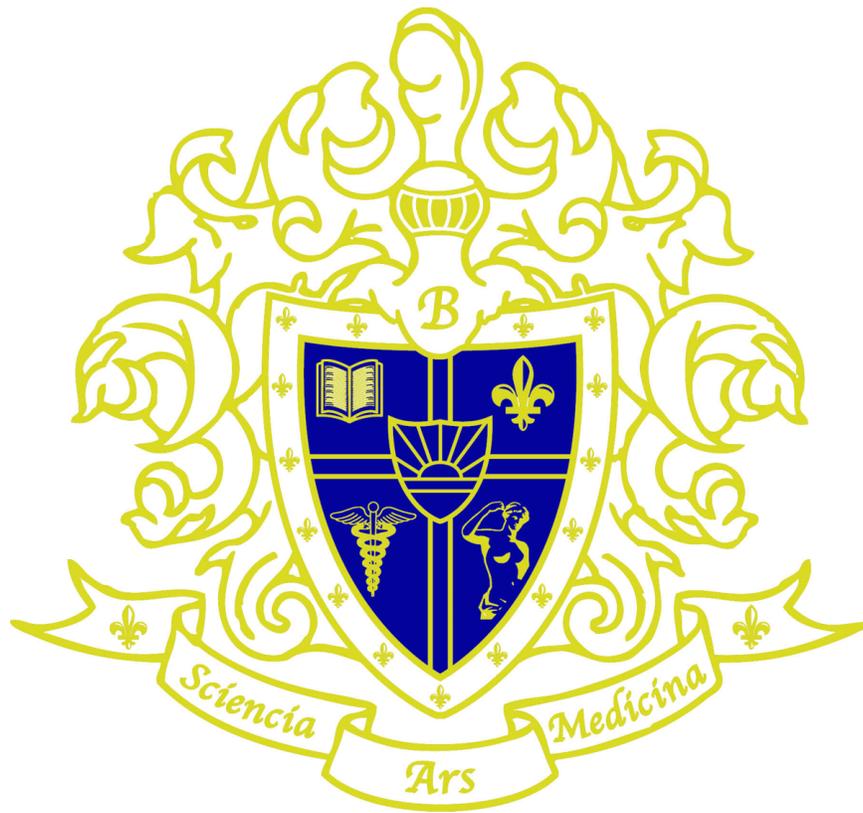


BOTOX

Botulinum Toxins and Neurotoxins: Their Role in Minimally Invasive Facial Cosmetic Surgery



Beeson Cosmetic Surgery



Today, Botox is the most commonly performed cosmetic surgery in the United States, with over 6.9 million procedures performed each year. Botox is used to treat facial wrinkling—forehead "frown lines" and deep creases or "11" lines that develop between the eyebrows. Botox is also used to help eliminate the "crow's feet" and fine lines under the eyes and, in some cases, is used to help lessen the deep creases in the upper lip and those unsightly "bands" or "cords" in the neck.

Neuromodulators can also be used to literally reshape the face by relaxing selective muscles. In this regard they can be used to help upturning the upper lip, providing more rounding to square mandibular contour, widening the eye aperture to more of an almond shape, and reducing fullness in the face by relaxing the buccinator muscle in the cheek–jaw area. Injections can also be used to help raise or lower

different points on the face. For example, lowering the eyebrow, lowering the upper lip to prevent a "gummy smile", or helping to elevate the drooping lateral corner of the mouth.

Its popularity continues to increase dramatically, because treatment is a quick office procedure, there is essentially no "downtime", and results typically last 4 months. Botox is medically referred to as a "neuromodulator". Just as "Kleenex" has become synonymous with "tissue paper", the word "Botox" has become synonymous with "neuromodulators".

Currently, there are 4 FDA approved neurotoxins available in the United States to treat facial wrinkling:

- Botox (onabotulinum toxin A)
- Dysport (abobotulinum toxin A)
- Xeomin (incobotulinum toxin A)
- Jeuveau (prabotulinum toxin A)

Onabotulinum toxin A (Botox – manufactured by Allergan Inc.)

