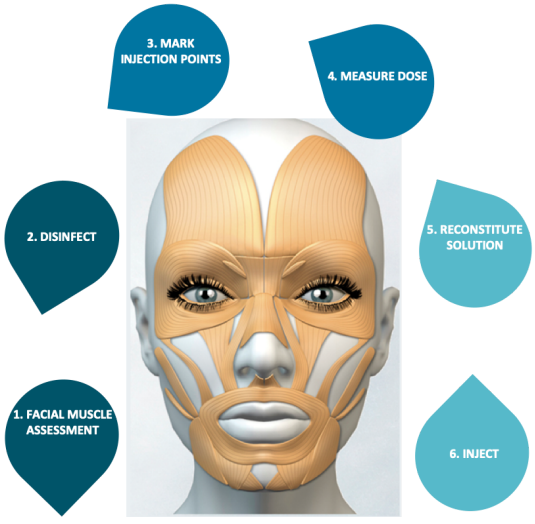
These syringes have a needle as well are are very vulnerable to blunting. So, take care not to touch the inner surface of the glass vial when withdrawing. Also withdraw slowly to limit the amount of air bubbles taken up.

A popular brand of syringe are the FMS syringes.

Once reconstituted, BoNTA should only be used to treat a single patient, during a single session.

Remember to remove any makeup and disinfect the skin prior to marking and injection.

The injecting process involves a number of steps.



We will cover a number of these steps later in the course.

Field of Effectiveness

The active Neurotoxin in all BoNTA products separate immediately from their complexing proteins when reconstituted. When injected this creates a field of effectiveness.

Any spread around the injection points depends on dose, volume and injection technique, as opposed to variations in complex size.

The active Neurotoxin across all BoNTA products is identical (150 KD)

Consequently, it is felt that other proteins in the toxin complex play no part in the spread of BoTNA and its field of effectiveness.

Diffusion and Spread of BoNTA

Diffusion and spread are often confused as the same, but they are notably distinct.

Spread is the physical motion of molecules moving from one area to another, which is dependent on injection technique, volume and possibly applied forces rather than the product properties.

Diffusion is a kinetic process, which occurs when a high concentration of any compound is introduced to an area with a low concentration.

Diffusion is a slow process which could explain why the full benefits of treatment are often seen days later.

Contraindications

1. Under 18 years of age. This is certainly the case for Aesthetic use.

2. Pregnancy and Breast feeding.

3. History of known allergy to Neurotoxin or any excipients e.g. Lactose, Human Albumin.

4. Infection at the site of injection.

5. Those with a history of Myasthenia Gravis, Lambert-Eaton Syndrome or Amyotrophic Sclerosis.

Care should be taken in those with;

1. History of dysphagia or aspiration.

2. Those with prolonged bleeding times.

3. Patients with very unrealistic expectations.

Therapeutic Indications for BoNTA

BoNTA is approved in more than 75 countries to treat a wide variety of disorders primarily neuromuscular.

Examples Include:

Cervical Dystonia. Neck muscle spasm causing the head to be pulled back or sideways.

Hemifacial Spasm. Involuntary contractions on one side of the face.

Blepharospasm. Rapid blinking or forced eye closure.

Bladder Dysfunction. Detrusor Instability with symptoms of urinary urgency and frequency.

Chronic Migraine. Unresponsive to other medical interventions.

Strabismus.

Upper and Lower Limb Spasticity.

Equine Foot Deformity in Childhood.

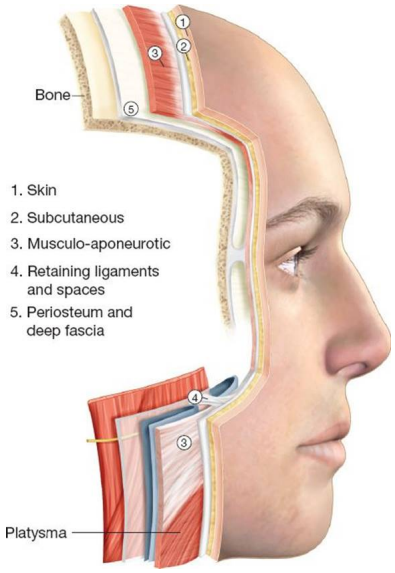
Focal Hyperhidrosis. Hands, feet and Axillary.

Anatomy

An understanding of facial anatomy is key to all aspects of Facial Aesthetics.

This ranges from a knowledge of the function of skin to the underlying structures including the muscles and vasculature.

The face is made of **layers**. In fact, the face has 5 distinct layers.



Layer 1. Skin.

This is composed of the epidermis and dermis.

The skin is the largest organ of the body and serves 3 basic functions. Protection, Sensation and Regulation.

Layer 2. Subcutaneous Fat.

This layer serves to cushion and contour the face. It also acts as a store of energy. In the face this fat layer can be further divided into various compartments separated by fibrous septa and ligaments.

Layer 3. Fibromuscular Layer.

In the face and neck this is known as the SMAS (Superficial **M**usculo-**A**poneurotic **L**ayer). This is a network of muscles and fibrous tissue connecting the facial muscles to the skin via fibrous septa and allowing these muscles to work in a coordinated manner.

Layer 4. Deep Fat.

This layer sits above the periosteum. This layer contours and acts as a glide plane for the overlying muscles.

Layer 5. Periosteum and Bone.

