2021

# PHYSICIAN EXTENDER RN/NP/PA INJECTOR COMPETENCE TRAINING Level 1: Basic

UNDERSTANDING THE BASICS OF INJECTION TECHNIQUES WITH NEUROMODULATORS AND HYALURONIC ACID SOFT TISSUE FILLERS

AMERICAN SOCIETY FOR AESTHETIC PLASTIC SURGERY

W

## WELCOME

Dear Participant:

We are delighted that you have chosen to take this course, Physician Extender (RN/NP/PA) Injector Competence Training – Level 1 – Basic: Understanding the Basics of Injection Techniques with Neuromodulators and Hyaluronic Acid Dermal Fillers. The course instructors are among the best in plastic surgery today. The content will not only broaden your knowledge of injectables, but also recognizes the important role you play in providing patients with safe and efficacious treatments.

Disclaimer: The content of this program handout is presented solely for educational purposes and is intended for use by medical practitioners in the plastic surgery specialty. This material is intended to express the opinions, techniques or approaches of the authors and presenters which may be beneficial and/or of interest to other practitioners. Sponsorship of this program and/or advertising is not to be construed, in any fashion, as an endorsement of the materials or products presented.

Again, thank you for choosing this course. We hope you will both learn from and enjoy the session!

Cordially,
The Aesthetic Society

## F | FACULTY |

**Miles Graivier, MD, FACS**
**Private Practice | The Graivier Center for Plastic Surgery**
**Alpharetta, GA**

**Z. Paul Lorenc, MD, FACS**
**Private Practice | Aesthetic Plastic Surgery**
**New York, NY**

**Kathy Jones, RN**
**Private Practice | Kathy Jones Aesthetics/Artistic Beauty & Medical Science**
**Cincinnati, OH**

**Karen Menard, RN**
**Skin Care Specialist | Biggs & Collins Aesthetic Plastic Surgery**
**Houston, TX**

## E | EDUCATIONAL OBJECTIVES |

**1.** Perform an aesthetic analysis of the face to identify potential facial rejuvenation strategies that may improve appearance in accordance with the patient's individual treatment goals.

**2.** When injecting neuromodulators, demonstrate knowledge of appropriate muscle(s) in order to achieve the desired result.

**3.** When injecting hyaluronic acid soft tissue fillers, demonstrate knowledge of product attributes, appropriate depth of injection and specific techniques in order to ensure optimal outcomes.

**4.** When injecting neuromodulators and/or HA fillers, describe the actions that can lead to adverse events/complications and categorize subsequent management.

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*NURSE INJECTOR COMPETENCE TRAINING* | CHAPTER 1

# FACIAL ANATOMY AND PATHOLOGY

01

## Introduction

The skin and facial muscles act together to create facial expression and appearance and are subject to change with aging and environmental exposure. Knowledge of both the skin structure and underlying facial nerves and muscles is important when considering therapies for non-surgical facial enhancement.

## The Skin

The skin is the largest organ in the body and is composed of multiple layers. To give you a frame of reference, the skin of a 150-pound adult male weighs about 9 pounds. The thinnest skin is typically found on the eyelid (.05 mm) and the thickest (1.5 mm) is on the soles of the feet. Infants and children have thin skin and, as one ages, the skin will thicken until the fourth or fifth decade, after which it begins to thin once again.

The skin is remarkable in that it constantly renews itself, while also producing material for its own nutrition and protection. The average person sheds about 4% of their skin cells each day.

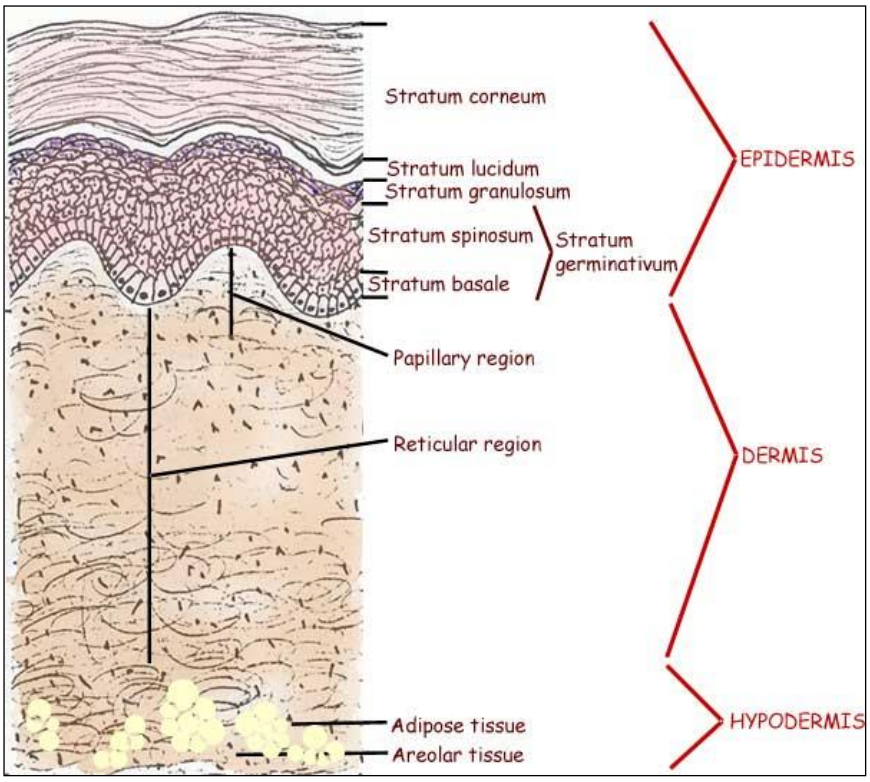
### Functions of the Skin

The skin has many important functions including thermoregulation, protection, metabolic function, and perception of sensory stimuli. Skin maintains body temperature at a steady 98.6° F at a pH of ~ 5.5.

The skin is the body's first line of defense against infection, water, and ultraviolet radiation. It also cushions internal organs from bumps and bruises. The skin removes waste and produces vitamin D. It absorbs some oxygen and carbon dioxide, small amounts of ultraviolet (UV) light, steroids, and fat-soluble vitamins. It can also absorb some toxins and pesticides. Sensory receptors in the skin detect touch, pain, pressure, heat, and cold. Finally, the skin has an aesthetic function by affecting how we present ourselves to others, and changes to its appearance can affect self-esteem.

Anatomy of the Skin

The skin consists of three primary layers: the epidermis, dermis, and hypodermis or subcutaneous layer.




**Layers of the Skin[1]**



Epidermis

The epidermis is the outermost layer of the skin, and accounts for 5% of skin thickness. The epidermis consists of continually renewing, stratified, squamous epithelium that keratinizes and gives rise to appendages (i.e., sweat glands). Living, nucleated cells divide and constantly push up through layers of the epidermis until they reach the surface, die, become non-nucleated, and flake away. Since it does not have blood vessels, the epithelium depends on lower layers of the skin for its nourishment.

Various types of cells appear throughout the epidermis. These include keratinocytes, melanocytes, Langerhan's cells, and Merkel's cells. Keratinocytes, which produce keratin, compose 80% to 90% of the epidermis. These cells are involved in production and loss of immunogenic molecules (interleukins, colony stimulating factors, interferons, tumor necrosis factors, transforming growth factors, growth factors).

[1] http://www.lionden.com/SkinLayers.jpg

Melanocytes are responsible for producing melanin (pigment) and are found in the basal layer of the epidermis. These cells have finger-like projections that connect to keratinocytes. Langerhans' cells defend against viruses, bacteria, and precancerous cells. These cells help detect foreign substances by attaching to them and alerting the immune system of their presence. Langerhans' cells contribute to development of skin allergies.
Merkel's cells function as touch receptors and consist of small, cup-shaped nerve endings in the skin.

The epidermis is further broken down into the following sub layers:

- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum germinativum (Basal Layer)

Dermis

The dermis is the tough, fibrous, elastic layer, beneath the epidermis and is sometimes called the "true skin" layer. In general, it makes up 95% of skin thickness, but its thickness varies according to where it is. The area around the eyes is the thinnest. The skin of the scalp and forehead is <2 mm compared with that of the abdomen and thighs where skin is 2 to 3 mm.

The dermis contains blood vessels, nerves, and sensory receptors for touch, temperature, pain, and pressure. It also contains hair follicles, sebaceous and sweat glands, and smooth muscle. Sebaceous glands secrete an oily acidic film over skin that serves as waterproofing and prevents growth of most microbes. The dermis supplies nutrition to the epidermis, through the thin layer of basement membrane that separates them.

The two main cell types in the dermis include fibroblasts and mast cells. Fibroblasts produce elastin and collagen. Type I collagen is the major component of the dermis. Elastin and collagen serve as architectural support to the skin. Mast cells produce histamines and enzymes that are responsible for inflammation responses.

The dermis has two layers, the papillary layer and the reticular layer. The papillary layer contains a rich supply of blood vessels, and its main function is to provide nutritional support to the avascular epidermis. The papillary layer also conserves or dissipates heat by increasing or decreasing blood flow. The reticular layer gives skin its strength and elasticity and holds important epithelial structures such as glands and hair follicles. These structures are important as they help with the restorative process after skin treatments.

Hypodermis or Subcutaneous layer or Subcutis

Below the dermis is a subcutaneous layer of connective tissue consisting primarily of adipose tissue. This layer provides insulation, stores energy, and protects internal organs. The subcutis connects skin to surface muscles. It contains additional sweat glands and hair follicles.

**Skin Types**

Fitzpatrick Skin Type Classification[2] is a scale to determine skin sensitivity level based on pigmentation and ultraviolet exposure. This system is sometimes used to help predict the outcome of skin treatments.

| TYPE | SKIN COLOR | EYE/HAIR COLOR | REACTION TO SUN EXPOSURE |
|---|---|---|---|
| Skin Type I | Very white or freckled; extremely fair skin | Blue or green eyes<br>Blond hair | Always burns, never tans |
| Skin Type II | White or fair skin | Green/brown eyes<br>Sandy to brown hair | Usually burns, tans with difficulty |
| Skin Type III | Medium white to light olive skin | Brown eyes<br>Brown hair | Average tan, sometimes mild burns |
| Skin Type IV | Moderate brown to olive skin | Brown or black hair<br>Brown or black eyes | Rarely burns, tans very easily |
| Skin Type V | Dark brown skin | Black eyes<br>Black hair | Very rarely burns, tans very easily |
| Skin Type VI | Black skin | Black eyes<br>Black hair | Never burns, tans very easily |

**Fitzpatrick Skin Type Classification**

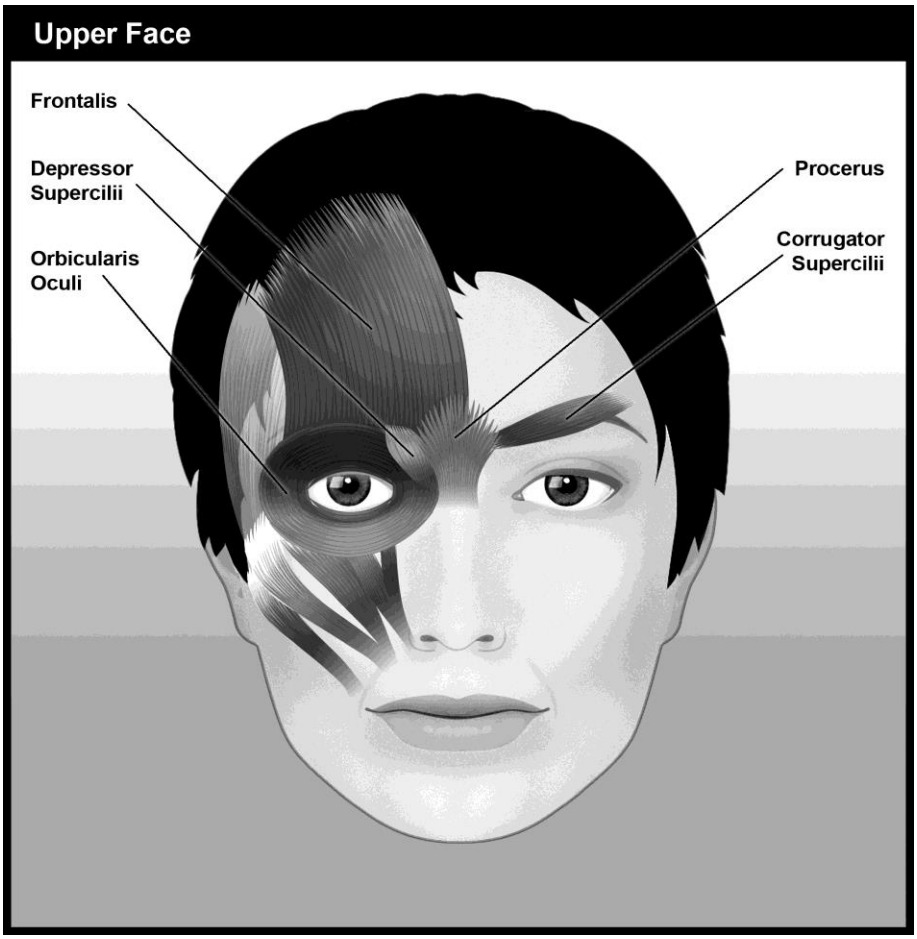
**Muscles of the Face**

Facial expressions are largely attributable to facial muscles, which work in concert to produce a considerable range of movements throughout the face. The muscles of the face are unique in that they are attached to various parts of the skin. Facial muscles surround and radiate from the mouth, nostrils, eyes, and ears. Some are used to open these orifices and others to narrow or close them. All the muscles are supplied by two main nerve branches, the right and left facial nerves, arising from the brain stem.

[2] Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol*. Jun 1988;124(6):869-71.

Muscles of the Upper Face

Muscles of the upper face are responsible for facial expressions involving the eyes, eyebrows and forehead. These muscles allow for expression of emotions such as smiling, surprise, grief, and suffering, and also for protective functions like blinking and squinting.






The corrugator supercilii muscle originates from the nasal bone and inserts along and into the skin above the middle third of the eyebrow. It is located deep to the frontalis. The corrugator supercilii pulls the eyebrow and skin from the center of the eyebrow toward the inner corner medially and down. Contraction of this muscle forms vertical wrinkles in the glabella area and horizontal wrinkles at the bridge of the nose. It often acts simultaneously with the depressor supercilii and procerus. Its action produces what appears as a frowning expression in the eyebrows and forehead, so it sometimes is called the muscle of grief and suffering.

The procerus pulls forehead skin in an inferior direction, draws the medial angle of the brow down, and produces transverse wrinkles over the nasal bridge. It rarely functions alone, but rather contracts in collaboration with the corrugator, orbicularis oculi, and/or nasal part of levator labii superioris.

The corrugator supercilii muscles and the procerus, which usually work together, are sometimes collectively referred to as the glabellar complex. Glabellar lines (frown lines) are vertical creases between the eyebrows, which are often the first wrinkles to concern middle-aged patients.

The depressor supercilii is a small muscle at the medial corner of the eyebrow which acts to depress the inner corner of the eyebrow and form horizontal wrinkles at the root of the nose. The depressor supercilii usually acts in conjunction with the orbicularis oculi, corrugator, and procerus, or levator labii superioris alaeque nasi.