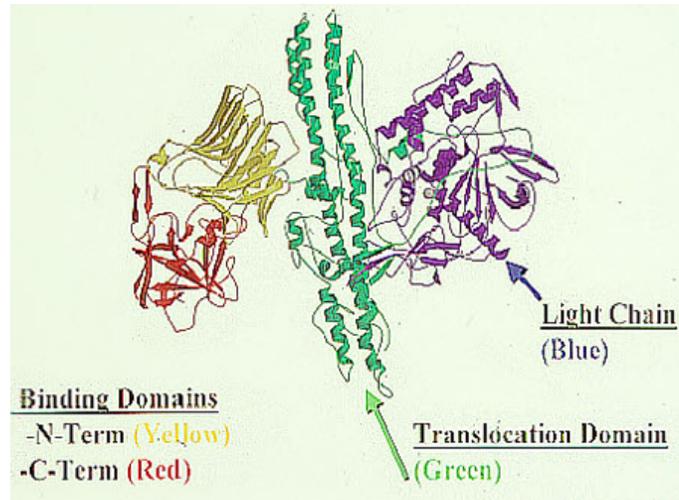
Abobotulinum toxin A (Dysport – manufactured by Galderma)

Incobotulinum toxin A (Xeomin – manufactured by Merz Pharma)

Prabotulinum toxin A (Jeuveau – manufactured by Evolus)



Chemically speaking, there are 8 biological subtypes of the botulinum toxin, but cosmetic neurotoxins are exclusively sero-type A biologics. All 4 of the neurotoxins are very similar. Essentially, the main difference is Botox (onabotulinum toxin A), Dysport (abobotulinum toxin A), and Jeuveau (prabotulinum toxin A) have a complex of protein surrounding the core neurotoxin. Xeomin (incobotulinum toxin A) does not have complexing proteins. This lack of a complexing protein helps to reduce antigenicity, which means there is less chance of forming antibodies against this type of botulinum toxin.



Botulinum toxins are protein substances synthesized by the clostridia bacteria. They are isolated and purified through a very complex production process where safety and efficacy are strictly monitored by the FDA.

Doses of commercially available botulinum neurotoxins available in the United States are expressed in terms of "units", a biologic activity.

Medications which can potentially impact the effect of the botulinum toxin muscle stimulation by interfering with what is termed "neuromuscular signaling" are:

- Aminoglycoside antibiotics
- Lincosamides antibiotics
- Polymyxin antibiotics
- Penicillamine
- Calcium channel blockers
- Neuromuscular blocking agents such as succinylcholine
- Anticholinesterases medications
- Magnesium sulfate
- Quinidine

Proteins which are used in the production of neurotoxins can stimulate our bodies' immunogenic response to develop antibodies in our bloodstream which can essentially neutralize the effect of the neurotoxins. It should be noted that non-responders to primary treatment are extremely rare. This can be due to a number of causes including improper dosing, product degradation, improper storage, and improper injection techniques.

Recent studies demonstrate that neuromodulators can elicit an immunological response, which leads to the production of neutralizing antibodies, which can result in reduced efficacy or treatment non-response.



This can be due to immunological response to the protein used in the manufacturing process. Reports also note that if neutral antibodies have developed, those individuals appear to exhibit resistance to the other neuromodulators. Thus, if the patient is non-responsive to treatment with Botox, switching to one of the other neuromodulators such as Dysport or Xeomin is unlikely to provide a favorable result – and visa versa. Fortunately, this does not appear to be common. A recent analysis of the FDA adverse event reporting system database found that a

decreased therapeutic effect was noted to be 2.2% for Xeomin (incobotulinum toxin A), 9.2% for Dysport (abobotulinum toxin A), and 11.6% for Botox (nabotulinum toxin A). Since Jeuveau (prabotulinum toxin A) was released in 2020, it was not included in the study.

(Journal of Drugs in Dermatology, January 2019 / Kazerooni R - paper presentation -TOXINS; 16-19 January 2019)

Essentially what this means is that approximately 10% of patients will be non—responsive to neuromodulators. Or to express it in a more positive way, neuromodulators will be effective in approximately 90% of patients.

Commercially Available FDA Approved Botulinum Toxins

Botox Cosmetic (onabotulinum toxin A) (Botox; Allergan, Irvine, California) was the first commercially available product in the United States. Its safety and efficacy are well established. It is the most widely used neurotoxin for treatment of facial cosmetic wrinkling in the United States.



Dysport (abobotulinum toxin A) (Ipsen pharmaceuticals) is a purified protein of botulinum toxin A. Results can often be seen as quickly as 2–3 days, compared to 7–14 days for other botulinum toxin injectables. Studies have also report the effects of Dysport to last up to 25% longer than other injectables.