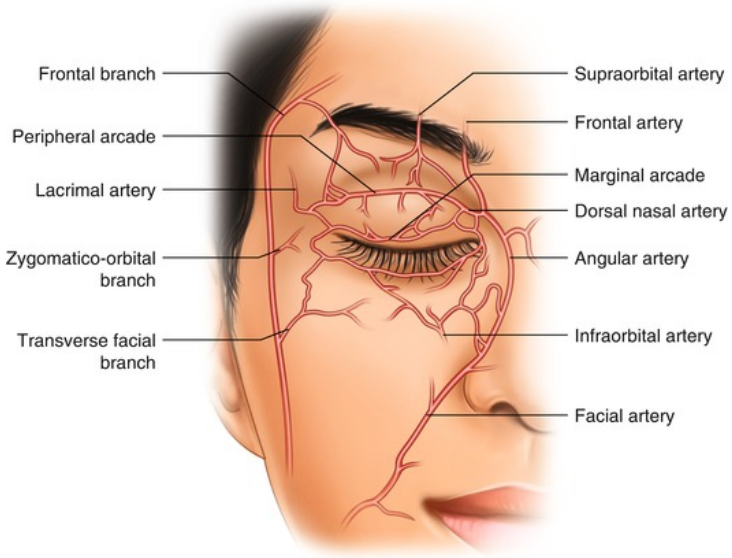
Facial Arteries and Nerves

Running through the various layers of the face are the essential arteries and nerves.

Arteries

A full and thorough appreciation of the facial vasculature is probably the most important part of Facial Aesthetics. Not only understanding the course of the various vessels but perhaps more importantly the **depth** of the vessels. This will be further discussed in subsequent courses relating to Anatomy and Dermal Fillers.

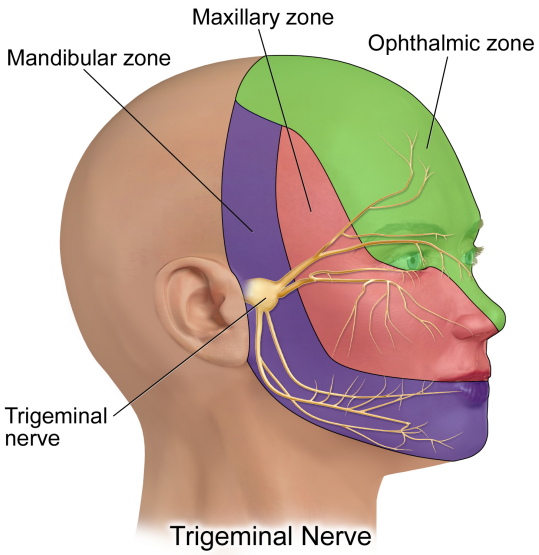
Reassuringly, with regards to Botulinum Toxin, there are potentially **No** serious issues related to intra-arterial injection at cosmetic doses.



The upper part of the face derives its blood supply from both the Internal Carotid System and well as the External carotid System.

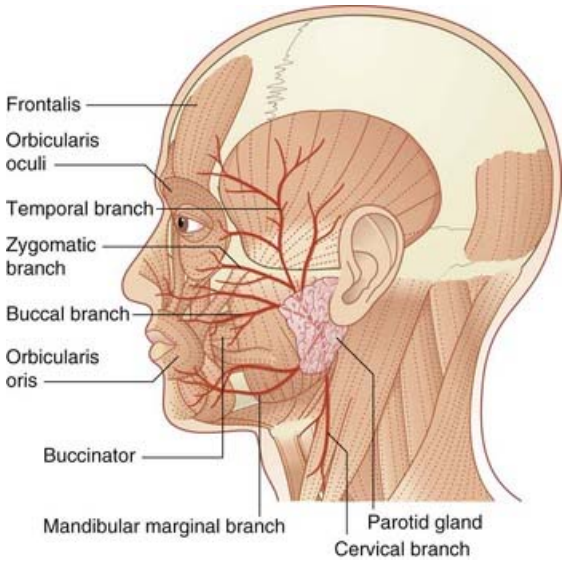
Nerves

The sensory innervation of the face come from the **Trigeminal Nerve**. It divides into 3 separate branches. The Ophthalmic, Maxillary and Mandibular Branches.



Trigeminal Nerve

The motor innervation of the face comes from **Facial Nerve**. The VII Cranial Nerve. This controls the muscles of facial expression.

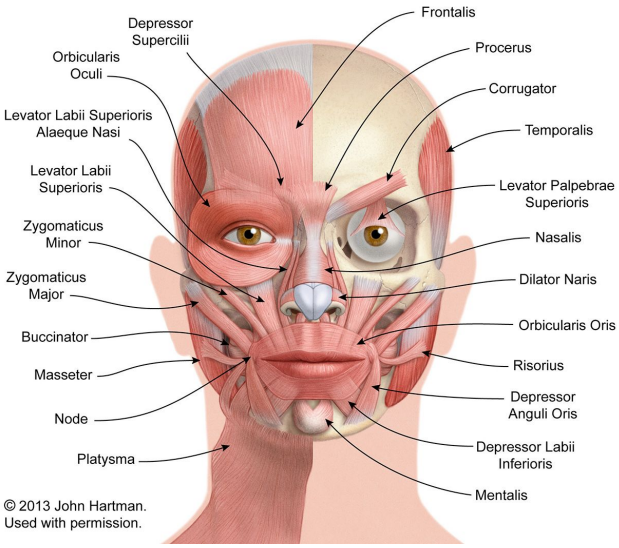


The Facial Nerve emerges through the stylo-mastoid foramen and traverses through the parotid gland.