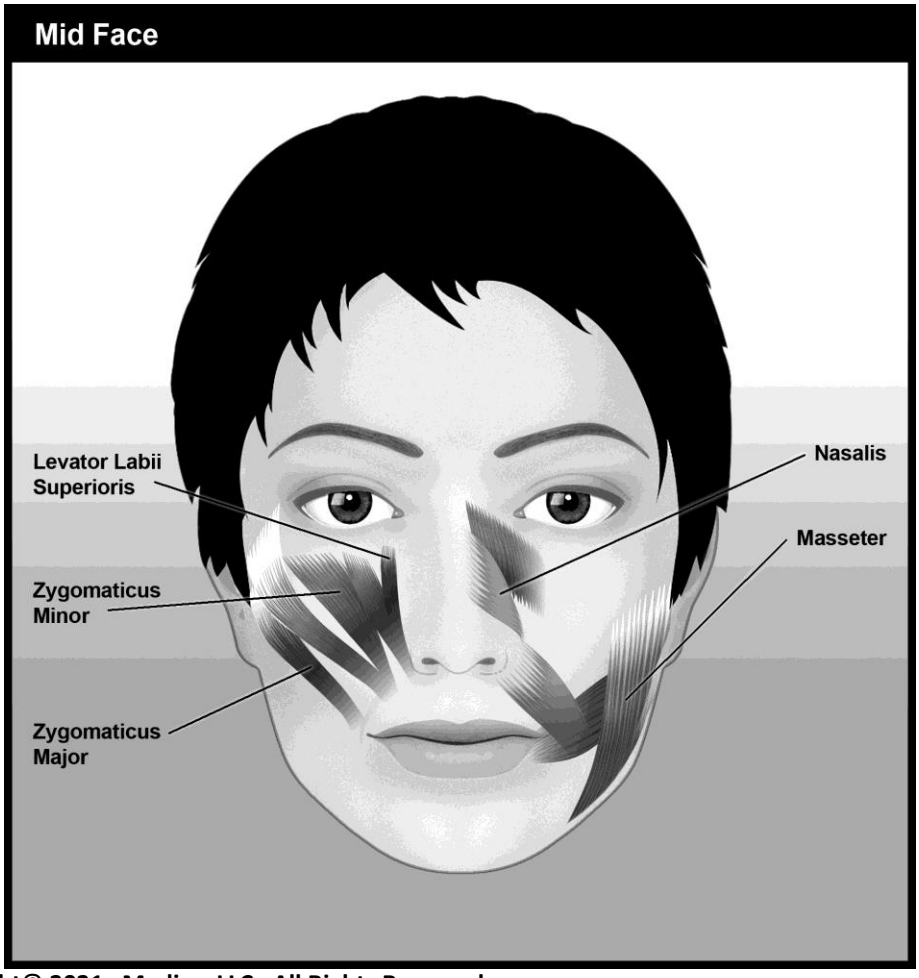
The frontalis is a superficial muscle with a small amount of subcutaneous fat overlying most of it. It is located within the forehead. Contraction of the frontalis raises the eyebrows and skin of the forehead and forms horizontal forehead wrinkles.

The orbicularis oculi is a very superficial muscle circling the eye socket. This muscle serves as the sphincter of the eye, narrowing the eye opening and closing the orbit of the eye, which contributes to protecting and moistening. The orbital portion of the muscle strongly depresses the eyebrow and the palpebral portion affects the motion of the eyebrow and eyelid. These motions are often involuntary (i.e., blinking). The orbicularis oculi is also active in squinting and smiling.

One of the scalp muscles, the occipitofrontalis has two parts (occipital and frontal). The frontal part includes the procerus, corrugator supercilii, and orbicularis oculi. The occipitofrontalis raises the eyebrows, weakly moves scalp skin anteriorly, and produces transverse wrinkles over the forehead.

Muscles of the Mid Face

The muscles in the middle part of the face allow movements such as dilation of the nostrils and lifting of the upper lip. They also produce smiling and frowning.





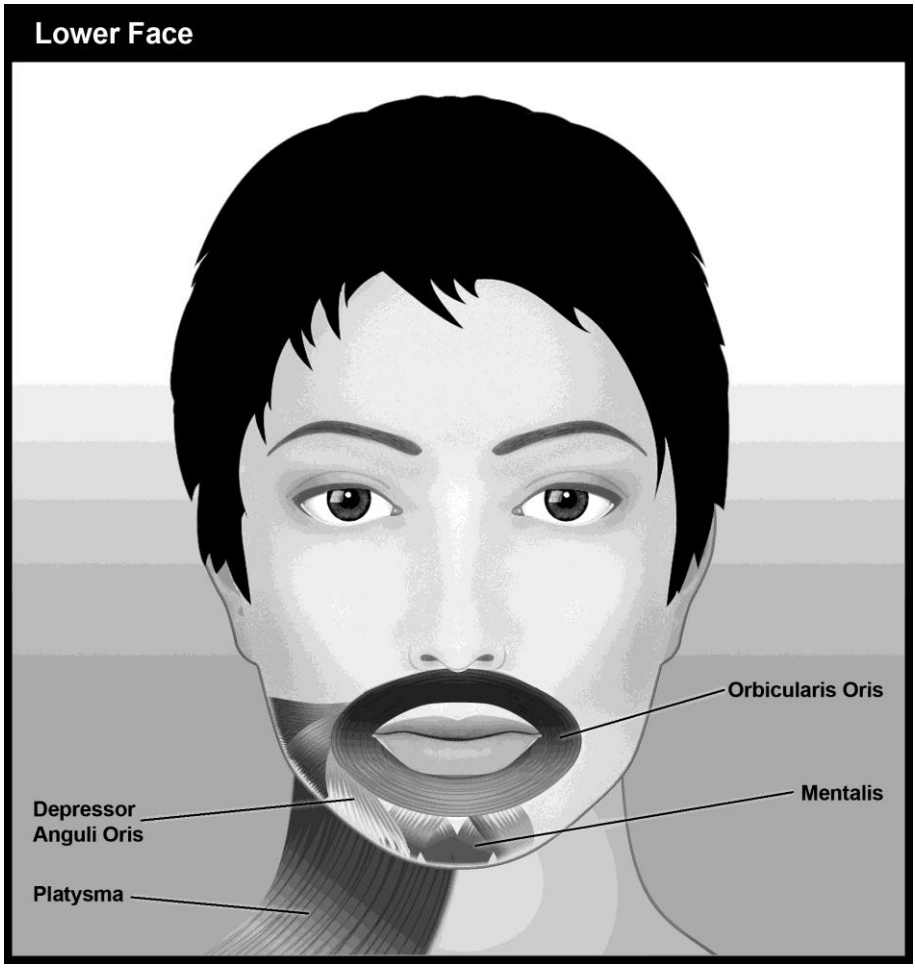

The nasalis muscle has two main parts: the compressor, which constricts the nostril, and the dilator, which flares the nostril.

The levator labii superioris raises the upper lip, stretches the nasal wing up, and wrinkles the nose.

A pair of muscles called the zygomaticus major and minor pulls mouth corners up into a smile.

Muscles of the Lower Face/Neck

Lower facial muscles are important aesthetically and are critical to actions needed for daily life, such as sipping, drinking, swallowing, speaking, and breathing.






The orbicularis oris is the sphincter of the mouth. This muscle, which lies between skin and mucous membranes of the lips, circles the mouth and extends up to the nose and down to between the lower lip and chin. Repeated pursing creates radial perioral lines, which can cause lipstick to bleed up.

The masseter muscle (see diagram of muscles of the mid face) is used to chew food. Although temporomandibular joint (TMJ) has many complex and diverse causes, tensing of the masseter can contribute to TMJ. Spasms of the masseter muscle cause a condition known as trismus. Hypertrophy of the masseter (from teeth grinding) can cause the jaw line to appear enlarged.

The mentalis muscle, which is located on the chin, raises and protrudes the lower lip. Tonic contraction produces a horizontal crease in the upper chin. In elderly people who have atrophy of the chin, contraction of the mentalis accentuates attachment sites for the subcutaneous

musculoaponeurotic system to the dermis, giving an appearance of a “pebbly chin” or “apple dumpling chin,” also called “mentalis chin irregularity.”

The depressor anguli oris originates from the mandible and inserts into corners of the mouth. It depresses the mouth corners into a frown. Involuntary persistent contraction may create a look of fixed disapproval. The muscle also contributes to lateral oral commissure wrinkles.

The platysma originates from fascia over the pectoralis major and deltoid muscles, stretches across the clavicle, and ascends at a slant along the sides of the neck, where it is inserted into the skin of the lower face and mandible. It depresses the lower lip and forms ridges in the skin of the neck and upper chest when it contracts. Expressions produced by the platysma can convey stress and anger. It also has minimal activity in neck flexion and helps to pucker the lips. (A minority of people use the platysma muscle in forming a smile.) With age, as subcutaneous fat is lost, the platysma becomes more prominent creating vertical platysmal bands or horizontal “necklace” lines. As some people age, the band shortens and can tug on the overlying skin producing a stretched appearance.

## Facial Nerves

The facial nerve is the seventh of the twelve cranial nerves. The branches of the facial nerve activate the facial muscles and surface skin causing them to lift, lower, contract or expand. The facial nerve branches into many segments controlling everything from the sensation of itching to taste. Its most important function is motor or movement of the face. The trigeminal nerve, which is the fifth cranial nerve, is responsible for sensation in the face.

When considering facial rejuvenation, effective pain management is crucial to help ensure positive patient outcomes. Topical anesthetics are often used in resurfacing procedures as well as with fillers and injectables. While many of the hyaluronic acid fillers are now available with lidocaine, in some cases, additional numbing is needed, and this can be achieved with the use of nerve blocks. Infraorbital and mental nerve blocks have been the most common regional blocks used in facial enhancement procedures. They are especially effective for lip augmentation procedures although they may not completely block the corners of the mouth.

It is important to have knowledge of facial vascular and nerve anatomy to ensure proper placement of the blocking agent. There is also some risk of nerve injury or intravascular injection with regional nerve blocks. Please refer to chapter 4 for more information on pain management techniques when using dermal fillers.

## Vascular Architecture

Most of the blood to the face is supplied by the external carotid artery, which branches into the superficial temporary artery and the internal maxillary artery. The internal carotid artery also supplies blood to the face, but to a lesser extent. The veins of the face run parallel to arteries and drains blood from middle of face to internal jugular vein.

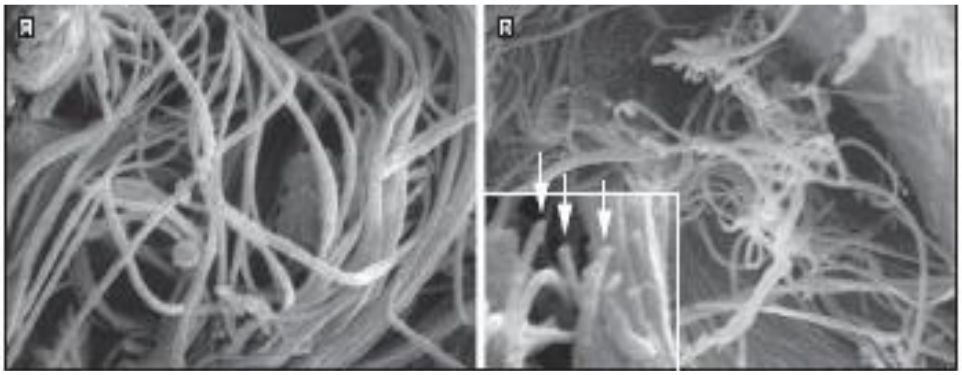
When injecting soft tissue fillers, it is important to have a good understanding of the depth of the arteries so that you can understand where the tip of the needle is going to be; either behind, or in front of the artery. Injecting into an artery can cause distal emboli resulting in skin necrosis. In the upper face, injection into an artery can also cause vision problems and/or blindness. It is also important to understand the depth of the facial artery. It is a branch of the external carotid and is located about a centimeter in front of the anterior border of the masseter and runs towards the alar groove. The facial artery begins its path lying on bone and continues up in the face in a deep plane passing under zygomaticus major and minor muscles. As the artery approaches the alar groove, the depth changes and varies greatly.

**Facial Aging**

Aging effects can be either intrinsic (chronological/natural aging) or extrinsic (environmental aging). Signs of intrinsic aging include fine wrinkles, thin or transparent skin, hollowed cheeks/eye sockets, noticeable loss of firmness on hands and neck, and sagging and dry skin. Extrinsic accelerators of these aging effects include exposure to harmful topical agents (toxins, soaps), alcohol consumption, smoking, and sun exposure ("photo-aging").

Facial aging is a complex process involving the three main layers of the skin:

- Surface or epidermal layer – Changes in the epidermis are mainly due to photo-aging and other environmental factors. As one ages, the epidermal changes include a thinning and flattening of the skin. As the skin loses elasticity, it begins to sag and can have a crepe-like appearance.
- Dermal layer – Levels of both collagen and elastin are reduced. The collagen matrix is weakened and fragmented which also causes fibroblasts to collapse.

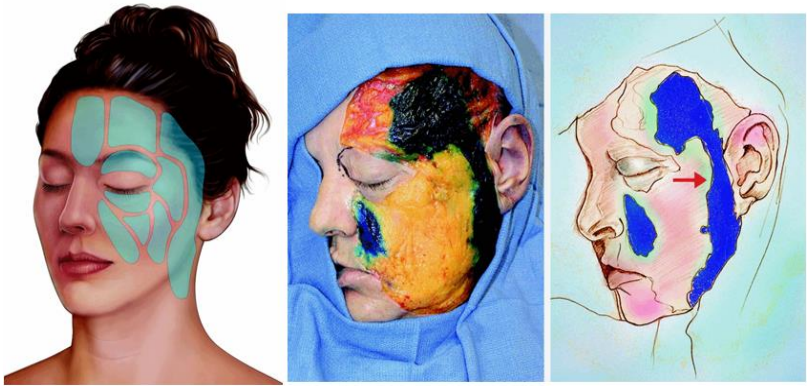


**Scanning electron micrographs of collagen fibrils in young vs. photo damaged, older adult human skin.[3]**

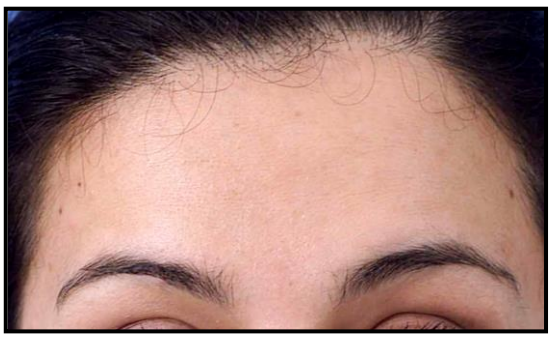
- Structural or subcutaneous layer - Aging of this layer is characterized by weakening of facial muscles, loss of fat and resorption of bone. This is manifested by a deflated look which is due to overall volume deficiency.

[3] Gary Fisher, PhD; James Varani, PhD. John Voorhees, MD. Looking older f*ibroblast collapse and therapeutic implications*. *Arch Dermatol,* May 2008; Vol 144, No 5, pps. 666 – 672.

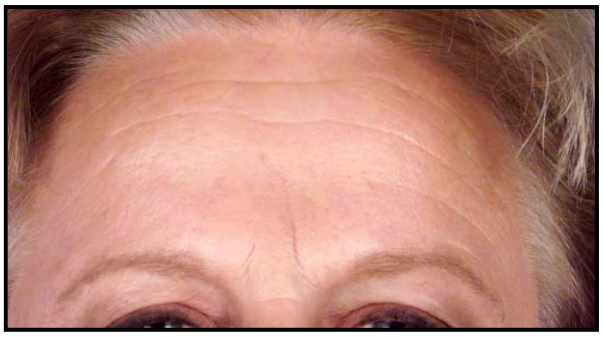
Fat loss is particularly noticeable as one ages. A study published in 2007 (Rohrich and Pessa) [4]found that subcutaneous facial fat is partitioned into multiple, independent anatomical compartments. Their conclusion is that facial aging, in part, is characterized by how these compartments change with age.



The following photos demonstrate the aging process, particularly as it affects the brows, eyes and mouth.