Xeomin (incobotulinum Toxin A) is the third botulinum toxin type A that is FDA approved for the treatment of facial wrinkling. It is more similar to Botox than Dysport. Like Botox, the effects are temporary and repeated treatments are necessary every 3-4 months to maintain the softening appearance of wrinkles and furrows. It is sometimes called "naked botulinum toxin", meaning that there is no additional protein content which may lower the risk of patient's developing antibodies to the product.



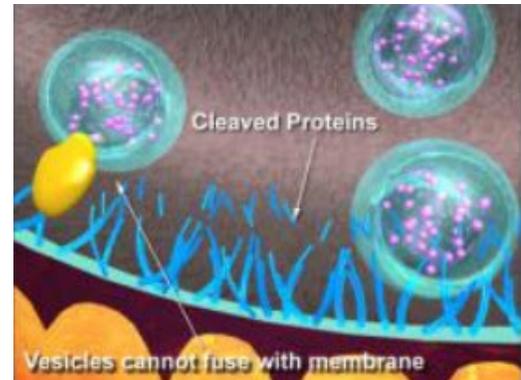
Patients with dynamic wrinkles can obtain dramatic results with Botox and are the most ideal candidates. Patients with static wrinkles (wrinkles noted at rest) are also able to obtain excellent results. However, multiple treatment sessions may be required. In some cases, the deep static wrinkles will not completely be eradicated with the neurotoxin. In these cases, combination treatments with botulinum toxin to decrease muscle movement combined with dermal fillers to "fill-in" wrinkle lines will provide the most optimum results. However, it should be noted that in the great majority of cases, the neuromodulator alone will provide the desired results. Patients can vary widely in the amount (number of units) of botulinum toxin needed to provide the desired result. In general, patients with thick, more sebaceous skin tend to require more units, as do men.

Pretreatment

Bruising can be minimized by discontinuing aspirin-containing compounds at least 5–7 days prior to treatment. Many patients find it advantageous to also decrease various herbs and vitamins, including garlic, ginseng, and ginkgo as they have been associated with decreased platelet aggregation and subsequent increased bruising.

Treatment

Makeup is removed, and an antibiotic soap is used to clean the areas to be treated. Alcohol is not used, because alcohol can deactivate the neurotoxin. A topical anesthetic cream can help further reduce the discomfort of the injection. Very small gauge needles (30-gauge or smaller) are used to make tiny injections, which are almost imperceptible. The neurotoxin can have a slight burning sensation when injected. The more concentrated the neurotoxin, the more potential discomfort. The more "dilute" the less discomfort, but the wider spreading or diffusing the neurotoxin and the less long acting.



Botulinum toxins work by blocking nerve ending receptor sites. This means that using twice the number of units necessary to block the receptor sites does not mean that the effect will be twice as long. Ideally, one would want to be able to inject the precise number of units to block all the receptor sites in that area and no more. Because botulinum toxin neuromodulators are "biologicals", this is very difficult to calculate, and there are multitude of factors which influence the number of units necessary to obtain the desired result.

Anatomic Considerations and Treatment

In general, one can think of facial wrinkles as being formed by repetitive contraction of the underlying facial muscles. Over time, this repeated movement results in breakdown or atrophy of the dermis, resulting in formation of wrinkle lines. Wrinkles are usually perpendicular to what is medically called the "long axis" of the muscle or the way it contracts. There are 2 types of wrinkles—dynamic wrinkles and static wrinkles. Dynamic wrinkles occur with muscle contractions. Static wrinkles are wrinkles that are visible at rest.



The muscles of facial expression are unique and different from other muscles in our bodies. This is because muscles in the face have soft tissue attachments to the skin called retinacular structures, which join the skin with the superficial muscular aponeurotic system. This differs from other muscles in the body, which have primarily bony attachments. When the facial muscles contract, the overlying skin moves with the resultant formation of wrinkles developing perpendicular to the direction of muscle contraction. These are referred to as "dynamic wrinkles", because they occur as a

result of the muscle contraction. Neurotoxins work by chemically "turning off" the muscle contractions in selected areas where the neurotoxin is placed and essentially eliminating the dynamic wrinkles from forming.

Forehead

Wrinkles in the forehead area occur secondary to contraction of the frontalis muscle. This muscle serves to elevate the eyebrows and extends from the lateral portion of the eyebrow medially. While the frontalis muscle contraction effects position of the eyebrow.