It then divides into 5 branches supplying the face and neck.

Again, as with the arterial supply of the face, the risk of damage to the nerves of the face with Botulinum Toxin injections is extremely low.

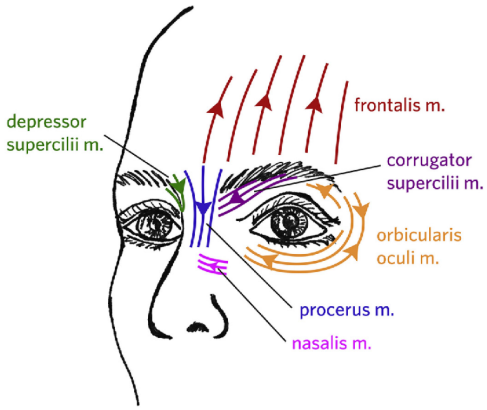
Facial Muscles



The facial musculature is extremely complex.

With the exception of Orbicularis Oris, all the muscles have a boney origin and a skin insertion.

In addition, we should also understand that we can further divide these muscles into muscles that **elevate** and muscles that **depress** depending on their action.



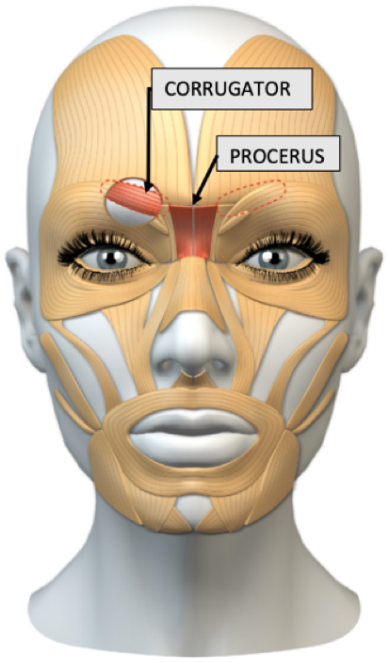
In the upper part of the face Frontalis tends to be the principal elevator.

The principal depressors are Procerus, Corrugators and Lateral Orbicularis Oculi.

Understanding this principle is vital, when trying to prevent depression or, to create lift e.g. lateral brow lift.

Upper Face Muscular Complex

Glabella Complex



The Glabella is composed of the muscles Procerus and Corrugators.

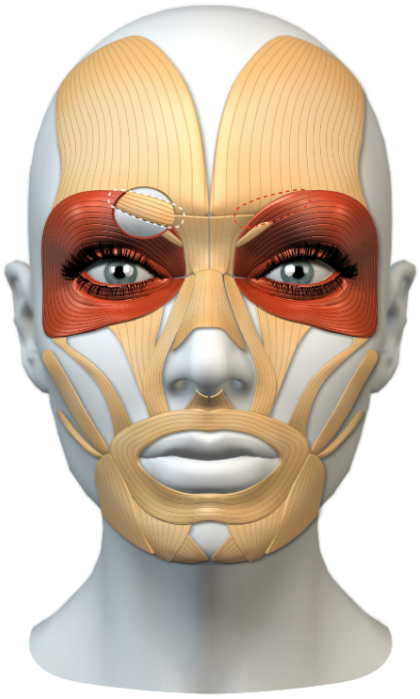
The **Procerus** muscle originates from the nasal bone and inserts into the skin of the brow.

It is responsible for pulling the medial brow down and contributes to horizontal lines on the bridge of the nose. It is a BROW DEPRESSOR.

The paired **Corrugator** muscles originate from the medial boney brow and insert into the skin of the lateral brow.

They are responsible for pulling for pulling the medial brow down and inwards and contribute to the vertical frown lines. They are BROW DEPRESSORS.

Orbicularis Oculi



The **Orbicularis Oculi** muscles originate from the medial orbital margin and lacrimal sac and insert into the lateral palpebral raphe.

They are responsible for closing the eyes and aiding in the passage and drainage of tears. Contraction of the muscle contributes to lateral canthal lines or Crow's Feet.

There are 3 portions to Orbicularis Oculi Muscle.

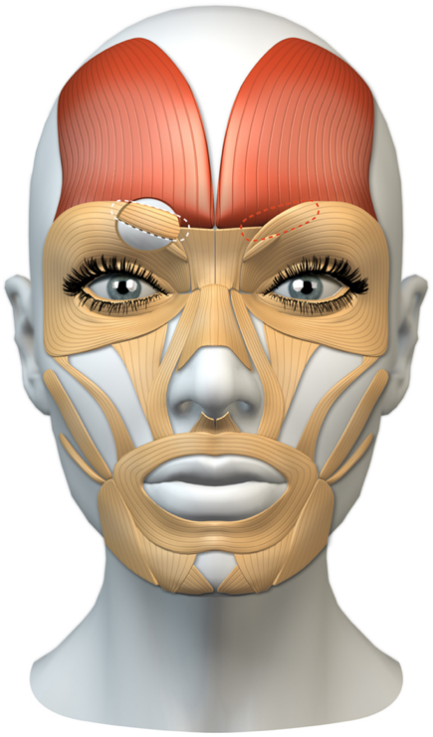
The Orbital Portion which is responsible for voluntary eye closure.