**Youthful Brow**

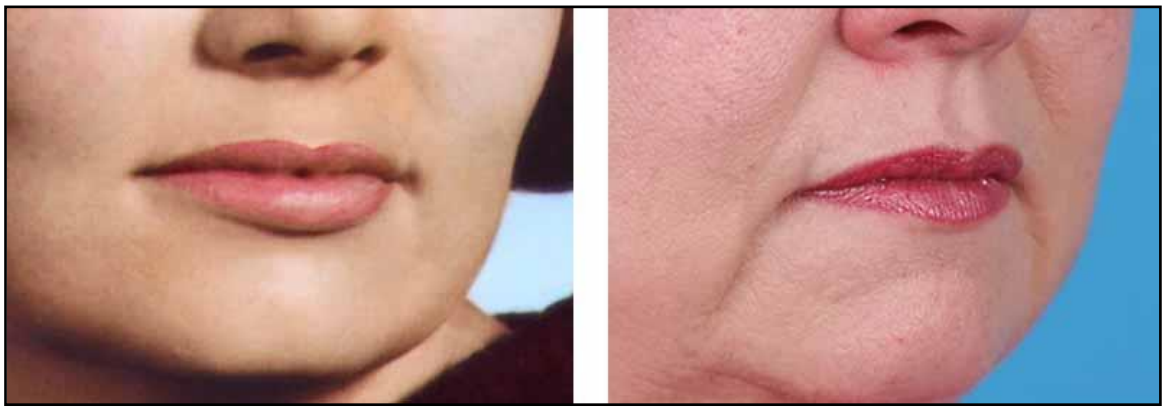


**Aging Brow**

**Youthful Eyes**

**Aging Eyes**

[4] Rohrich RJ, Pessa JE. The fat compartments of the face: anatomy and clinical implications for cosmetic surgery. *Plast Reconstr Surg* 2007;119(7):2219-27

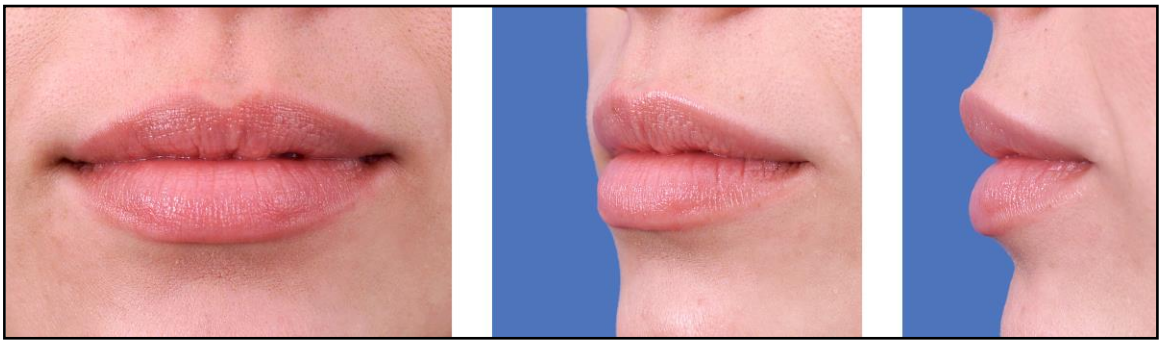


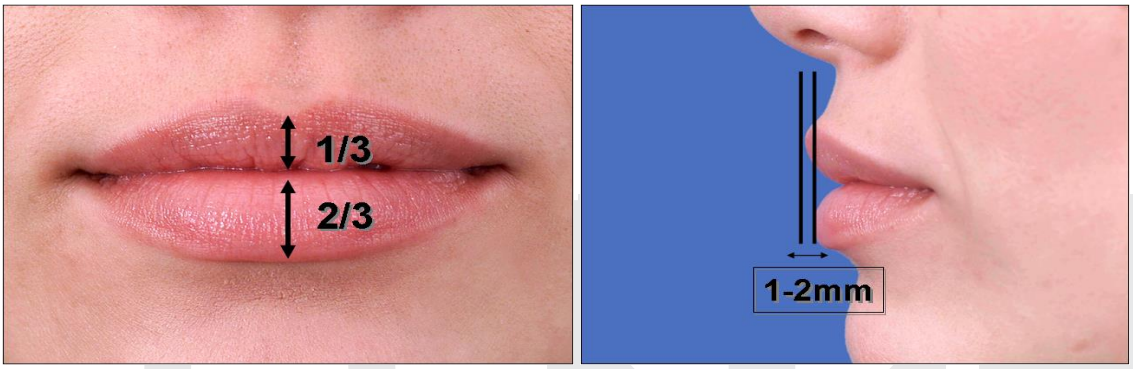
**Youthful Mouth** **Aging Mouth**

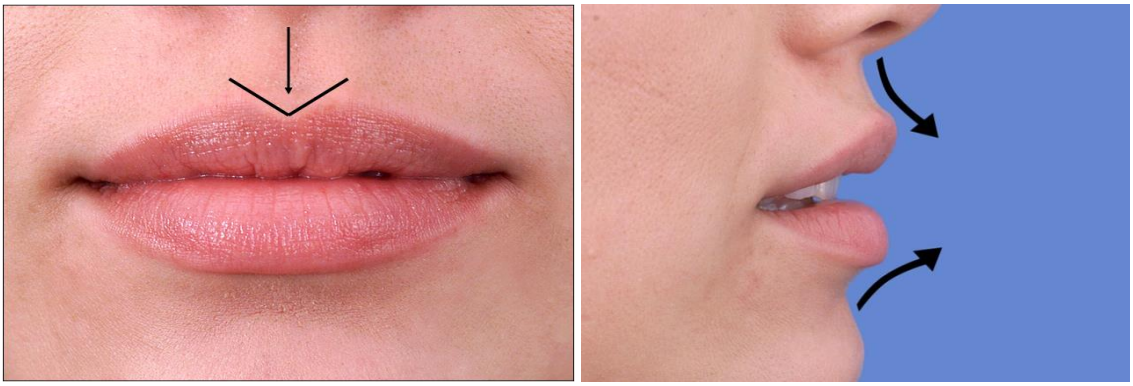
Photos courtesy of Rod Rohrich, MD

**Elements of the "Perfect Lips"**

The aesthetic evaluation of the lips must include a review of many variables. In a well-proportioned face, the length of the closed, relaxed mouth should equal the distance between the medial aspects of the irises. Elements of the "perfect lips" include the upper lip shape including the Cupid's bow, lower lip volume, philtral columns, and the balance of upper and lower lip, texture and lower lateral support.





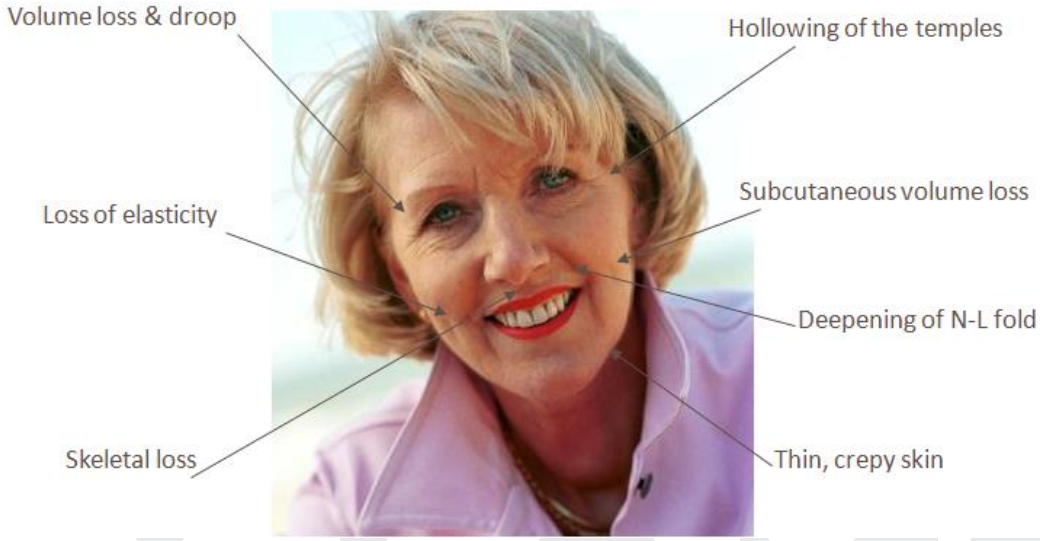


Photos courtesy of Rod Rohrich, MD

While genetics has much to do with the overall shape, texture and fullness of the lips, volume and structural loss are a normal part of the aging process. Specifically, there tends to be less exposed vermillion, a general loss in volume in both the upper and lower lips, lengthening of the lips as well as loss of structural support in the commissures resulting in a downturn. Extrinsic factors such as smoking, and sun exposure will take a toll on lip volume and can also contribute to perioral rhytids.

In summary, as one ages, the dermis thins, and the skin can become almost translucent or have a crepe-like appearance. Bony landmarks, such as cheekbones, become more visible or prominent and the cheek and mouth area tend to hollow out. As volume is depleted and skin loses elasticity, the facial fat pads descend which can cause a "jowling" appearance. This sagging can also cause the nasolabial folds to deepen.

In the lower part of the face, lips tend to thin and lose volume while the corners of the mouth will droop or descend. The tip of the nose also tends to droop. These changes and others are often due to a general decrease in support in the lower third of the face.



**Aesthetic Analysis**

A thorough aesthetic analysis is perhaps the single most important thing you can do to ensure a successful outcome before beginning facial enhancement procedures. This is the time to set realistic expectations with your patients.

When performing an aesthetic analysis with your patient, there are many considerations to include:

- Assess patient's desires
- Take an accurate patient history
- Look at the overall picture
- Detect potential problems
- Assess how you may be able to improve facial shape
- Assess overall symmetry
- An analysis of wrinkles and folds:
    - Location
    - Depth
    - Degree of asymmetry
- Examine volume loss
- Assess any prior treatments – can you maximize results?

Patient specific details are also an important part of the overall assessment process:

- Discuss the patient's goals. Talk about the specific areas of the face the patient would like to improve and which treatment(s) you think would help achieve their goals. Explain the selected procedure - what will happen, how long it will take, etc.
- Does the patient have an important event soon?
- Let them know about the limitations of each procedure, the expected length of duration and benefits/risks.
- Understand the patient's threshold for pain and suggest appropriate pain management options.
- Be sure the patient is aware of any possible complications. Talk about potential complications: any pain, bruising, or swelling that may result.
    - Be sure to fully explain the difference between normal complications vs. true adverse events. This will help the patient be better prepared to understand and handle normal side effects from the procedure.
- Provide information to the patient about appropriate pre- and post-treatment actions that will help minimize or prevent the occurrence of complications.
- What is the patient's financial commitment? You and your patient must be clear on the cost of the selected treatment and whether it will require additional visits.
- Under promise and over deliver!

All these factors are important as you develop a patient specific treatment plan.

**Photography**

It is important to take good quality photos of your patients prior to treatment. Photos should be taken with the same background and lighting every time. It is important to have minimal make-up so results are not artificially hidden or enhanced. Pre-treatment photos will help you and your patient as people tend to forget what they looked like prior to therapy.

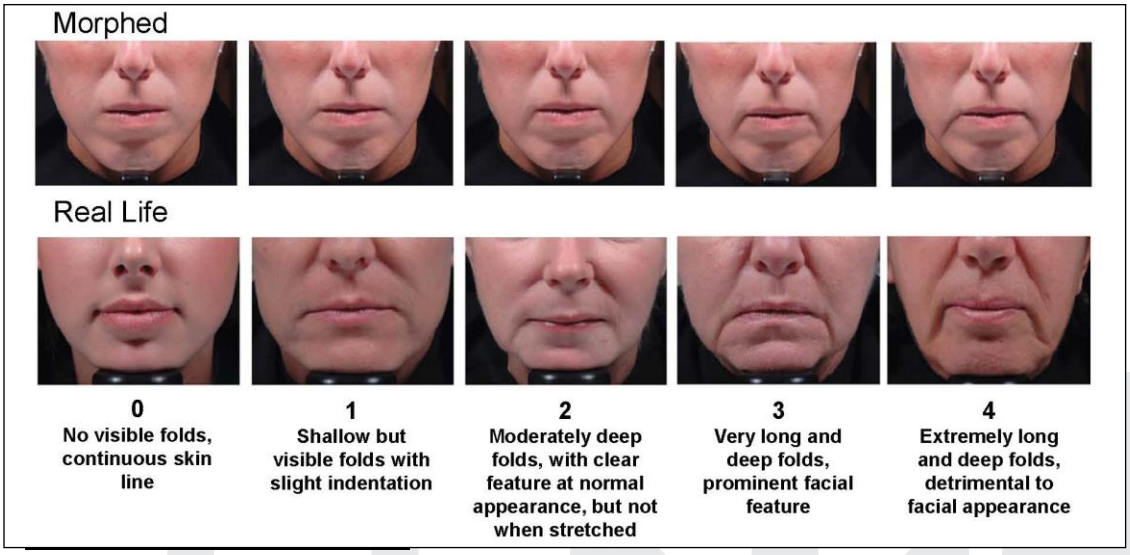
**Educational Materials**

There are a variety of educational print materials you can give your patient. Be sure to review what you hand out and encourage phone calls if there are any questions. A full understanding of all aspects of treatment will help you and your patient make the right decisions during the aesthetic analysis.

A tool, known as the Aesthetic Aging Scales,[5] was published in November 2008 and attempts to standardize the way clinicians measure and talk about age-related changes with patients, in publications and amongst themselves. These scales were designed to be a simple, user-friendly, 5-point photo numeric scale. They depict the aging process without complex measurements and are based on a computer-simulated photograph of the same individual using morphing technology. The currently published scales looked at:

- Lip fullness
- Brow positioning
- Marionette lines
- Hands
- Forehead lines
- Crow's feet

**Marionette Lines Grading Scales[6]**




[5] Carruthers, J, Carruthers, A, et al. Advances in Aesthetic Scales. *Dermatol Surg*, Nov 2008: Vol 34, No 2.
[6] Carruthers, J, Carruthers, A, et al. Advances in Aesthetic Scales. *Dermatol Surg*, Nov 2008: Vol 34, No 2:S169.

**Summary**

While there are many ways to approach the facial analysis, it is important that the technique you use be easy to remember and applied consistently. In this way, a routine, systematic approach can be developed that, over time, should help maximize your results. From the moment, you walk into the examination room, you are acting in several roles. As a medical professional, you must evaluate the client's general health and physical readiness for treatments. As a "therapist", you must be able to listen to client's concern and respond in a way that is helpful. It is important to seek their motivation for treatment and set clear expectations, up front. Your and your staff's communication skills are by far, one of the most important aspects of any treatment. Ensuring everyone is on the same page sets you and your client up for the best possible outcomes.

# NEUROTOXINS

## History

The history of botulinum toxin can be traced back to the 1820s when Dr. Justinus Kerner, a German physician and poet, described a case of food poisoning in a batch of blood sausage by using the terms "sausage poison" and "fatty poison." In 1895, Émile van Ermengem isolated the bacterium *Clostridium botulinum*. In 1980, Alan B. Scott, MD, used botulinumtoxin type A to treat strabismus. From this "most poisonous of all poisons"[1] has come a wealth of potential medical uses, from providing relief from the functional blindness of blepharospasm to improving the quality of life for patients with spasticity.

No use, however, has received as much press as the use in facial aesthetics. The discovery that botulinumtoxin type A could soften or eliminate lines and wrinkles began an aesthetic revolution like none other in modern history. In the mid-1990s, Drs. Jean and Alastair Carruthers, an ophthalmologist and dermatologist team, earnestly began studying and publishing the effects of BOTOX® Cosmetic on wrinkles and frown lines. In April 2002, BOTOX® Cosmetic received Food and Drug Administration (FDA) approval for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients <65 years of age.

The botulinum toxin known simply as "Botox" brought facial enhancement to the population at large. For a relatively small monetary investment, the average consumer can enjoy significant improvement in facial shape and see wrinkles fade away. This has an obvious and powerful appeal. Since 1997, botulinum toxin injections have grown to become the most popular, non-invasive aesthetic procedure overall.[2]

## Overview of Botulinum Toxin

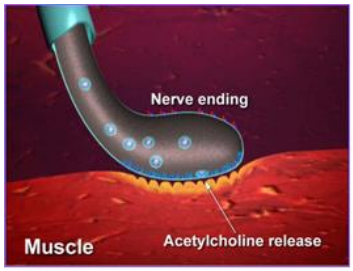
*C. botulinum* is an anaerobic bacterium that produces a neurotoxin. Seven distinct antigenic toxins produced by *C. botulinum* have been identified and are designated types A, B, C, D, E, F, and G.