Glabella

The frown lines between the eyebrows are often referred to as glabellar wrinkles or "11 lines". These vertical wrinkles occur as a result of contraction of muscles that run in an inverted V-shape from the base of the nose to the mid forehead area.



Before

After

Brow Contouring

Neurotoxins can aid in manipulating brow position and contour. Skillfully balancing the opposing effects of antagonistic muscles with neurotoxin can help elevate and selectively sculpt the eyebrow. The resting position of the eyebrow is dictated by a balance between the depressors and the eyebrow elevator, the frontalis muscle. Chemical denervation of the glabellar muscle complex (corrugator superciliary muscle, procerus muscle, depressor supercillii muscle, and medial portion of the orbicularis muscle) can produce as much as 2 mm medial brow elevation. Lateral brow elevation can be achieved by injecting the superior lateral orbicularis oculi muscle immediately beneath the desired area of elevation.

Lateral Canthal Lines

Lateral canthal wrinkling (crow's feet) represent one of the early signs of aging. Wrinkles, rhytids, or crow's feet as they are frequently referred to in the lateral periorbital region, are created by the contraction of the orbicularis oculi muscle. Patients who frequently smile or squint continually can develop a roll or bulge in the lower eyelid area immediately beneath the lash line. This is due to hypertrophy or overactivity of the inferior portion of the orbicularis oculi muscle. A minimal amount of neurotoxin injected into this area (1–2 units) can frequently relax this muscle and provide cosmetically pleasing smoothing of the lower eyelid area.

Perioral Wrinkles

The orbicularis oris muscle surrounds the mouth and functions in a sphincter fashion. The dynamic movement of this circular muscle results in the formation of dynamic wrinkles in the upper lip—the so called "smoker's lines". Neurotoxins work by decreasing muscle contraction and, in selected cases; they can be effective in reducing the dynamic wrinkles in the upper lip. However, it is extremely difficult to control how the neurotoxins absorb in this area and to accurately gauge their effect. This can result in asymmetries and lack of ability for a person to pucker their lips. For this reason, neurotoxins are commonly contraindicated or performed with caution in singers, public speakers, and musicians.



Marionette Lines

The depressor anguli oris is a muscle that runs from the mandible to the corner of the mouth where it inserts into the orbicularis oris muscle. It has a downward pulling function at the corner of the mouth. Relaxing this muscle with 2–4 units of Botox can reduce drooping of the corner of the mouth in selected individuals. However, there is significant risk that asymmetry and distortion can be created. For that reason, this area is treated very cautiously and with trepidation.

Neck

The platysma muscle is a rudimentary muscle that runs from the chest and inserts along the mandible. With aging this muscle becomes more relaxed and unsightly cords or bands can develop in the neck. In selected cases, Botox can be injected into these bands to relax muscle contraction and make the cording less apparent. Small injections of Botox are placed at 1-2 cm intervals into the band. Results can be dramatic in selective patients, but are only temporary and larger volume of Botox may be required to achieve desired results.

Aftercare

Avoid being supine for the first 4 hours following the treatment. It is important to activate the muscles for the first 4 hours after treatment, as the neurotoxin tends to migrate into the activated muscles. If one "took a nap" immediately after an injection (supine position) and had been injected with a highly diluted solution, that would facilitate wider diffusion of the neurotoxin into surrounding tissues. Being in a reclining position facilitates the botulinum toxin migrating into the periorbital tissues and negatively impact eyelid and eyebrow mobility and positioning. For that reason, it is recommended the patients increase muscle activation for the first 4 hours following treatment.

Following treatment, it is best to avoid vigorous physical activity and alcohol for 24-48 hours as both can cause increased vasodilatation and potentiate bruising. Many doctors also recommend refraining from laser/IPL treatments, facials, and facial massage for 1-2 weeks after injections.

Results and Follow-up

Typically, the effect of the neuromodulator begins to be noted on the first and second day following treatment. However, it usually takes approximately 2 weeks to obtain the desired effect, and in some cases, changes and improvement can be noted for up to 1 month following the injection. Some individuals feel that Dysport has a quicker onset of action as compared to Botox.

Return of muscle function is gradual, usually 3–4 months following treatment.



Post Treatment Tips:

If you decide to try Botox treatment for facial wrinkling, these are some tips that we share with our patients:

For the first 4 hours after treatment, frown and squint—move those muscles you want to "turn off". Research has shown that the medication is absorbed more affectively into muscles that are moving.