The Palpebral Portion which is responsible for involuntary eyelid closure.

The lacrimal Portion which is responsible for lacrimal sac compression.

Lateral Orbicularis Oculi are BROW DEPRESSORS.

Frontalis



The **Frontalis** Muscle originates from the Galea Aponeurotica and inserts into the skin of the brow. It's usually comprises of two muscular bellies.

This muscle is responsible for lifting the eyebrows and its action contributes to horizontal forehead lines. This muscle is a BROW ELEVATOR.

Remember that lines or creases caused by these muscles will appear **perpendicular** to the action of the muscle.

Patient Assessment

Sufficient assessment pre-injection is essential to a successful outcome.

Appropriate Patient Selection.

Take a full medical history including a full drug/OTC history. Ensure the patient is within the age limits set for your clinic. Look for potential contraindications.

If required, consider taking a mental health history. Watch for evidence of Body Dysmorphic Syndrome. Consider using the various assessment tools that are available now.

Evaluate the Lines

Examine the face fully both statically and dynamically. Assess whether the lines are treatable. Dynamic lines are more likely to be managed with BoTNA than static lines.

Use the various assessment tools that are available to you now.

Look for asymmetries and unique characteristics in your patients. Consider pointing these out to your patient prior to treatment.

Understand your patient's motivation and expectations. These need to be managed carefully to avoid disappointment.

REMEMBER to consider other treatment modalities as well e.g. filler, laser, peels, skincare etc.

Clinical Assessment Tools

A number of useful tools are available for assessing your patient.

Glogau Photo Ageing Scale

Group Classification	Typical age	Description	Skin Characteristics
I Mild	28-35	No wrinkles	Early Photoaging: mild pigment changes, no keratosis, minimal wrinkles, minimal or no makeup
II Moderate	35-50	Wrinkles in motion	Early to Moderate Photoaging: Early brown spots visible, keratosis palpable but not visible, parallel smile lines begin to appear, wears some foundation
III Advanced	50-65	Wrinkles at rest	Advanced Photoaging: Obvious discolorations, visible capillaries (telangiectasias), visible keratosis, wears heavier foundation always
IV Severe	60-75	Only wrinkles	Severe Photoaging: Yellow-gray skin color, prior skin malignancies, wrinkles throughout—no normal skin, cannot wear makeup because it cakes and cracks

You may consider using this in patients who you may not think appropriate for BoNTA

Merz Aesthetic Scale

This is a graded scale provided by Merz Pharma to assess and moderate expectations.

Realistically it maybe we can improve lines by one or two points on the scale.

Mirror Stretch Test

Simple test. Hold a mirror in front of your patient and stretch the line or wrinkle to be treated laterally. If the line is still present at full stretch, then it is likely that BoNTA will not fully eradicate the problem.

Whichever method you use please **ensure** that you monitor your patient's progress with photography.

Clinical Photography

Taking good quality photographs will benefit you and your patient.

You can demonstrate to your patients the benefits or improvement at review.

You can show the patient that asymmetries or imperfections were actually present prior to treatment and were not as a consequence of your treatment.

Regular photography will help you build up your treatment portfolio.

You can also use photography to assess treatment shortcomings and further improve your technique.

Using a high-quality camera, consistent lighting and background is imperative. Also consider taking a short video to assess dynamic lines.

Consent

Consent now is probably the most important part of the whole pre-treatment process.

Informed consent allows the patient to understand the benefits of treatment but also consider the risks and complications that are inevitably associated.

Please do NOT assume that the patient will read the consent form. It is advisable to go through you consent form verbally as well.

Consider giving your patient a cooling off period if they seem unsure.

Remember a properly completed consent form will also be helpful in the event of litigation.

Financial Considerations

Another area that medics are often embarrassed to talk about.

Prior to treatment make sure your patient is fully aware of the costs of treatment and any additional costs that may be incurred at a later date.

Pain Management

Inevitably, with any invasive procedure associated with a break to the skin, pain will be a feature.

This may be potentiated by patient anxiety, needle phobia or cyclical hormonal issues.

Generally, the discomfort associated with BoNTA injections is minimal, but pain relief may be required for some patients.

What can you Do?

Talk to your patient. Explain the procedure and outcome. This is often enough.

Use other methods of distraction e.g. stress ball or music.

Consider using ice or another cooling device before injection.

You may need to use a topical anaesthetic. These are usually lidocaine-based creams or ointments.

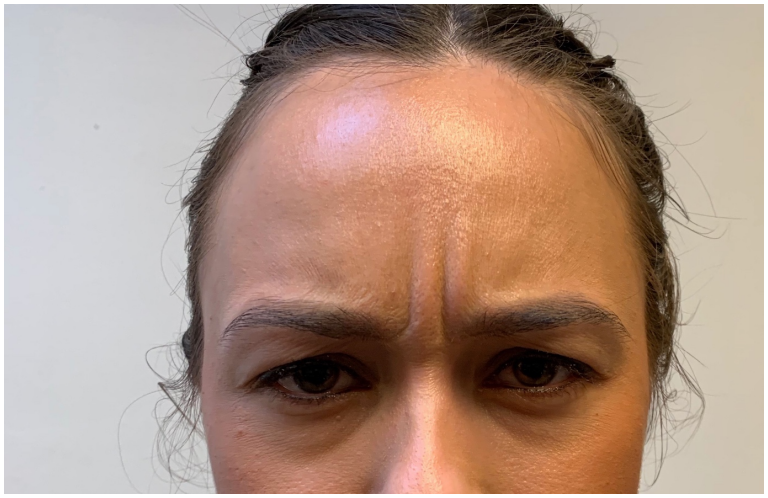
Also please remember to use Bacteriostatic Saline as your diluent. This is reported to reduce the pain associated with injection. Do **NOT** use water for injection. This is not at physiological PH and is uncomfortable.