In 1989, the FDA approved the first commercial preparation of botulinumtoxin type A (Oculinum) in the world for the treatment of blepharospasm and strabismus. Around that time, clinical development began for treatment of cervical dystonia and other conditions. The current formulation of BOTOX® Cosmetic was approved by the FDA in 1997 for the same indications. The current formulation has a reduced neurotoxin complex protein load of approximately 5 nanograms/100 units, compared with approximately 25 nanograms/100 units for the original preparation. This makes the current formulation significantly less immunogenic than the original formulation.

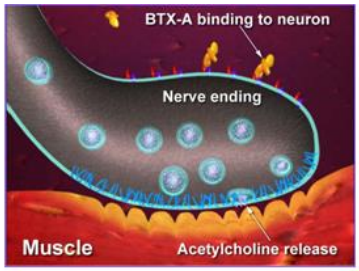
[1] Simpson LL. Botulinum toxin: a deadly poison sheds its negative image. *Ann Intern Med* 1996;125(7):616–617.
[2] From the American Society for Aesthetic Plastic Surgery 2012 statistics. http://www.surgery.org/media/statistics Accessed March 4, 2017.

## Mechanism of Action

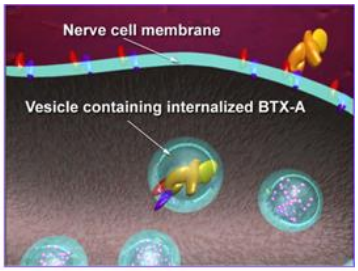
Simply stated, *C. botulinum* produces a protein that blocks the transmission of acetylcholine into injected muscles. Although the nerve endings remain connected, neuromuscular transmission failure occurs, and the muscle responds as if denervated (losing nerve supply). The primary steps involved in the mechanism of action of BOTOX® Cosmetic are demonstrated in the following illustrations and accompanying descriptions.[3]



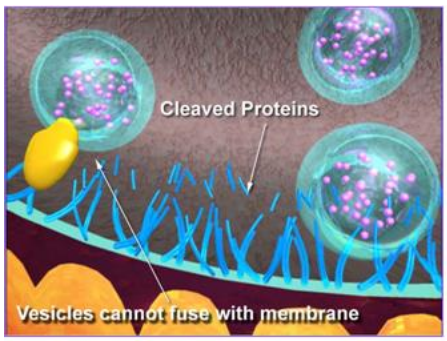

- Before BOTOX® Cosmetic: Endplate sits upon muscle fiber



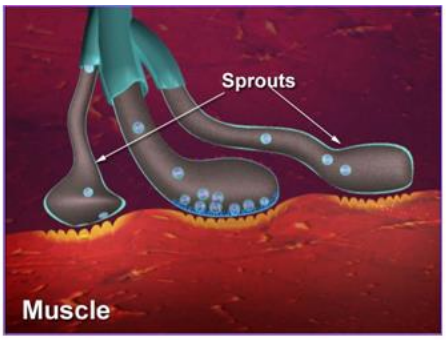

- BOTOX® Cosmetic binds to nerve terminal




- The neurotoxin is internalized via receptor-mediated endocytosis




- Light chain blocks fusion of neurotransmitter vesicle with nerve membrane by cleaving SNAP-25




- The endplate expands and collateral axonal sprouts emerge. Sprouts subsequently retract and are eliminated; parent terminal is re-established

Although both types A and B work similarly, they have different properties and actions.

[3] Adapted from http://www.botoxcosmetic.com/botox_physician_info/clinical_info/BotoxModule1.ppt accessed March 3, 2008.

## FDA-Approved Products

Until 2009, there was one approved botulinumtoxin type A product, BOTOX® Cosmetic, manufactured by Allergan, and one type B product, MYOBLOC®, manufactured by Solstice Neurosciences. In May 2009, the FDA approved Dysport®, originally manufactured by Medicis and now Galderma and in 2011, Merz Aesthetics received approval for Xeomin®. 2019 saw the approval of Jeuveau™ by Evolus. All these products are botulinumtoxinA products; however, their properties, including dilution rates and diffusion characteristics, are different. The differences led the FDA to assign new generic names to all botulinum toxin products[4]:

- BOTOX® Cosmetic is known as onabotulinumtoxin A
- Dysport® is known as abobotulinumtoxin A
- Xeomin® is known as incobotulinumtoxin A
- Jeuveau™ is known as Prabotulinumtoxin A-xvfs

## Product Details

BOTOX® Cosmetic: Onabotulinumtoxin A

- Company: Allergan
- Aesthetic indications:
  - For temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤65 years of age
  - For temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.
  - For moderate to severe forehead lines associated with frontalis activity
  - For the treatment of severe primary axillary hyperhidrosis
- How supplied:
  - Vial containing 100 units of *C. botulinum* type A neurotoxin complex in a sterile, vacuum-dried form without a preservative
  - Vial containing 50 units of *C. botulinum* type A neurotoxin complex in a sterile, vacuum-dried form without a preservative for use as a single-use vial (required in the state of Nevada)
- Must be stored under refrigeration
- The package insert (PI) states that before administration, BOTOX® Cosmetic should be reconstituted with 0.9% sterile, preservative-free saline. Many injectors, however, often use 0.9% sterile preserved saline because it is less painful for the patient.
  - The PI indicates that the product should be administered within 4 hours of reconstitution; however, studies have demonstrated that BOTOX® Cosmetic maintains efficacy up to (and perhaps beyond) 14 days after reconstitution.
- Retreatment frequency: No more than every 3 months

[4] Info available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175013.htm accessed March 6, 2010.

Dysport®: Abobotulinumtoxin A

- Company: Galderma
- Average response rate: 4 days[5]
- Aesthetic indications:
  - For temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients <65 years of age
- How supplied:
  - Single-use, sterile 300-unit vial for reconstitution with 2.5 or 1.5 mL of 0.9% sodium chloride injection (without preservative)
- Must be stored under refrigeration
- The PI states that before administration, Dysport® should be reconstituted with 0.9% sterile, preservative-free saline. Many injectors, however, often use 0.9% sterile preserved saline because it is less painful for the patient.
  - The PI indicates that the product should be administered within 4 hours of reconstitution.
- Retreatment frequency: No more than every 3 months

Jeuveau™: Prabotulinumtoxin A-xvfs

- Company: Evolus
- Aesthetic Indications:
  - For temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and/or corrugator muscle activity in adult patients
- How supplied:
  - Vacuum-dried powder supplied in a single-dose vial in a 100-unit vial.
- Must be stored under refrigeration
- The package insert (PI) states that before administration, Jeuveau™ should be reconstituted with 0.9% sterile, preservative-free saline. Many injectors, however, often use 0.9% sterile preserved saline because it is less painful for the patient.
  - The PI indicates that the product should be administered within 24 hours of reconstitution.
- Retreatment frequency: No more than every 3 months

Xeomin®: Incobotulinumtoxin A

- Company: Merz Aesthetics
- Aesthetic indications:
  - For temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients
- How supplied:
  - Type 1 borosilicate glass single-use vials with latex-free rubber closures and tamper-proof aluminum seals in the following package sizes:

[5] Baumann L, Brandt FS, Kane MA, Donofrio LM. An analysis of efficacy data from four phase III studies of botulinum neurotoxin type A-ABO for the treatment of glabellar lines. *Aesthet Surg J* 2009;29[suppl 6]:S57–S65.

  - Xeomin® 50 units, lyophilized powder
  - Xeomin® 100 units, lyophilized powder
- Unopened vials can be stored at room temperature. Reconstituted product should be stored in a refrigerator and administered within 24 hours.
- The PI states that prior to injection, reconstitute each vial of Xeomin® with sterile, preservative-free 0.9% sodium chloride.
- Retreatment frequency: No more than every 3 months

Botulinumtoxin Type A Boxed Warning

**WARNING: DISTANT SPREAD OF TOXIN EFFECT**

*See full prescribing information for complete boxed warning*

The effects of _____ and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults, particularly those patients who would have an underlying condition that would predispose them to these symptoms.

While botulinumtoxin type A is remarkably effective for treating a variety of indications, its usage is associated with the risk that the effects may diffuse beyond the injection site. All FDA-approved botulinumtoxin type A products must include the above statement. Per the BOTOX® Cosmetic package insert, "No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX® Cosmetic at the labeled dose of 20 units (glabellar lines), 24 units (lateral canthus lines), 44 units (simultaneous treatment of both) or 100 units (severe primary axillary hyperhidrosis) have been reported." [6]

## Neuromodulators in Development

RT002 Injectable

- Company: Revance
- Daxibotulinumtoxin A
- Phase III clinical trial results submitted to the FDA
- Approval anticipated 2021

## Understanding the Differences Among the Approved Neuromodulators

It is important for clinicians to understand the differences among the approved botulinumtoxin A products currently available. Although the results achieved with all can be comparable, the individual products are not the same.

[6] BOTOX® Cosmetic [package insert]. Irvine, CA: Allergan, September 2017.

**The potency units of each of the botulinumtoxin type A preparations are specific to their individual preparation and assay method used. They are not interchangeable with each other, and, therefore, units of one cannot be compared with or converted to units of another.**

In other words, 100 units of BOTOX® Cosmetic do not equal 100 units of Dysport®, Jeuveau™ and/or Xeomin®. Keep in mind this does not indicate that one product is better than the other! The differences between them are caused by multiple factors: differences in the strain of bacteria, different manufacturing processes, and the size of the protein complex. According to a recently published supplement to the *Aesthetic Surgery Journal*, "…in general, abobotulinumtoxin A (Dysport®) is less active on a unit-per-unit comparison with onabotulinumtoxin A (BOTOX® Cosmetic), which means that more units of Dysport® are required to achieve similar effects."[7]

The newest botulinumtoxinA product, approved in 2019 is Jeuveau™, by Evolus. Following is a comparison of general characteristics of the 4 products.

| | Dysport® | BOTOX® Cosmetic | Xeomin® | Jeuveau™ |
|---|---|---|---|---|
| **Vial Size** | **300 U** | **100 U*** | **100 U*** | **100 U** |
| **Composition** | Clostridium botulinumtoxin type A hemagglutinin complex | | | |
| | 125 µg (0.125 mg) human serum albumin | 500 µg (0.5 mg) human serum albumin | 1000 µg (1.0 mg) human serum albumin | |
| | 2.5 mg lactose | 0.9 mg NaCl | 4.7 mg sucrose | 0.9 mg NaCl |
| **Molecular Wt.** | 150 kDa (150-900kDA) | 150 kDa (900kDA) | 150 kDa (150kDa) | 900 kDa |
| **Bulk Active Substance** (total protein content) | ~ 3ng | ~ 5ng | 0ng | Non-disclosed |
| **Storage** (pre-& post – reconstitution) | Refrigerate: (2◦ to 8◦C) until vial expiration. Store at 2 to 8°C and use within 4 hrs once reconstituted | Refrigerate: (2◦ to 8◦C) for up to 36 months or until vial expiration. Store at 2 to 8°C and use within 4 hrs once reconstituted | Store at room temperature (20 to 25°C), in a refrigerator at 2 to 8°C, or a freezer at -20 to -10°C for up to 36 months. Store at 2 to 8°C after reconstituted and use within 24 hours | Refrigerate: (2◦ to 8◦C) until vial expiration. Store at 2 to 8°C and use within 24 hrs once reconstituted |

*BOTOX®Cosmetic and Xeomin® are also available in 50 U vials.

[7] Examination of a new US botulinum neurotoxin type A: Safety, efficacy immunogenicity and practice guide. Supplement to *Aesthet Surg J* 2009;29[suppl 6].

**Reconstitution of BotulinumtoxinA Products**

There is variability regarding dilution rates when reconstituting BOTOX® Cosmetic. In practice, many injectors choose a range of dilutions and injection volumes, according to personal preference and the area of the face being treated. In addition, most use preserved saline because it is more comfortable for patients. To evaluate the effect of different dilutions, Carruthers et al.[8] randomized eligible study participants to receive a total dose of 30 units of BOTOX® Cosmetic at dilutions of 100, 33.3, 20, or 10 units/mL at baseline. The dose was divided among seven intramuscular injections at glabellar sites with varying volumes depending on dilution. No differences in efficacy or safety were observed among the four dilution groups.

**BOTOX® Cosmetic Vial Dilutions**

| Diluent Volume (mL) | Units/mL | Units/0.1 mL |
|---|---|---|
| 1.0 | 100.0 | 10.0 |
| 1.5 | 66.7 | 6.7 |
| 2.0 | 50.0 | 5.0 |
| 2.5 | 40.0 | 4.0 |
| 3.0 | 33.3 | 3.3 |
| 4.0 | 25.0 | 2.5 |
| 5.0 | 20.0 | 2.0 |

The volume of diluent determines the unit dosage of the product per 0.1 mL. It also has been anecdotally reported to potentially affect the rate of diffusion of the drug into the muscle. If predicted and controlled, diffusion can be a helpful technique during treatment. It can also adversely affect the treatment outcome if not properly used.

Reconstitution with a 3:1 Ratio

| | BOTOX® Cosmetic Units (BU) - 100 Unit Vial | Xeomin® Units (XU) 100 Unit Vial | Dysport® Units (DU) 300 Unit Vial | Jeuveau™ |
|---|---|---|---|---|
| **Saline Diluent Vol** | U/0.1 mL | U/0.1 mL | U/0.1 mL 3:1 DU:BU-XU ratio | U/0.1 mL |
| **1.0 mL** | 10.0 | 10.0 | 30.0 | 10.0 |
| **1.5 mL** | 6.7 | 6.7 | 20.0 | 6.7 |
| **2.0 mL** | 5.0 | 5.0 | 15.0 | 5.0 |
| **2.5 mL** | 4.0 | 4.0 | 12.0 | 4.0 |
| **3.0 mL** | 3.3 | 3.3 | 10.0 | 3.3 |
| **4.0 mL** | 2.5 | 2.5 | 7.5 | 2.5 |
| **5.0 mL** | 2.0 | 2.0 | 6.0 | 2.0 |

[8] Carruthers A, Carruthers J, Cohen J, Alain J. Dose dilution and duration of effect of botulinumtoxin type A (BTX-A) for the treatment of glabellar rhytids. Poster presented at the Annual Meeting of the American Academy of Dermatology, New Orleans, LA, February 2002.

Standard Dosing

The appropriate dosing for each patient's procedure depends on several variables, both physical and psychological. Physical cues to be considered in selecting the appropriate dose include gender, area to be treated, muscle mass, facial animation, and anatomic variation. Psychological considerations include the patient's previous experience with aesthetic procedures and his or her individual aesthetic preference.

The overall goals of treatment are to achieve a personalized, balanced result for your patient. Wrinkle effacement is only one facet of the overall treatment plan. As such, you can treat multiple areas and combine neuromodulators with fillers or other treatments for the same patient in the same session. Current practice recommends using the smallest dose possible to yield the desired results. It is recommended that the dose of neuromodulators be referred to by units rather than by volume (e.g., 10 units, not 0.5 or 1.0 mL). Unit dose relates to active drug, whereas volume is a function of the dilution.

## Injection Techniques with Neuromodulators

Successful treatment with neuromodulators depends on recognition of the patient's individual characteristics. Accurate injection based on the patient's anatomy and the injector's clinical analysis is the best tool for achieving optimal outcomes. Although treatments need to be individualized for each patient, the techniques described facilitate the safest and most effective results.

Applications with Neuromodulators

All botulinumtoxinA products are indicated for the treatment of moderate to severe glabellar lines associated with procerus and/or corrugator muscle activity in adult patients. In addition, Allergan received an expanded indication for BOTOX® Cosmetic for the treatment of moderate to severe lateral canthal lines and most recently, received an indication for the treatment of moderate to severe forehead line associated with frontalis activity. In practice, all products are used to treat different areas of the face.