You can reduce your chance of bruising after treatments by being off aspirin or aspirin containing compounds for 5-7 days before treatment. Also, stop taking herbs and vitamin compounds that start with the letter "G"—garlic, ginseng, ginkgo—as they can affect how your platelets work and cause additional bruising.

Beware of "counterfeit" Botox from black market sources. The FDA has published a consumer alert to let people know that there can be problems with efficacy and possible contamination when people are treated with these cheaper "imitations".

Finally, be sure that the person treating you is probably trained and qualified—just because they have a "M.D." or "D.O." behind their name does not mean that they have the knowledge expertise you're looking for.

Contraindications to Botox Injections:

- Infection in treatment area
- History of keloid scarring
- Neuromuscular disorder such as amyotrophic lateral sclerosis (ALS) and myasthenia gravis
- Pregnancy or breast-feeding
- Bell's palsy
- Skin conditions and treatment area such as psoriasis or eczema
- Individuals who depend on facial expression for their livelihood, such as actors, teachers, musicians, and public speakers
- Individuals with unrealistic expectations
- Immune compromised patients

Contraindications

Botulinum toxin is contraindicated in patients who have certain types of neuromuscular disorders such as myasthenia gravis. It should also be avoided in patients who have a history of forming keloid scars, women who are pregnant or breast-feeding, people who have skin infections in the area that is to be treated, patients with Bell's palsy, immune compromised patients, people with unrealistic expectations, and individuals who require facial expression for their work, such as certain stage actors who need to emphasize expressions.

Relative contraindication would be using botulinum toxin in patients who have conditions or who are taking medications that could impact the effect of the botulinum toxin. While some patients would find increasing the effect desirable, this could be a contraindication in others. Medications which may increase the effect of botulinum toxin include aminoglycosides. Other medications such as penicillamine, quinine, chloroquine, and hydroxychloroquine and may reduce the effect of botulinum toxin.

There are a limited number of medications which can potentially react with botulinum toxin and impact results. Certain antibiotics called aminoglycosides are thought to increase the strength of the botulinum toxin which may result in a more profound effect on the muscles that are causing the facial wrinkling. This is because some antibiotics reduce the neuromuscular transmission, impacting the level of messaging that the muscles receive from the brain on stimulation. Antibiotics in the aminoglycoside group include clindamycin, tobramycin, gentamicin, lincomycin, streptomycin, neomycin, and amikacin.



Other antibiotics which are felt to interact with botulinum toxin include D-penicillamine, polymyxins, and cyclosporine. While some patients would find increasing the effect desirable, this could be a contraindication in others. For this reason it is recommended that patients finish the course of these medications before having a botulinum toxin treatment. This is because the antibiotics can have a separate weakening effect on the muscles which is in addition to the effect of the botulinum toxin treatment. This can result in a stronger paralysis effect than would be intended. Although there are no long-term problems associated with this, it could potentially create some undesirable side effects which could include eyebrow droop or a more "frozen" look.

In contrast, some drugs have the opposite effect and can decrease the effectiveness of the botulinum toxin. Two antimalarial medications, chloroquine and hydroxychloroquine, are examples of medications that could potentially work to limit the neurotoxin's ability to reduce your wrinkles by restricting its effect on the muscles.

Medications such as calcium channel blockers for blood pressure control and blood thinning agents such as warfarin or aspirin may result in bruising and could be considered a relative contraindication. Some contend that these medications may also cause some degree of dilatation of blood vessels and increased blood flow into tissues, which could facilitate the botulinum toxin spreading, and affecting muscles that were not intended to be treated.

Complications

Injections with botulinum toxin are extremely well tolerated by most patients, and there are very few side effects. There can be mild discomfort, localized edema, redness (erythema) and mild bruising associated with the trauma of the injection. However, in most cases, very small needles (30-gauge or smaller) are used and topical anesthetics, which greatly minimize these effects. Mild headache, malaise, mild nausea, and influenza-like symptoms have been reported with botulinum toxin injections, but are very rare.

Closing

The use of botulinum toxins has revolutionized the treatment for facial wrinkling and has become the “gold standard”. It is one of the most frequently performed cosmetic procedures in the world and continues to increase in popularity. Precise knowledge and understanding of the functional anatomy of the facial muscles is critical for the correct use of botulinum toxins in cosmetic surgery.