Lastly, use as finer needle as possible to inject.

Be mindful that very fine needles blunt easily, so you will need to change your needle frequently.

Treating the Glabella

Contraction of the Glabella complex of muscles results in the formation of dynamic vertical frown lines and the horizontal frown line along the bridge of the nose.



Treatment with BoNTA reduces the lines by inhibiting contraction of the muscles Procerus, the corrugators and depressor supercilii.

Typically, this area is treated with 5 injection points.

One injection into procerus.

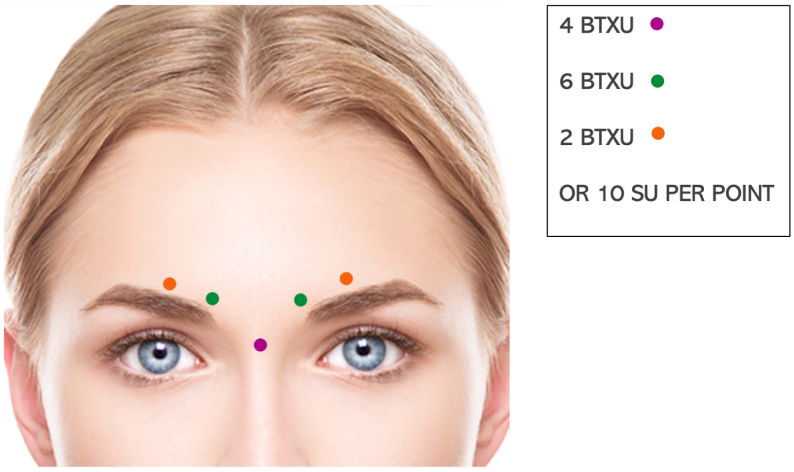
Two injections into each corrugator.

As your experience and skill develop you will modify and fine tune your injection points accordingly.

Usual dosing for Glabella complex is;

20-30 BU or 50-75 SU

Note that males tend to have a larger muscle bulk and will need a higher average dosing.



Injection Tips

- Procerus injection point is found at the intersection of two lines drawn from the inner canthus on one side and the ipsilateral brow on the other. Inject perpendicular to the skin.
- Medial Corrugator injection point is found on the vertical line ascending from the inner canthus. This is usually 0.5-1cm above the orbital rim. Remember to hold the muscle between finger and thumb and inject in-between. Inject perpendicular to the skin.
- Lateral Corrugator point is found where there is visible pulling of the skin. Keep this injection point 1cm above the superior orbital rim and just medial or lateral to the mid pupillary line. Keep the injection point superficial to reduce the risk of eyelid ptosis.
- Try not to hit bone as this is painful and can cause headache.
- You may wish to guard the orbital rim with the non- injecting hand to reduce the risk of product migration.

Studies, at standard doses, have demonstrated that all BoNTA products have a **diffusion radius of 1cm**. Keep this as your safety margin.

Duration of Effect

This is typically between 3-4 months but there can be considerable variation.

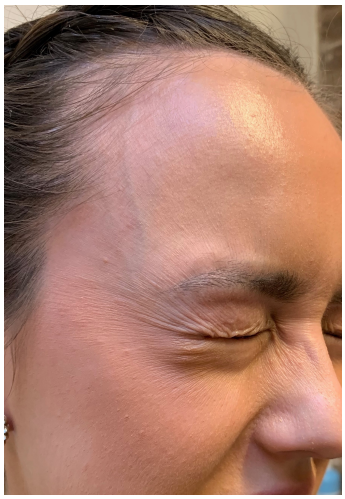
Complications

See section on side effects and complications.

Treating the Crow's Feet

Crow's Feet or Lateral Canthal Lines are dynamic lines caused by the contraction of Orbicularis Oculi muscle.

Typically, these lines radiate from the lateral canthus perpendicular to the action of the muscle.



Injection of BoNTA results in inhibition of muscular action and a softening of these lines.

Typically, each eye is treated with 3 injection points.

Figure 2:

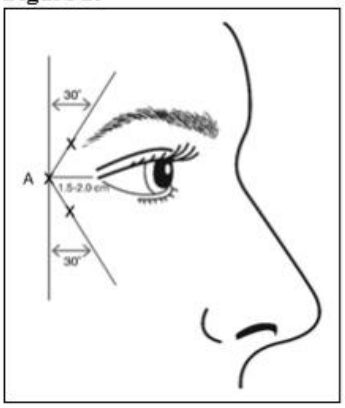
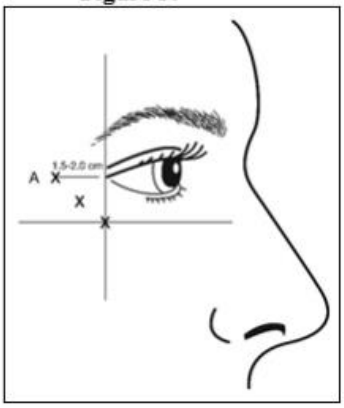


Figure 3:



The pattern of injections will vary depending on the distribution of lines.