Cosmetic applications of neuromodulators can be divided into basic procedures and advanced techniques. The latter require significant experience and are best conducted by those with extensive knowledge of the product and the procedure.
Common applications include:

- Horizontal forehead lines
- Glabellar frown lines
- Crow's feet
- "Bunny" lines

These procedures, although still requiring significant knowledge and excellent technique, are generally more straightforward and easier to perform on most patients.

Increasingly popular, but more challenging, applications include:

- Asymmetry (i.e., brow)
- Lower eyelid
- Mouth frown
- Lip lines
- Neck lines

The above require a more advanced understanding of the use of the different products and should not be performed until the injector attains a significant level of experience.

**Upper Face**

The most commonly treated areas in the upper face:

- Glabellar frown lines
- Horizontal forehead lines
- Crow's feet

Glabellar Frown Lines

The glabellar area is the most common, and only indicated, aesthetic procedure for type-A neuromodulators. Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles, which draw the eyebrows together, wrinkle the brow, and are involved in squinting. The corrugator and orbicularis oculi pull the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. Activity of these muscles is the most common cause of glabellar lines. However, the location, size, and use of these same muscles can vary greatly among patients.

The prescribing instructions for BOTOX® Cosmetic[9], Dysport®[10], Jeuveau™[12], and Xeomin®[11] are very similar regarding glabellar injection technique:

- To reduce the occurrence of blepharoptosis, avoid injecting near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge. (In practice, this appears to be higher than what is often done.)
- Do not inject BOTOX® Cosmetic closer than 1 cm above the central eyebrow.

What differ are the recommended units to achieve the desired result. BOTOX® Cosmetic and Xeomin® have the same recommendations while Dysport® is different:

- Inject 4 units of BOTOX® Cosmetic into each of five sites: 1 unit in the procerus muscle and 2 units into each corrugator.
- Inject a total of 50 units of Dysport® administered in five equal aliquots of 10 units each.
- Inject 4 units of Xeomin® into each of 5 sites: 1 unit in the procerus muscle and 2 units into each corrugator.

[9] BOTOX® Cosmetic [package insert]. Irvine, CA: Allergan, September 2013.
[10] Dysport® [package insert]. Dallas, TX: Galderma, Revised 7/15.
[11] Xeomin® [package insert], Greensboro, NC: Merz Aesthetics, April 2012.

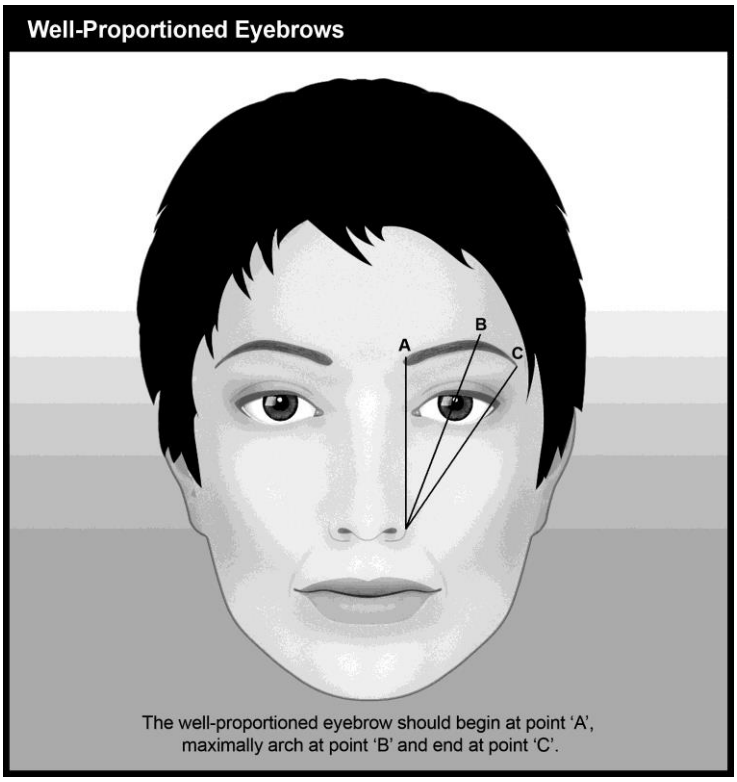
In practice, many injectors vary the above instructions to create an individualized approach for the patient. When muscular anatomy indicates, additional injection sites can be added to improve the result. The most popular addition is that of two additional bilateral injection points 1 cm above the superior orbital rim. Patient gender can affect the recommended dosing and placement of injection sites. The shape of the ideal male eyebrow in comparison to the ideal female eyebrow can change the placement or the allocation of the dosage among the injection sites. Additionally, men tend to have larger muscle masses and might require a larger overall dose. The Botox Consensus Group[11] presented recommendations on the use of botulinumtoxin type A in facial aesthetics. The authors recommend a total dose starting range of 20 to 30 units for female patients and a total dose starting range of 30 to 40 units for male patients.[12] Similar recommendations have been made regarding use of Dysport®. In one study, male patients received a total volume of 60, 70, or 80 units whereas female patients received 50, 60, or 70 units.[13]

Patient ethnicity can impact the appropriate starting dose. The Botox Consensus Group suggests that when treating Asian women, the injector should use a starting total dose of 10 units and evaluate after 2 weeks to assess results.

Horizontal Forehead Lines: Frontalis Muscles

Horizontal forehead lines are formed by the action of the frontalis, a vertically positioned muscle in the forehead. The goal in treating this area is to maintain some expressivity through movement of the frontalis muscle. When treating the frontalis, one must consider the aesthetic effect it will have on brow shape and position. Brow shape and position are critical factors in determining emotional mood and altering either has a dramatic effect on how others will perceive your patients.

[12] Carruthers J, Fagien S, Matarasso SL, Botox Consensus Group. Consensus recommendations on the use of botulinum toxin type a in facial aesthetics. *Plast Reconstr Surg* 2004;114[suppl 6]:1S–22S.
[13] Kane MA, Brandt F, Rohrich RJ, Narins RS, Monheit GD, Huber MB, Reloxin Investigational Group. Evaluation of variable-dose treatment with a new U.S. botulinum toxin type A (Dysport®) for correction of moderate to severe glabellar lines: Results from a phase III, randomized double-blind, placebo-controlled study. *Plast Reconstr Surg* 2009;124(5):1619–1629.






Despite these challenges, experience does provide some guidelines for approaching a patient treatment plan.

- In general, the number of injection sites average between four and six, depending on the variables discussed above. Regardless of the number of injection sites, all injections should remain 1 to 2 cm above the orbital rim to reduce the potential for brow ptosis.

Dosage recommendations from the Botox Consensus Group for BOTOX® Cosmetic:

- A total starting dose of 10 to 20 units is recommended for women, and a total starting dose of 20 to 30 units is recommended for men. Again, gender differences in muscle mass and eyebrow shape impact the difference in dosing.
- In general, the total dose of BOTOX® Cosmetic to be injected can be divided by the number of injection sites to determine the number of units to inject per site. For example, a total starting dose of 10 units divided among six injection sites would yield just over 1.5 units per site.

Dosage recommendations from the *Aesthetic Surgery Journal* [14] supplement for Dysport®:

- Forehead: 30 to 60 units divided among three to six areas, 1 cm apart
- Brow "lift": 10 to 12 units 0.5 cm above the orbital rim in the lateral fibers of the orbicularis oculi muscle
- Treat forehead depressors and avoid elevator muscles

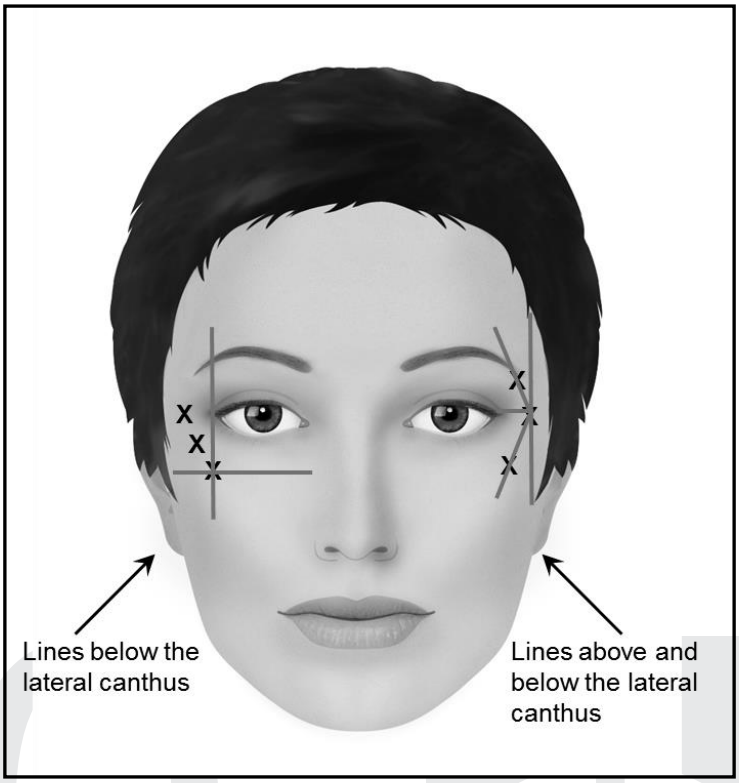
[14] Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport®): Clinical indications and practice guide. *Aesthet Surg J* 2009:29[suppl 6]:S72-S79

Crow's Feet: Orbicularis Oculi Muscles

Crow's feet result primarily from the activity of the orbicularis oculi in combination with the effects of photoaging. The treatment goal is to soften the lines without impairing the function of the muscle.

BOTOX® Cosmetic is the only botulinumtoxin type a product with an approved indication for treating lateral canthus lines. Injection sites should also be well above the upper margin of the zygoma and the needle should be pointed away from the eye. According to the package insert, injections should be 1.5-2.0 cm temporal to the lateral canthus and just temporal to the lateral rim. If the lines are below the lateral canthus, results can be achieved by injections below the lateral canthus. If the lines in lateral canthal regions are both above and below, the injection pattern should follow as shown.

Treatment of crow's feet is usually to the lateral portions of the muscle, with two to five injections sites per side. To avoid complications, injections should be at least 1 cm lateral to the orbital rim or 1.5 cm lateral to the lateral canthus. Injection sites should also be well above the upper margin of the zygoma. Bruising can be reduced by subcutaneous rather than intramuscular injections, avoiding the superficial veins. Using magnification loops can also help the injector avoid tiny blood vessels further reducing the chance of bruising.



The Botox Consensus Group recommends injecting 3 to 4 units of BOTOX® Cosmetic per injection site in conjunction with the following starting dose ranges:

- 8 to 16 units per side for women
- 12 to 16 units per side for men

The *Aesthetic Surgery Journal* [15]supplement recommends 40 to 60 units of Dysport® divided among four to six areas, 1 cm lateral to the bony orbit.

Bunny Lines: Nasalis Muscles

So called "bunny lines" occur from regular wrinkling of the nose because of contraction of the transverse portion of the nasalis. Treating this area with neuromodulators provides refinement for balancing the upper and central face and, in practice, is often combined with treatment of glabellar lines.

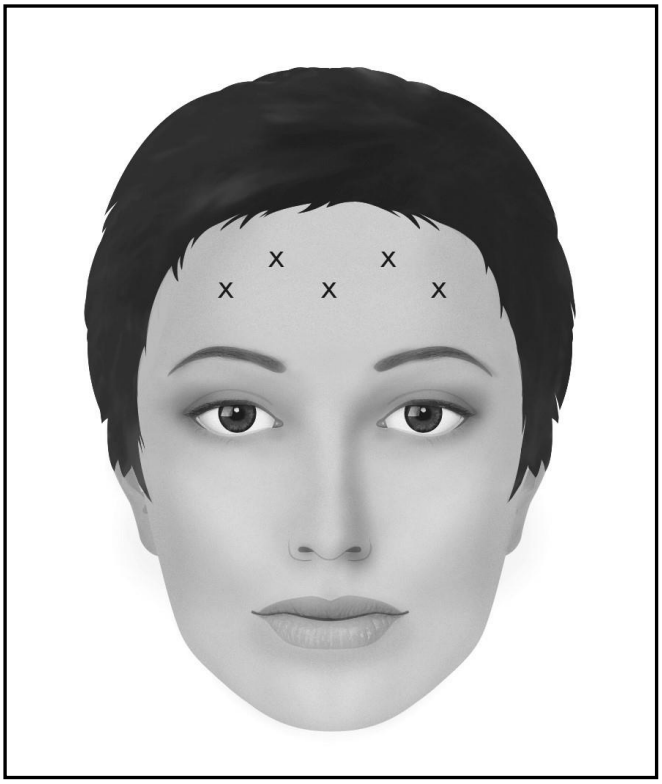
Treatment of bunny lines with BOTOX® Cosmetic, as recommended by the Botox Consensus Group, involves low-dose injections in one to three injection sites, totaling from 2 to 5 units. The *Aesthetic Surgery Journal*[16] supplement recommends 6 to 15 units of Dysport® divided between two points on either side of the nose, with an additional 3 to 5 units injected centrally, if necessary. Injections should be superficial and in symmetric locations and amounts. The nasalis is best approached over nasal bones, well above the nasofacial groove where lip elevators are located. Injecting too low in the nasofacial groove can cause upper lip ptosis.

Forehead Lines: Frontalis Muscle

One's face is constantly "in use"! Being worried, surprised or animated is usually manifested in the eyes and forehead. Wrinkling of the forehead causes temporary lines and over time, these can become permanent fine lines and eventually, wrinkles. The loss of skin elasticity, exposure to the sun and weaker muscles all play a role in the aging face and the result are lines and wrinkles. The use of botulinumtoxin type A to treat forehead wrinkles is not new but until recently, has been an off-label use. Allergan recently received FDA-approval for BOTOX® Cosmetic (Onabotulinumtoxin A) to treat forehead lines and currently, is the only product with this indication.

[15] Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport®): Clinical indications and practice guide. *Aesthet Surg J* 2009:29[suppl 6]:S72-S79

[16] Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport®): Clinical indications and practice guide. *Aesthet Surg J* 2009:29[suppl 6]:S72-S79





From the BOTOX® Cosmetic (Onabotulinumtoxin A) approved label[6]:

- It is recommended to treat forehead lines in conjunction with the glabellar lines to minimize the potential for brow ptosis
- The approved dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units.
- For simultaneous treatment of all 3 areas, the dose is 20+24+20 (20 Units forehead, 24 Units, lateral canthal lines and 20 Units glabellar liens) for a total dose of 64 Units.

The Botox Consensus Group averages 4-6 injection sites fir the forehead and recommends they remain above the orbital rim to reduce the risk of brow ptosis.

**Lower Face**

The approach to treating a patient with neuromodulators in the lower face is much more conservative than the approach to the upper face. The lower facial musculature is of paramount importance in aesthetics but also in the actions of daily living: drinking, swallowing, speaking, and even breathing. Injection of too high a dose in the lower face can mimic acute facial paresis that can last for approximately 6 months, turning a cosmetic client into a medical patient with complications. It is strongly recommended that you be an experienced, trained injector, with a solid understanding of facial musculature before you offer these procedures to your patients.

In general, it is recommended to proceed slowly in the lower face, starting with lower dosages in each patient, and titrate to a greater dose to the desired response to avoid complications. With

careful analysis and skill, minimal use of neuromodulators can have a maximal effect in the lower face.