Usual dosing in this area is;

6-12 BU per eye or **15-30 SU** per eye

Injection Tips

- Treatment is typically with 3 injection points per eye to lateral Orbicularis Oculi.
- Orbicularis oculi is a relatively superficial, flat muscle so it is important to keep injection points superficial. Angle the injecting needles at a shallow angle to create a bleb in the skin.
- This is a highly vascular area and prone to bruising. Keep an eye out for visible veins and avoid injecting through them.
- Remember the diffusion radius of BoNTA is about 1cm, so keep your injection points at least 1cm away from the orbital rim.
- Ensure that your lowest injection points are above the zygoma. Inadvertent migration into the Zygomatic muscles can result in cheek and mouth ptosis. In addition, cheek ptosis can lead to a ridge between the lower lid and upper cheek which is aesthetically unappealing.
- Remind you patients that BoNTA cannot treat cheek lines caused by contraction of Zygomaticus muscles.
- If extending injections under the eye, please check the snap test. Over treatment here can result in ectropion of the lower eyelid, oedema and worsening of lower eye bags.

Duration of Effect

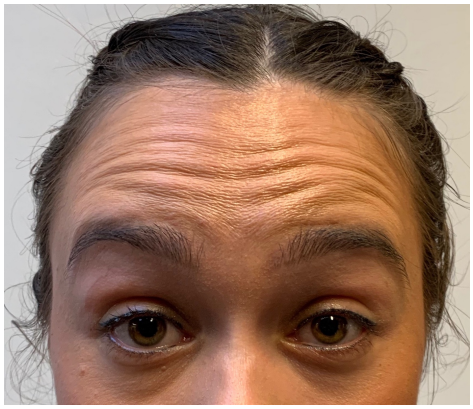
This is typically between 3-4 months but there can be considerable variation.

Complications

See section on side effects and complications.

Treating the Forehead

Horizontal forehead lines are dynamic lines caused by contraction of Frontalis Muscle.



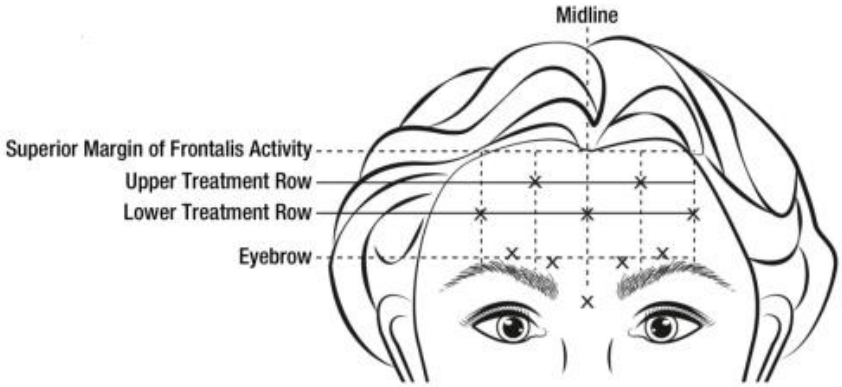
Treatment with BoNTA inhibits the function of this muscle resulting in softening of these lines.

Having said this, in the opinion of the author, the forehead is the most challenging area of the upper face to treat well.

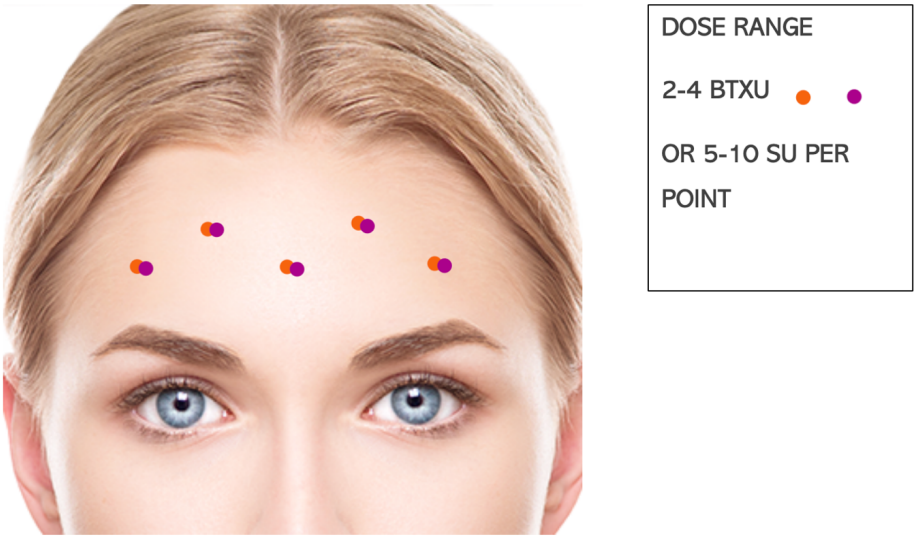
Remember that a number of patients will show evidence of compensated brow ptosis. Treating these patients will unmask this ptosis leading to flattening and heaviness of the brow.

Patient selection is particularly important when considering this treatment area.

Typically, this area is treated with 5 injection points. Although the number of injections can range from 4 to10 points.



Usual dosing of the forehead is **5-20 BU** or **15-50 SU**



The forehead is particularly sensitive to BoNTA so it may be prudent to start at a lower dose.

However, because dose and longevity are related, your patient may find the beneficial effects of BoNTA in the forehead disappearing after 6-8 weeks.

Injection Tips

- Lower treatment row is between the brow and upper line of Frontalis activity. Ensure this row is at least 2cm above the brow.
- Upper treatment row is between the lower row and upper line of Frontalis activity.
- The most lateral points of the lower row should be at least 1cm medial to the Temporal Fusion Line. The Temporal Fusion Line is a palpable boney ridge separating the temporal Fossa and the lateral margin of Frontalis.
- Ensure the lower injection points are at least 2cm above the brow reducing the risk of Brow ptosis.
- Keep injections superficial and avoid hitting the bone.
- Consider treating the forehead more laterally to avoid unsightly lateral brow elevation.
- In the older patient consider whether treatment is advisable at all.
- Watch for forehead lines extending into the hair line. These may need to be treated in addition.

Duration of Effect

This is typically between 6-16 weeks but there can be considerable variation.

Complications

See section on side effects and complications.

Potential Side Effects

Side effects are the effects of a drug that are unwanted but are generally predicted and expected.

Complications are unwanted and unexpected events due to a treatment. However, they are recognised as events that can happen.

All BoNTA products licensed for cosmetic use in the UK undergo rigorous trial and testing, however undesirable side effects are occasionally reported.

Reassuringly most side effects are mild to moderate and self-limiting.

The most common side effects after injection are injection site reactions and headache (in about 10% of cases).

Recognised Side Effects of BoNTA

Nervous system	**Very Common** Headache **Common** Temporary facial paresis (due to temporary paresis of facial muscles proximal to injection sites, predominantly describes brow paresis) **Uncommon** Dizziness
Eye disorders	**Common** Asthenopia, Eyelid ptosis, Eyelid oedema, Lacrimation increased, Dry eye, Muscle twitching (twitching of muscles around the eyes) **Uncommon** Visual impairment, Vision blurred, Diplopia **Rare** Eye movement disorder
Skin	**Uncommon** Pruritus, Rash **Rare** Urticaria
General disorders	**Very Common** Injection site reactions (e.g. erythema, oedema, irritation, rash, pruritus, paraesthesia, pain, discomfort, stinging and haematoma)
Immune system	**Uncommon** Hypersensitivity

The frequency of undesirable side effects is classified as follows:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

As discussed earlier most side effects are of a transient nature usually resolving within the first week following treatment.

Studies suggest no long-term cumulative safety issues with BoNTA.

In the exceedingly rare event of an overdose patients should seek urgent medical advice.

Possible symptoms may include;

- Extreme neuromuscular weakness
- Respiratory issues
- Diplopia
- Swallowing or speech disorders

The LD50 (Lethal Dose) for BoNTA is;

1.3-2.1ng/kg iv or im

10-13ng/kg inhaled

1000ng/kg by mouth

For comparison a 100u vial of Botox™ contains about 5ng of BoNTA.

Complications

Side effects are the effects of a drug that are unwanted but are generally predicted and expected.

Complications are unwanted and unexpected events due to a treatment. However, they are recognised as events that can happen.

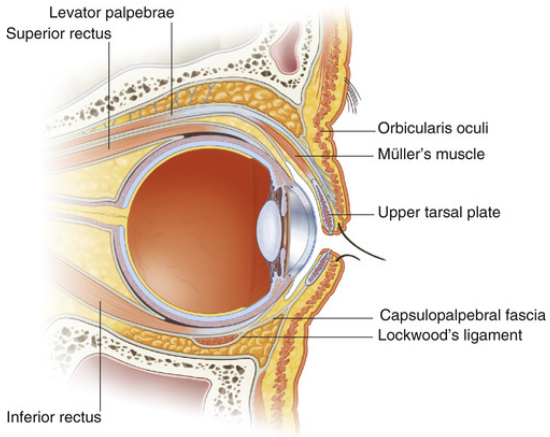
Eyelid Ptosis

This is usually the result of diffusion of BoNTA into the Levator Palpabrae Superioris Muscle.

The **Levator Palpabrae Superioris** Muscle originates from the periosteum of the lesser wing of the sphenoid bone within the orbit and inserts into the upper eyelid skin.

Its function is to retract and elevate the upper eyelid.

Muller's muscle also maintains elevation and retraction of the upper eyelid. However, it differs from the Levator muscle, being composed of smooth muscle and is controlled by the sympathetic nervous system. Damage to this muscle causes eyelid ptosis as seen in **Horner's Syndrome**.



Diffusion of BoNTA into the levator palpabrae muscle results in drooping or ptosis of the eyelid.

This effect can last from 2-12 weeks (typically 2-6 weeks) and can be the cause of much patient dissatisfaction.

Eyelid ptosis is usually the result of inaccurate placement of BoNTA in the tail of the corrugator muscle.

So, Prevention is key. Keep these injections away from the mid-pupillary line and stay 1cm above the orbital rim. Also, bear in mind that the tail of the corrugated muscle inserts superficially into the skin.

With that in mind, keep this injection point superficial.

Treatment is usually watchful waiting and patient reassurance.

However, you may wish to consider a short-term treatment. **Iopdine** (apraclonidine 0.5%) will cause temporary contraction of Muller's muscle resulting in elevation of the eyelid. The dose is usually 1-2 drops tds. **Please note** this medication is for short term use as it can result in eye redness and irritation.

Brow Ptosis

This is usually the result of over treatment of the frontalis muscle. Remember, this is the only elevator of the brow.