The most common lower face treatment areas with neuromodulators are:

- Vertical lip lines
- Dimpled chin
- Depressor anguli oris (DAO)
- Platysmal bands

Vertical Lip Lines: Orbicularis Oris Muscle

The lips are central to the aesthetics of the lower face. Normal actions of the orbicularis oris, accentuated by aging and behaviors such as smoking, cause vertical lip lines to form. Neuromodulators can be used to treat vertical lip lines, also called lipstick lines, which allow lipstick to "bleed." Combining neuromodulators with fillers or resurfacing can greatly improve the overall appearance in this part of the face. It is important to remember however, that overtreatment of the perioral area can cause significant dysfunction. Treatment of the lower lip is to be approached with caution.
Suggestions made by the Botox Consensus Group for BOTOX® Cosmetic treatment of vertical lip lines include:

- Administer BOTOX® Cosmetic in a symmetric, superficial vermillion-cutaneous border injection.
- Injections should be very low dose, 1 to 2 units per site, with a total dose of 4 to 10 units divided among four to six sites.
- Exercise caution when injecting both the lower and upper lips simultaneously.

The *Aesthetic Surgery Journal*[17] supplement recommends 2 to 6 units of Dysport® at two or four injection points. Another panel of core aesthetic physicians (represented by dermatology, plastic surgery and facial and oculoplastic surgery) met in November 2011 and their recommendation, published in a supplement to the *Aesthetic Surgery Journal* [18] was a total starting dose of 4 – 10 units (inco, ona) divided among 4-6 injection sites.

Dimpled Chin: Mentalis Muscle

Contraction of the mentalis muscle in conjunction with the loss of subcutaneous fat and collagen caused by aging can cause a dimpled appearance in the skin of the chin. It is difficult to correct this condition with fillers or resurfacing, but neuromodulators remain an excellent option. The Botox Consensus Group recommends a dose ranging from 5 to 10 units, usually accomplished with one injection of BOTOX® Cosmetic directly into the midline of the mentalis

[17], Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport®): Clinical indications and practice guide. *Aesthet Surg J* 2009:29[suppl 6]:S72-S79
[18], Lorenc, Z.P., et al. (2013). Consensus panel's assessment and recommendations on the use of 3 botulinum toxin type A products in facial aesthetics. *Aesth Surg J* 33, 35S-40S

muscle, just above the tip of the chin. The *Aesthetic Surgery Journal* [19]supplement recommends 10 to 20 units of Dysport® in one site or separated into two sites.

Depressor Anguli Oris (DAO)

Contractions of the DAO muscle, which can become more pronounced as a patient ages cause the ends of the mouth to droop down; often portraying an appearance of perpetual sadness or anger. Treatment of the contracted DAO can be dramatic, and treatment is typically 1 injection into each side. The average recommended dose is 2.5 units (ona or inco) per side. It is important to be careful when placing product as injecting too high can negatively impact the movement of the orbicularis oris, creating an uneven smile. The core aesthetic panel recommends an average of 2.5 units/side (ona, inco) when treating the DAO.[20]

Platysmal Bands: Platysma Muscle

Neuromodulators can be used for the treatment of vertical or horizontal neck bands. Prominence of the platysma is associated with age-related loss of subcutaneous fat. You might also see the need for this procedure for the treatment of recurrent bands in patients who have undergone a face-lift or neck lift. Despite the effectiveness of neuromodulators in this area, it is important to treat the platysmal bands with care.

Tips for successful treatment of this area from the published recommendations of the Botox Consensus Group:

- Administer BOTOX® Cosmetic in multiple low-concentration injection sites, approximately three to five sites per band, although more or less might be required.
- Inject along the bands in symmetric locations and amounts, directly into the belly of the muscle.
- Very broad guidelines for total starting dose are from 10 to 30 units for women and from 10 to 40 units for men.

The *Aesthetic Surgery Journal* [21]supplement recommends:

- 40 to 80 units of Dysport® per band, divided into four to eight injections
- Separate each injection by 1 to 2 cm.

[19] Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport®): Clinical indications and practice guide. *Aesthet Surg J* 2009:29[suppl 6]:S72-S79

[20] Lorenc, Z.P., et al. (2013). Consensus panel's assessment and recommendations on the use of 3 botulinum toxin type A products in facial aesthetics. *Aesth Surg J* 33, 35S-40S

[21] Matarasso A, Shafer D. Botulinum neurotoxin type A-ABO (Dysport®): Clinical indications and practice guide. *Aesthet Surg J* 2009:29[suppl 6]:S72-S79

## Avoiding and Managing Complications

Side effects of neuromodulators can be divided into two groups:

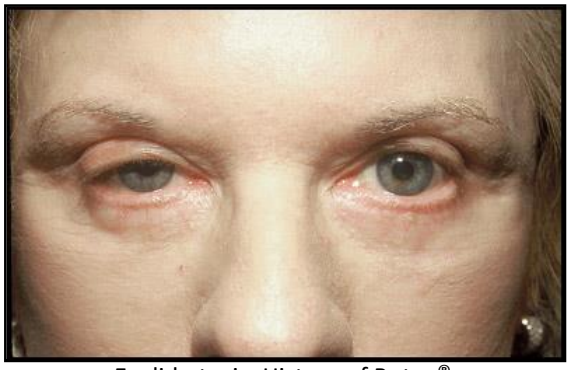
| Technique-related | Injection-related |
|---|---|
| • Asymmetry<br>• Upper eyelid ptosis<br>• Brow ptosis<br>• Cheek ptosis<br>• Perioral dysfunction<br>• Over-animation | • Bruising<br>• Headache |

A study[22] was conducted to observe the most commonly treated side effects of BOTOX® Cosmetic. Striking decreases were observed with repeated treatments in all events, including headache and ptosis. Results are shown below.

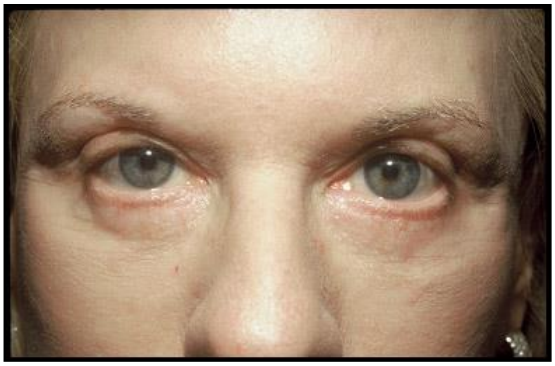
| Adverse Event | 1st BTX-A Treatment (N=501) | 2nd BTX-A Treatment (N=362) | 3rd BTX-A Treatment (N=258) |
|---|---|---|---|
| Any Event | 23.0% | 6.1% | 3.5% |
| Headache | 9.8% | 2.2% | 0.8% |
| Blepharoptosis | 3.0% | 2.2% | 0.8% |

**Most Common Treatment-Related Adverse Events with BOTOX® Cosmetic**

Eyelid Ptosis



Eyelid ptosis: History of Botox® injections 1 month previously



Results: 5 minutes after treatment with Naphcon A®

**Photos courtesy of Steven Fagien, MD. All Rights Reserved**

[22] Carruthers JD, Lowe NJ, Menter MA, Gibson J, Eadie N, Botox Glabellar Lines I and II Study Groups. One-year, two-period study of the safety and efficacy of repeated treatments with botulinum toxin type A in patients with glabellar lines: Four-month, double-blind, placebo-controlled period followed by an eight-month, open-label period. Presented at the Annual Conference of the American Academy of Dermatology, Washington, DC, March 2001.

The photo on the left shows a patient who presented for consultation for correction of acute right upper eyelid ptosis after findings of an extensive neurological evaluation were deemed negative. After questioning the patient and obtaining her history, the patient was asked whether she had ever received Botox®, to which she responded, "1 month prior, to the forehead." The photo on the right shows the same patient 5 minutes after placing Naphcon A® ophthalmic eyedrops, which were successfully used for the next 2 to 3 weeks until the upper eyelid ptosis resolved.

Treatment of Eyelid Ptosis

Müller muscle is an adrenergic muscle lying just beneath the levator muscle of the upper eyelid. The use of an alpha-1 adrenergic agent can cause contraction of the Müller muscle and improve eyelid ptosis. The alpha-1 adrenergic agent needs to be applied three to four times daily until ptosis disappears (2–4 weeks). This type of treatment works for mild lid ptosis and can also help brow ptosis. Rescue products for lid ptosis are shown below.


**Photo courtesy of Steven Fagien, MD - All Rights Reserved**

Brow Ptosis

The photos below demonstrate brow ptosis secondary to excessive neuromodulator dosing of the frontalis muscle.

**Photos courtesy of Rod Rohrich, MD - All Rights Reserved**

Asymmetry

The photo below demonstrates the effects of asymmetric injection of the lip depressors.

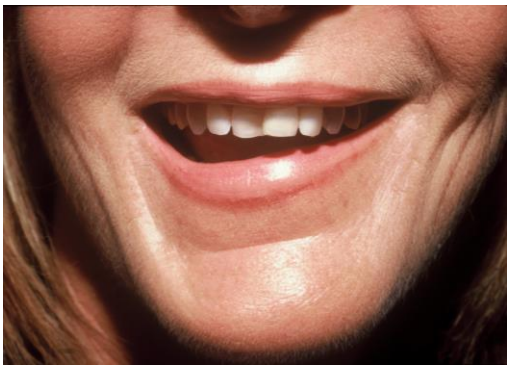
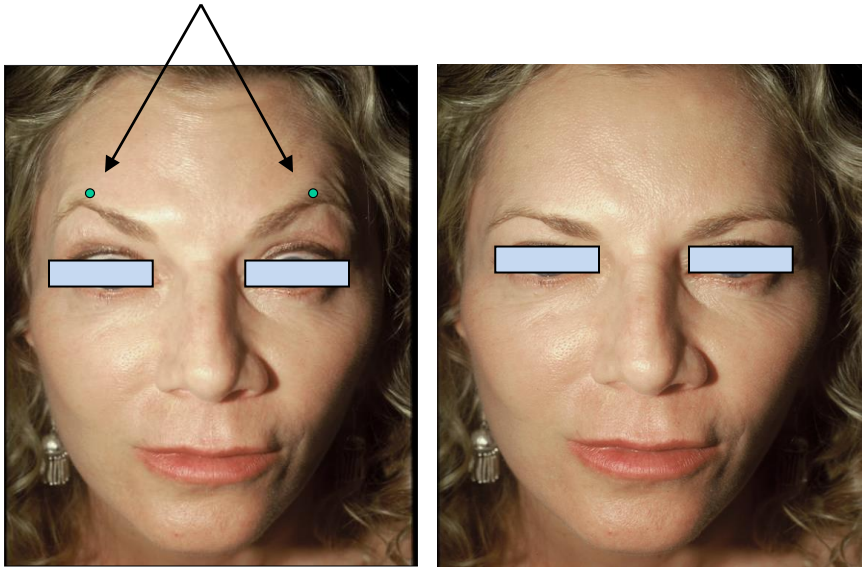


**Photo courtesy of Steven Fagien, MD - All Rights Reserved**

Over-Animation

Incorrectly placed injections can give a client an over-animated appearance. The photos below demonstrate how two additional injections of BOTOX®Cosmetic can correct an over-animated result.



**Photos courtesy of Steven Fagien, MD - All Rights Reserved**

**Summary**

Although once used for simple line eradication, neuromodulators have proven to be safe and effective for use in a wide variety of facial rejuvenation options, including improvement and restoration of facial shape. Additionally, these products can be value-added adjunctive agents when used in combination therapy with soft tissue fillers and resurfacing therapy.

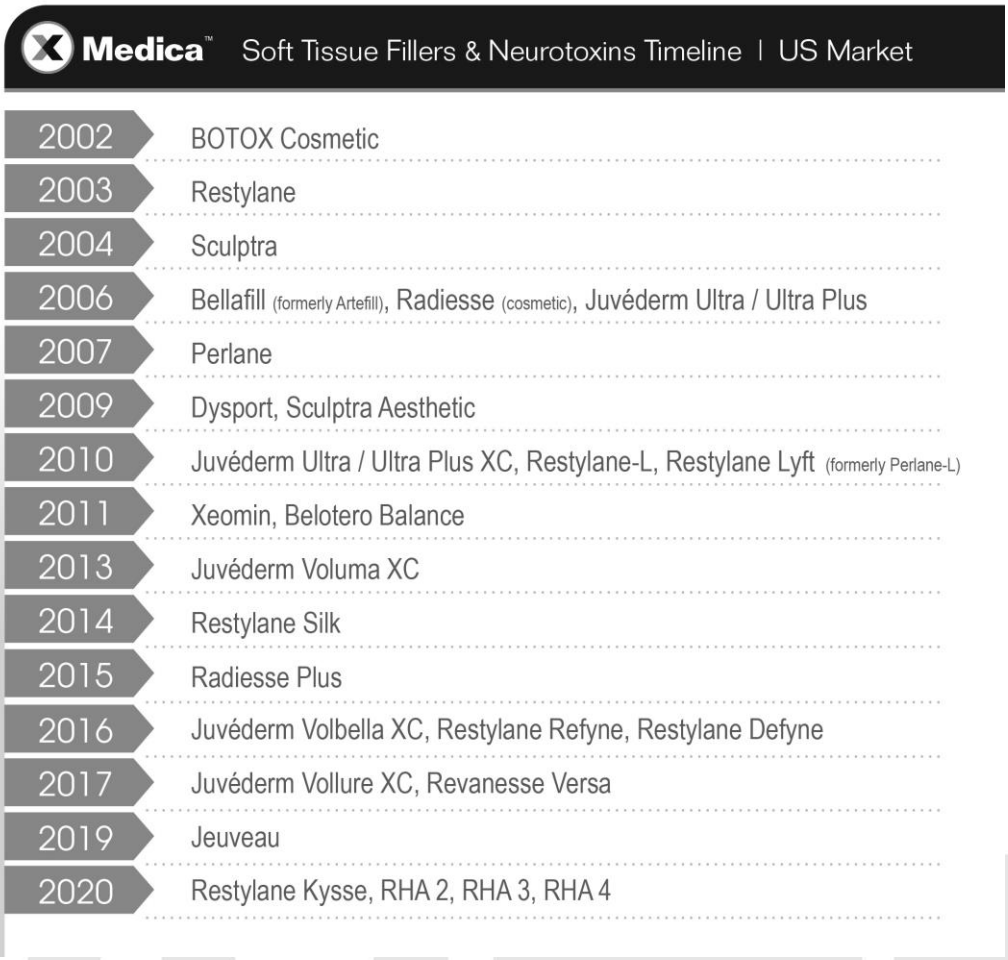
# OVERVIEW OF FACIAL INJECTABLES

03

**Introduction**

The American Society for Aesthetic Plastic Surgery (ASAPS) publishes annual statistics regarding cosmetic procedures. Their 2019[1] data indicate that BotulinumtoxinA injections remain the number one non-surgical procedure, as they have since 1999. Hyaluronic acid filler injections remain # 2 and the use of calcium hydroxylapatite increased over 9%.

Although there are a multitude of injectable fillers available on the worldwide market, there was a gap of more than 20 years between the approval of Zyderm® (first collagen filler approved in the US in 1981) and the introduction of the next new injectable for cosmetic use in the US. In 2002, the FDA approved the use of BOTOX® Cosmetic. Restylane® was the first hyaluronic acid filler approved in the US (12/2003) and these products have paved the way for a new era in nonsurgical facial rejuvenation. The diagram below shows the timeline of facial injectable products.






[1] From the American Society for Aesthetic Plastic Surgery 2019 statistics. http://www.surgery.org/media/statistics.

## Classification of Soft Tissue Fillers

While no universally accepted classification system for fillers exists, there are product features and attributes that differentiate one from another. The most common differentiators include the source of product, mechanism of action and length of duration. Duration of action is somewhat arbitrary as that can be affected by multiple factors such as age, gender, animation characteristics, metabolism, and number of past treatments. In addition, injector technique affects a product's longevity. Placing a product too deeply can dramatically shorten its duration simply because the results are not visible.

Following is a review of the most used FDA approved soft-tissue fillers, categorized by product type. These include hyaluronic acid fillers, biostimulatory fillers and permanent, synthetic fillers.