In addition, poor patient assessment can contribute to this complication.

In the author's experience, most patients over the age of 45 years will exhibit some evidence of compensated brow ptosis. Unfortunately, the addition of BoNTA unmasks this ptosis resulting in brow depression, fullness and swelling of the upper eyelids and general dissatisfaction.

Compensated brow ptosis is brow droop that is corrected subconsciously by the patient through contraction of the frontal to raise the brow to a more functional position.

Prevention is key.

Assess your patient and consider not treating frontal muscle with BoNTA.

Consider other treatment modalities.

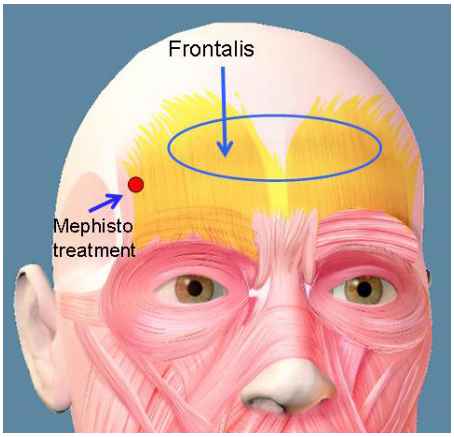
If you intend to inject BoNTA consider using lower doses and keep injection point higher (at least 2cm above the orbital rim).

Unfortunately, if frontalis is completely immobile, there will be little that can be done other than waiting. It can continue to be an issue for the patient up to 12 weeks.

Mephisto / Spock Sign

These terms are used to describe excessive lateral brow elevation following BoNTA treatment. This can happen when only the central portion of the forehead is treated resulting in lateral frontalis overactivity.

This can be easily corrected with the simple placement of BoNTA at the point of maximum contraction in the lateral brow as indicated below.



The usual dose here is 0.5-1BU per point or 1-2.5SU per point.

Ectropian of the Lower Eyelid

This rare occurrence is usually the result of BoNTA weakening the lower orbicularis oculi muscle leading to a lack of support.

This is usually seen in older patients. Unfortunately, there is no treatment other than waiting for resolution. The patient may require some form of eye lubricant in the meantime.

Therapeutic Failure

Therapeutic failure in cosmetic use is very rare and true resistance has been reported in only a handful of cases.

It is thought that resistance is due to the development of antibodies to BoNTA.

The factors that seem to be most important in the development of the antibodies is;

- Dose per session.
- Interval between dosing.

Patients treated in the medical arena with much higher dosing (e.g. 300BU per session) and frequent intervals are much more likely to develop clinically significant levels of antibodies.

The doses used in the cosmetic arena are much lower and the risk of resistance is very unlikely.

In this rare event a trial of different serotype may be considered. eg BoNTB.

The Yellow Card Scheme

The Medicines and Healthcare products Regulatory Agency (MHRA) is the executive Agency of the Department of Health and Social Care that acts on behalf of the Ministers to protect and promote public health and patient safety, by ensuring that medicines and medical devices meet appropriate standards of safety, quality and efficacy.

The Yellow Card Scheme is the UK system for collecting and monitoring information on suspected safety concerns or incidents involving medicines and medical devices.

The Scheme is run by the MHRA and currently relies on voluntary reporting of suspected ADRs by health professionals and patients.

The purpose of the Scheme is to provide an early warning that the safety of a product may require further investigation. Reports can be made for all medicines including vaccines, blood factors and immunoglobulins, herbal medicines and homeopathic remedies, and all medical devices available on the UK market.

This includes Botulinum Toxin and Dermal Fillers.

The Scheme collects information on suspected problems or incidents involving

- Side effects (also known as adverse drug reactions or ADRs).
- Medical device adverse incidents
- Defective medicines (those that are not of an acceptable quality)
- Counterfeit or fake medicines or medical devices
- Safety concerns for e-cigarettes or their refill containers (e-liquids)

You can report to the Yellow card Scheme by;

- Completing an online form on www.mhra.gov.uk/yellowcard
- Calling on 08081003352.
- Completing a form found in the back of the BNF or from a pharmacy.

Aftercare

Providing verbal and written aftercare is extremely important for your patient and yourself.

It will ensure that outcomes are maximised, risk to the patient are minimised and you can protect yourself from litigation (up to a point).

Inform your patients that;

- Any bumps caused by the injections should disappear within hours of treatment.
- They should exercise the injected muscles following treatment. This is thought to improve BoNTA uptake in the muscle fibres.
- They may notice some effects within 24 hours but realistically the full results can take 7-10 days to evolve.
- They should understand treatment isn't permanent. It will need to be repeated to maintain the effect.

In addition, offer some further general advice;

- On the day of the treatment avoid lying down for 4hrs immediately after treatment.
- Don't touch the treated area or engage in activities that might increase the risk of product migration e.g. rigorous exercise, heat to the face or facials. This is applicable for the first 24hrs.
- Static lines will be slower to respond and may need repeated treatments to demonstrate significant improvement.

Follow up Appointment

Follow up appointment is usually recommended 2-3 weeks after treatment. This is especially the case with new patients.

- Allows the clinician to assess the results and take photographs to add to their portfolio.
- gives the clinician the opportunity to correct any imperfections or to meet patient expectations.
- Helps the clinician assess their own techniques for further improvement.
- Inform the patient that repeat treatment will be required in 3-4 months' time.