## Hyaluronic Acid Fillers

Hyaluronic acid fillers are now the most widely used injectable products, with a dramatic increase in global sales from $40 million in 2000 to over $300 million in 2005. The 2018 ASAPS statistics show over 700,000 injections of hyaluronic acid fillers in the United States.[2] Since hyaluronic acid is a natural substance found in the body, these fillers tend to have a low rate of allergic reaction and are typically well tolerated by patients. While initial labeling indicated HA fillers typically last between 6-12 months, recent studies have shown a longer duration of action. The Juvéderm® line is currently approved for a 12-month indication and the newest addition, Juvéderm® Voluma can last up to 24 months. The Restylane® line has received approval for an 18-month duration of action. One study, using Restylane®, demonstrated that patients who were treated to optimal or full correction and were re-treated at either 4.5 or 9 months showed longevity at 18 months. [3] Per one study published in 2007, it is thought that this increased persistency is due to stimulation of type 1 collagen. This may be due to the stretching of the fibroblasts by the HA filler. The fibroblasts in turn are stimulated to synthesize collagen.[4]

The following HA fillers are currently available in the United States:

Belotero® Balance +

- Company: Merz Aesthetics
- Bacteria-based HA (streptococcus equi)
- FDA approved: November 2011
- CPM (Cohesive Polydensified matrix) cross-linking technology
    - Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Belotero manufacturing results in a cohesive gel thus there is no average particle size

[2] From the American Society for Aesthetic Plastic Surgery 2017 statistics. http://www.surgery.org/media/statistics.
[3] Narins, R, et al. Persistence and improvement of nasolabial fold correction with nonanimal-stablizied hyaluronic acid 100,000 Gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. *Derm Surg.* June 2008*; 4:S2-S8.*
[4] F. Wang, MD, L. Garza, MD, PhD, S Kang, MD, J. Varani, PhD, J. Orringer, MD, G. Fisher, MD, J. Voorhees, MD. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol.* 2007;143(2):155-163.

- Total HA concentration: 22.5mg/mL
- Indication:
    - For injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as the nasolabial folds)

Juvéderm® Ultra/ Ultra XC & Juvéderm® Ultra Plus/Ultra Plus XC

- Company: Allergan
- Bacteria-based HA (streptococcus equi)
- FDA approved:
    - Juvéderm® Ultra/Ultra Plus - June 2006
    - Juvéderm® XC family - February 2010
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- XC family contains 0.3% lidocaine
- Juvéderm® manufacturing results in a smooth gel vs. a gel particle suspension (no particle size published)
- Total HA concentration: 24 mg/mL
- Indications:
    - For deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related mid-face volume deficit in adults over the age of 21.
    - For injection into the mid-to-deep dermis for correction of moderate to severe wrinkles and folds (such as nasolabial folds)
    - Ultra XC is also indicated for injection into the lips and perioral area for lip augmentation in adults over the age of 21
- In 2007, Juvéderm® received FDA approval for duration of action up to one year
- In Oct. 2015, Juvéderm® Ultra XC received FDA approval for injection into the lips and perioral area for lip augmentation in adults over the age of 21

Juvéderm® Voluma XC

- Company: Allergan
- Bacteria-based HA (streptococcus equi)
- FDA approved: October 2013
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Uses proprietary VYCROSS® technology which blends different molecular weights of hyaluronic acid, contributing to the gel's duration
- Total HA concentration: 20 mg/mL
- Indication:
    - For deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over 21

Juvéderm® Volbella XC

- Company: Allergan
- Bacteria-based HA (streptococcus equi)
- FDA approved: June 2016
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)

- Contains 0.3% lidocaine
- Uses proprietary VYCROSS® technology which blends different molecular weights of hyaluronic acid, contributing to the gel's duration
- Total HA concentration: 15 mg/mL
- Indications:
    - For deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related mid-face volume deficit in adults over the age of 21
    - For use in the lips for lip augmentation and for correction of perioral rhytids, commonly referred to as perioral lines, in adults over the age of 21

Juvéderm® Vollure XC

- Company: Allergan
- Bacteria-based HA (streptococcus equi)
- FDA approved: March 2017
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Uses proprietary VYCROSS® technology which blends different molecular weights of hyaluronic acid, contributing to the gel's duration
- 17.5 mg/mL of hyaluronic acid
- Indications:
    - For deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over 21
    - For the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds in adults over the age of 21

Restylane®, Restylane®-L

- Company: Galderma
- Bacteria-based HA (streptococcus equi)
- FDA approved:
    - Restylane® - December 2003 (First FDA approved HA filler)
    - Restylane®-L – February 2010
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Restylane®-L contains 0.3% lidocaine
- Uses proprietary NASHA® technology which provides precision and structure
- Average particle size for Restylane® and Restylane®-L: 400µm
- Total HA concentration: 20mg/mL
- Indications Restylane® and Restylane®-L:
    - For mid to deep-dermal implantation for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
    - For submucosal implantation for lip augmentations in patients over 21 yrs.
- In 2008, Restylane® received approval for duration of action up to 18 months

Restylane® Kysse

- Company: Galderma
- Bacteria-based HA (streptococcus equi)
- FDA approved: 2020
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Uses proprietary XpresHAn® technology, creating gels that offer a range of flexibility and support.
- Total HA concentration: 20mg/mL
- Indication:
    - For injection into the lips for lip augmentation and correction of upper perioral rhytids in patients over the age of 21.

Restylane® Lyft (Formerly Perlane®-L)

- Company: Galderma
- Bacteria-based HA (streptococcus equi)
- FDA approved:
    - Perlane® - May 2007
    - Perlane®-L - February 2010
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Uses proprietary NASHA® technology which provides precision and structure
- Average particle size: 900µm
- Total HA concentration: 20mg/mL
- Indication:
    - For implantation to the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles (such as the nasolabial folds)

Restylane® Defyne

- Company: Galderma
- Bacteria-based HA (streptococcus equi)
- FDA approved: December 2016
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Uses proprietary XpresHAn® technology, creating gels that offer a range of flexibility and support.
- Total HA concentration: 20mg/mL
- Pressed through a fine mesh for product-consistent textures and smoothness
- Restylane® Defyne is more crosslinked than Restylane® Refyne
- Indication:
    - For the treatment of nasolabial folds or “laugh lines” in patients over the age of 21.

Restylane® Refyne

- Company: Galderma
- Bacteria-based HA (streptococcus equi)

- FDA approved: December 2016
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Uses proprietary XpresHAn® technology, creating gels that offer a range of flexibility and support.
- Total HA concentration: 20mg/mL
- Pressed through a fine mesh for product-consistent textures and smoothness
- Restylane® Refyne is less crosslinked than Restylane® Defyne
- Indication:
    - For the treatment of nasolabial folds or "laugh lines" in patients over the age of 21.

Restylane® Silk

- Company: Galderma
- Bacteria-based HA (streptococcus equi)
- FDA approved: 2014
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Indication:
    - For submucosal implantation for lip augmentations and dermal implantation for correction of perioral rhytids in patients over the age of 21

Revanesse® Versa™

- Company: Prollenium US
- Bacteria-based HA (streptococcus equi)
- FDA approved: April 2017
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Total HA concentration: 25mg/mL
- Particles are uniquely spherical and uniform
- Homogenous filler due to an advanced wet milling technology
- Indication:
    - For injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds in adults, 22 years of age or more.

RHA®2

- Company: Revance
- Bacteria based HA (streptococcus equi)
- FDA approved 2017. Marketed in 2020
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Total HA concentration: 23 mg/g
- Indications:
    - For injection in the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF) in adults over the age of 22.

RHA®3

- Company: Revance
- Bacteria based HA (streptococcus equi)
- FDA approved 2017. Marketed in 2020
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Total HA concentration: 23 mg/g
- Indications:
    - For injection in the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF) in adults over the age of 22.

RHA®4

- Company: Revance
- Bacteria based HA (streptococcus equi)
- FDA approved 2017. Marketed in 2020
- Cross-linking agent: BDDE (1,4-butanediol diglycidyl ether)
- Contains 0.3% lidocaine
- Total HA concentration: 23 mg/g
- Indications:
    - For injection in the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF) in adults over the age of 22.

**Biostimulatory Fillers**

The class of soft tissue fillers referred to as biostimulatory fillers contain synthetic, biodegradable materials. Products in this group, Radiesse® and Sculptra® Aesthetic, act in different ways, but contain synthetic material which stimulates endogenous tissue growth. The advantage to these products is that the duration of action is typically longer than with collagen and HA fillers; in some cases, reportedly up to 2 years. The disadvantage of a longer duration of action is that if results are not acceptable, the product must be removed which can be inherently difficult.

The following biostimulatory fillers are currently available in the United States:

Radiesse®, Radiesse® Plus

- Company: Merz Aesthetics
- Pure synthetic Calcium Hydroxylapatite (CaHA) composed of calcium and phosphate ions
- Radiesse® Plus contains 0.3% lidocaine
- CaHA particles:
    - Consistent uniform, smooth, spherical shape with a narrow size range of 25 to 45 µm
    - Fibrous tissue grows on the particles and holds them in place

  - Over time, the gel carrier is replaced by the patient's fibrous tissue (3 to 6 months)
- Indications:
  - For subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds
  - Intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.
  - Radiesse is indicated for hand augmentation to correct volume loss in the back of the hands.

Sculptra® Aesthetic

- Company: Galderma
- Synthetic polymer, from the alpha-hydroxy-acid family containing Poly-L-lactic acid (PLLA)
  - PLLA microparticles range in size from 40 to 63 µm in diameter
  - PLLA is suspended in sodium carboxymethylcellulose and mannitol.
  - Over time, the microparticles get reabsorbed and this process stimulates natural collagen formation.
- FDA approved: August 2004
- Indications:
  - For use in the treatment of HIV-associated facial lipoatrophy.
  - For use in immune-competent people as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies, and other facial wrinkles, in which deep dermal grid pattern (cross-hatch) injection technique is appropriate
- How supplied:
  - Sculptra® Aesthetic is supplied as a sterile, freeze-dried preparation for injection in a clear glass vial. The product must be reconstituted with sterile water (3-5 mL) 24 hours before injection and is stable up to 72 hours after reconstitution.

**Permanent Fillers**

The use of permanent fillers has been debated in the aesthetic field for many years due to the permanency factor. Physicians who inject permanent fillers must be well trained in facial aesthetics and understand the product nuances and injection techniques. Artefill®, introduced in 2006, was the first permanent filler approved for cosmetic use in the United States. The company filed chapter 11 in 2008, and in 2009, Suneva Medical acquired the rights to Artefill® and is actively marketing the product. In 2014, the name of the product was changed to Bellafill®

Bellafill®

- Company: Suneva Medical
- FDA-approved: October 2006
- Composed of a combination of precision-filtered microspheres made from polymethylmethacrylate (PMMA) and purified bovine collagen
- Bellafill® contains:
  - 20% microspheres of PMMA

  - 80% purified collagen gel consisting of:
    - 3.5% bovine collagen
    - 2.7% phosphate buffer / 0.9% sodium chloride
    - 0.3% lidocaine hydrochloride
    - 92.6% water for injection
- PMMA is a synthetic polymer which is non-biodegradable, immunologically inert, and relatively nontoxic.
- PMMA microspheres have a defined size of 30 to 50 microns in diameter and have a round, smooth surface.
- The collagen is absorbed into the body after 3 months, leaving the PMMA spheres permanently in place.
- After injection, the microspheres stimulate the body's own production of collagen and provide a permanent structure to support and prevent further wrinkles.
- Skin test required.
- Indication:
  - For the correction of nasolabial folds
  - For the correction of moderate to severe, atrophic, distensible facial scars on the cheeks in patients over the age of 21

**Summary - Overview of Fillers**

This section was designed to give the reader an overview of the US soft tissue filler market. While all FDA approved soft tissue fillers have been reviewed, the novice injector should become familiar with and first learn to properly inject the hyaluronic acid fillers before moving onto the longer lasting products. The next section takes a more in-depth look at the science and characteristics of HA soft tissue fillers.

# COMPREHENSIVE REVIEW OF SOFT TISSUE FILLERS

## Introduction

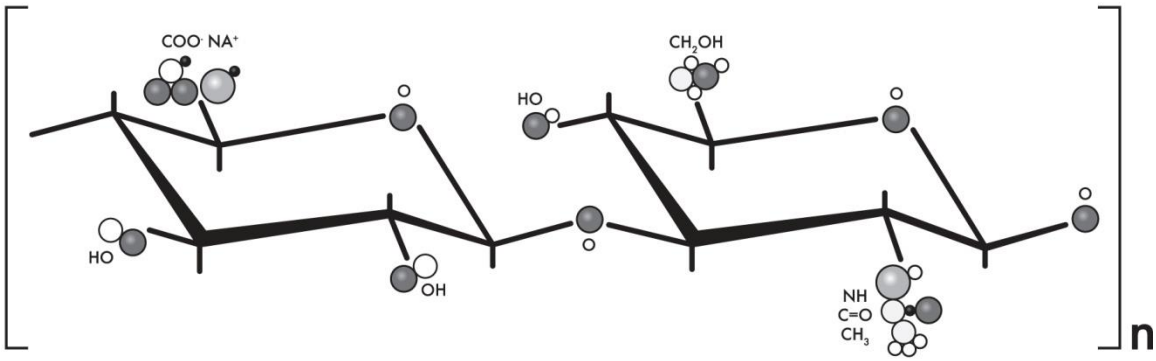
The following information will provide greater detail on the soft tissue fillers that are approved for use in the US market. A more comprehensive review is included for the hyaluronic acid (HA) fillers, which are by far the most popular fillers injected today. Care has been taken to provide the most accurate and up-to-date information available.

## Hyaluronic Acid (HA)

Hyaluronic Acid, a polysaccharide, was first isolated from bovine vitreous in the mid-1930s. Since then, it has been found in all tissues and in all vertebrates. The chemical structure of HA is the same, regardless of the species in which it is found. This makes HA an ideal substance for use as a biomaterial in health and medicine. Several medical applications of HA are currently in use, including eye surgery, tissue augmentation, anti-adhesion, and correction of joint disorders.

## Molecular Structure

HA is a type of polysaccharide (carbohydrate) called a *glycosaminoglycan* or *GAG*. Giant molecules of HA are made up of repeating disaccharide units. The molecule is a linear polysaccharide composed of repeating disaccharide units of *N*-acetyl-glucosamine and Na-glucuronic acid.






The molecular weight, measured in daltons, varies based on the source of the HA. HA is a hydrophilic or water-loving molecule. HA molecules are typically very long, and the coils intertwine and tangle to form a unique, three-dimensional structure. The three-dimensional structure, combined with a hydrophilic nature, allows the HA molecule to bind many times its own weight in water. This is an important fact about HA and is a key reason why it is very useful as a soft tissue filler.

**Physiological Functions**

HA helps maintain the structure and function of tissues.

- The three-dimensional structure of HA creates volume in tissues because it holds water and allows the passage of metabolites to and from cells.
- HA protects and lubricates tissues, joints, and tendons by stabilizing the intracellular space. It does this by creating a viscous, elastic matrix.
- The HA molecules assist in cell differentiation, migration, and wound repair.
- The high degree of permeability of HA helps to regulate the transportation of nutrients to and from cells.

**HA: Importance to Skin**

Although HA is found in many parts of the human body, the greatest percentage, ~56%, is found in the skin. As we age, the concentration of HA in the skin decreases. What impact does the decrease have on human skin and tissue? Consider this:

- HA is highly hydrophilic, so as it binds with water, it creates volume, providing the skin with a full and plumped appearance.
- HA protects and lubricates, thus helping to maintain the viscoelasticity, or suppleness, of the skin.

As we age, we have fewer HA molecules, which means less opportunity for water to bind and fewer molecules to protect and lubricate. The result is skin that is less hydrated, less elastic, and more susceptible to injury and infection.

**Stabilizing HA**

The overall turnover rate of HA is much faster than those of other extracellular components, such as collagen. Although the residence time of HA in most tissues can be up to a few days, the residence time in skin is less than 24 hours. For the majority of medical applications of HA, the product must remain intact for a number of weeks or months to have any useful clinical impact. Scientists began looking for ways to stabilize the HA molecule and have achieved stabilization through a process known as cross-linking. The degree of cross-linking is dictated by the manufacturing process of the final product.

**Sources of HA**

Commercial HA products are derived from one of two sources:

- Animal-based, extracted from the tissues in rooster combs (high concentration of HA in rooster combs)
- Human tissue (e.g. umbilical cords)
    - Recombinant strains of bacteria[1] (Streptococcus equi or Bacillus subtilis)

1. Kontis, T.C. (2013). Contemporary review of injectable facial fillers. JAMA facial plastic surgery *15, 58-64.*

**Characteristics of HA Fillers**

As the number of HA fillers continues to increase, it is important to have a level of understanding about some of the characteristics you might hear about, including the following:

- Molecular weight
- Cross-linking
- Gel hardness
- HA concentration (total and gel)
- Fluid HA, gel HA
- Particle size
- Hydration or swelling

The following is designed to provide a brief overview of these characteristics. An attempt has been made to summarize the important points without going into a detailed scientific review.

Molecular Weight

Molecular weight of animal-based HA is typically higher than that of bacteria-based HA.

Cross-linking

The cross-linking process contributes to many of the final characteristics of the HA filler and one of the most important reasons is to increase the durability of the product. Cross-linking is achieved through a chemical alteration of the molecule, and products such as butanediol diglycidyl ether (BDDE) and divinyl sulfone (DVS) are typically used for this purpose.

To simplify the process, think of the raw HA as a powder that is reconstituted. During reconstitution, the powder turns to a liquid and begins to get thicker. When the cross-linking agent is added, the molecules bond and intertwine, turning the consistency of the HA into a gel.
A recent study by Gold[2], et al shows the following degree of cross-linking of some commercialized HA fillers:

- Restylane®: 1.2%
- Revanesse® Versa™: 7%
- Juvéderm® Ultra: 9%
- Juvéderm® Ultra Plus: 11%

Gel Hardness, Fluid HA, Gel HA, Total HA Concentration, Gel Concentration

You might hear any of the above terms associated with an HA filler. What do they all mean and what is their significance?

- Gel hardness: Simply stated, as the product becomes more cross-linked, the gel becomes firmer or harder.
- Gel and fluid HA: The cross-linking process is just that: a step in the manufacturing process. Because cross-linking is a dynamic process, when this step is finished, the resulting product contains HA molecules that are fully cross-linked and some HA molecules that are only partially or not cross-linked. The HA that is fully cross-linked is often referred to as *gel HA*, and it is the part of the product that contributes to longevity

[2] Gold, MA. A multicenter, double-blinded, randomized, split-face study of the safety and efficacy of a novel hyaluronic acid gel for the correction of nasolabial folds. Data on File. Prollenium, US.

of effect. The non- or partially cross-linked HA that remains is sometimes referred to as *fluid HA* (or *modified* or *free HA*). Some HA fillers have fluid HA added at the end of manufacturing because doing so provides lubrication and makes the product flow more easily.

- Total and gel HA concentrations: Different products list different characteristics in their marketing materials. Suffice it to say that total HA concentration refers to the total amount of HA, both gel and fluid in a product. Gel concentration indicates the percentage of active or gel HA in the product.

Particle Size

Once the HA has finished the cross-linking process, the bulk product is homogenized and sized. Some HA products have smaller average particle sizes, whereas others have larger particle sizes. Some products are listed as homogenized and do not state specific particle size.

Hydration and Swelling

HA is a water-loving molecule. The degree that the molecule binds with water during the manufacturing process determines the degree of hydration of the final product. Some products are more highly hydrated than others, which mean that they will attract less water once injected, resulting in less swelling. Others will attract more water after injection, resulting in more swelling. Regardless, the swelling is temporary and typically subsides in a few hours to a few days.

**Summary of HA Characteristics**

What is the importance of the characteristics of HA? Does it mean that any one product is superior to the other? Little, if any, scientific data have compared the different HA products with each other. Most achieved FDA approval by demonstrating their equality or superiority to collagen, typically Zyderm®. The faculty agree that each product has its own unique characteristics and that one of the most important factors affecting outcomes is proper injection technique. The following HA fillers have been approved for use and are available in the US.

| Product | Company | Approval |
|---|---|---|
| Restylane® | Galderma | 12/2003 |
| Juvéderm® Ultra<br>Juvéderm® Ultra Plus | Allergan | 6/2006 |
| Perlane® | Galderma | 5/2007 |
| Juvéderm® Ultra XC<br>Juvéderm® Ultra Plus XC | Allergan | 2/2010 |
| Restylane®-L<br>Restylane Lyft – formerly Perlane®-L | Galderma | 2/2010 |
| Belotero Balance +® | Merz Aesthetics | 11/2011 |
| Juvéderm® Voluma XC | Allergan | 10/2013 |

| | | |
|---|---|---|
| Restylane® Silk | Galderma | 6/2014 |
| Juvéderm® Volbella | Allergan | 6/2016 |
| Restylane® Refyne & Restylane® Defyne | Galderma | 12/2016 |
| Juvéderm® Vollure | Allergan | 3/2017 |
| Revanesse® Versa™ | Prollenium US | 8/2017 |
| RHA® 2,RHA® 3, RHA® 4 | Teoxane SA | 10/2017 |
| Restylane® Kysse | Galderma | 05/2020 |

**Biostimulatory Fillers**

Biostimulatory fillers are those that are composed of synthetic, biodegradable material. Although products in this group, Radiesse®, Radiesse® Plus and Sculptra® Aesthetic, act in different ways, both contain synthetic materials that stimulate endogenous tissue growth. The advantage to these products is that the duration of action is typically longer, up to 2 years in some cases. The disadvantage of a longer duration of action is that if results are not acceptable, and the product must be removed, it can be difficult. The Radiesse® family and Sculptra® Aesthetic are the two fillers currently approved for use in the United States that fall into this category.

Radiesse® and Radiesse® Plus

Radiesse® is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds such as the nasolabial folds. In addition, it is indicated for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus (HIV). Radiesse® is composed of round calcium hydroxyapatite (CaHA) particles that range in size from 25 to 45 microns. The methylcellulose gel carrier degrades in 3 to 6 months, whereas the CaHA microspheres provide a scaffold for connective tissue (collagen) ingrowth. The CaHA particles are slowly dissolved into calcium and phosphate ions through normal metabolic processes. The duration of action for Radiesse® is reported to be approximately 18 to 24 months. Radiesse® Plus, which contains 0.3% of lidocaine was approved for use by the FDA in January 2015. In June 2015, Radiesse® was FDA approved to correct volume loss in the dorsum on the hand.

Radiesse® is supplied in syringes containing 1.5 and 0.8 mL of product. The design of the syringe has been updated with an ergonomically engineered “tulip” handle. The depth of injection for Radiesse is dependent on the area to be injected and the depth of the wrinkle or fold. Overall, deep dermal or subcutaneous injections work best with Radiesse.

Sculptra® Aesthetic

Sculptra®, injectable poly-L-lactic acid (PLLA), is intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with HIV. In 2009, the product, now known as Sculptra® Aesthetic, received cosmetic approval, indicated for use in immune-competent people as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate.

PLLA is a synthetic polymer that is derived from natural components. It is both biodegradable and biocompatible. The PLLA microspheres are reabsorbed over a period of time and in the process, stimulate collagen growth, which helps increase skin thickness. Sculptra® Aesthetic is provided as a freeze-dried product that must be reconstituted with 3 to 5 mL of sterile water for injection. It is stable for up to 72 hours after reconstitution. Many clinicians reconstitute Sculptra Aesthetic with more diluent, including a small amount of lidocaine. The lidocaine helps in pain management, and the rationale for more diluent is to reduce the potential for lumps.

Sculptra® Aesthetic should be injected into the deep dermis or subcutaneously. It should not be injected superficially. The linear threading technique has been described for injecting Sculptra® Aesthetic in the mid and lower face, whereas serial puncture is often used in the upper face and temple area. It is important not to overcorrect with the product, and massage is recommended immediately after injection and for a period thereafter (by the patient) to help evenly distribute the product and reduce the potential for lumps to form. Patients might notice an immediate result, which tends to diminish during the first week. Dermal thickening gradually occurs and continues for up to 2 years. Patients often achieve best results when treated multiple times over the course of weeks to months.

## Permanent Fillers

The use of permanent fillers has been debated in the aesthetic field for many years because of the permanency factor. Physicians who inject permanent fillers must be well trained in facial aesthetics and understand the product nuances and injection techniques. Artefill®, introduced in 2006, was the first permanent filler approved for cosmetic use in the United States. The product contains bovine collagen, which means that patients must undergo a skin test before administration. Artes Medical, the company that introduced Artefill® to the US market, closed in 2008, and the product was temporarily unavailable. Suneva Medical purchased the product and now actively markets Artefill®. In 2015 the product name was changed from Artefill® to Bellafill®. Indications are for the correction of nasolabial folds and in January 2015, Bellafill® received approval for correction of moderate to severe atrophic, distensible facial acne scars.

Much has been debated about the use of permanent fillers because they are far less forgiving should subsequent problems occur. Although the side effects of permanent fillers are similar to those of other fillers, this product category is best left to experienced injectors.

**Pain Management - Overview**

It is important that patients have a positive experience during their treatment. Proper education will help patients better understand what they can expect during and after an injection session. Understanding your patient's pain tolerance is also very important. If the patient has undergone previous procedures, he or she can provide you with a better sense of what can be tolerated. Adequate pain control helps to ensure better treatment outcomes and causes less stress for you, the patient, and staff. Pain can come from the injection itself and from the product components. Physical injury to nerve endings and altered physiology of sensory nerve endings caused by inflammation or contact with injected substances are potential causes of pain. Consider which part of the face you are treating, because some areas are more sensitive than others.

There are different pain management options to consider:

- Topical anesthetic products
- Ice
- Products that are premixed with lidocaine
- Manually mixing products with lidocaine
- Nerve blocks

Topical Anesthesia

Traditionally, topical anesthesia and nerve blocks have been used to minimize or eliminate the pain associated with facial injectable procedures. A variety of products can be applied topically to numb the skin and for maximum effect they should be applied liberally 20 to 30 minutes before treatment. Many physicians also use ice before, during, and after treatment.

Products Pre-Mixed with Lidocaine

Many HA fillers are now available already mixed with lidocaine. Advantages are that the amount of lidocaine used is consistent and the products are mixed in a uniform fashion prior to filling the syringe.

Manual mixing with Lidocaine:

Prior to the availability of products premixed with lidocaine, physicians often mixed the products themselves using a transfer device. Many physicians still prefer to manually mix products with lidocaine because it gives them flexibility as to which strength of lidocaine can be used as well as choosing a formulation with epinephrine. Mixing with lidocaine can also render the product slightly more viscous which can make the flow out of the syringe easier.

Nerve blocks:

The use of nerve blocks has greatly diminished as the availability of products which are pre-mixed with lidocaine has increased. While there are pros and cons to using commercially available products mixed with lidocaine, there are disadvantages to the use of nerve blocks including:

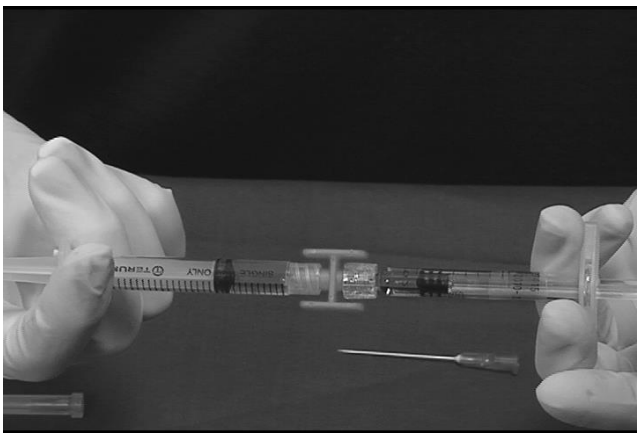
- Anesthetic volume required for effect can distort the anatomy, making it difficult to accurately assess results

- Can result in more bruising
- The initial injection is still painful, and many patients do not like the prolonged anesthesia effects

Locals:
As the use of cannulas has increased, some injectors now put a small amount of lidocaine into the site where the pilot needle will be inserted.

**Manual Addition of Lidocaine for Pain Management**

Initially, the technique of adding lidocaine to the filler was done manually and is accomplished with a syringe-to-syringe transfer device. The typical quantity of lidocaine is 1 mL, however dosing is not standardized. Some injectors use lidocaine with epinephrine, and some use it without; some use 1% lidocaine, and others use 2%. Except for Radiesse, mixing fillers with lidocaine is clearly an off-label use; however, it is a widespread practice. It is important to understand that mixing lidocaine with the filler product alters the concentration of the filler to some degree, which can have unknown effects on its characteristics. Over time, filler manufactures have added lidocaine to their products and have received FDA approval for these products. There are very few fillers available today that do not contain lidocaine.



One of the more recently approved HA fillers, Revanesse® Versa, does not contain lidocaine. While those that do contain lidocaine reduce the need to add it to the product via mixing, there will still be times when mixing is necessary. As always, you should follow the guidelines of the physician you work with when approaching any off-label use of products.

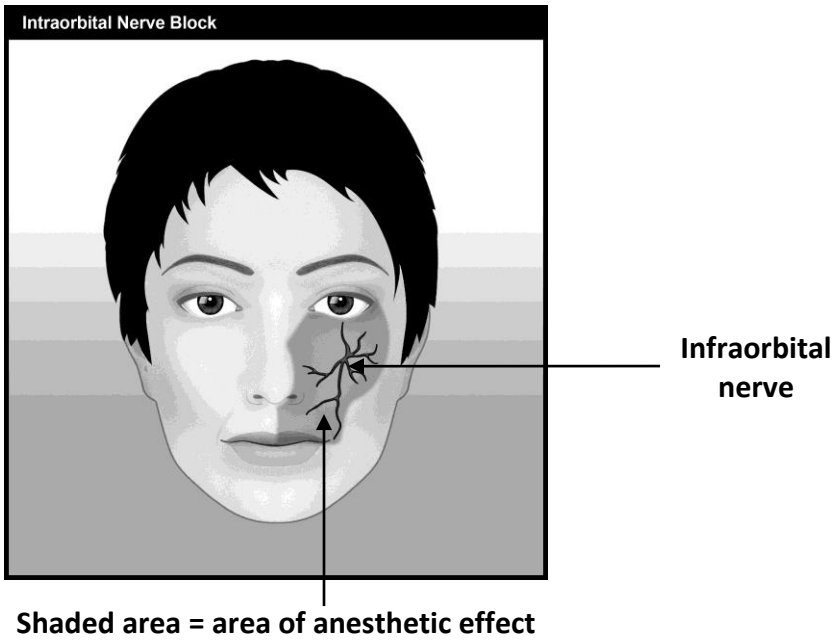
## Infraorbital Nerve Blocks[3],[4]

While the addition of lidocaine to many of the soft tissue fillers has dramatically reduced the number of regional nerve blocks performed, there are some clinicians (and patients) who still prefer the total numbing effect that can only be achieved using a nerve block. Because of this, following is a review of the infraorbital, mental nerve and commissure blocks.

The infraorbital nerve, a branch of the second division or maxillary branch of the trigeminal nerve, innervates the upper lip, lateral portion of the nose, and medial aspect of the cheek. Two techniques are used for this block:

- Intraoral: An application of a topical anesthetic is usually applied to the mucosa to minimize injection discomfort. One to 2 mL of anesthetic is injected near the infraorbital foramen.
- Cutaneous: A direct cutaneous injection near (but not into) the infraorbital foramen can be used. A bolus of approximately 0.5 to 1 mL of anesthetic can be used, or the anesthetic can be injected in small depots around the nerve.

Care must be taken to avoid injecting too much volume, which can distort the anatomy of the area, which could result in under-correction of the defect. Potential side effects of infraorbital blocks include swelling of the lower eyelid and/or ecchymosis.

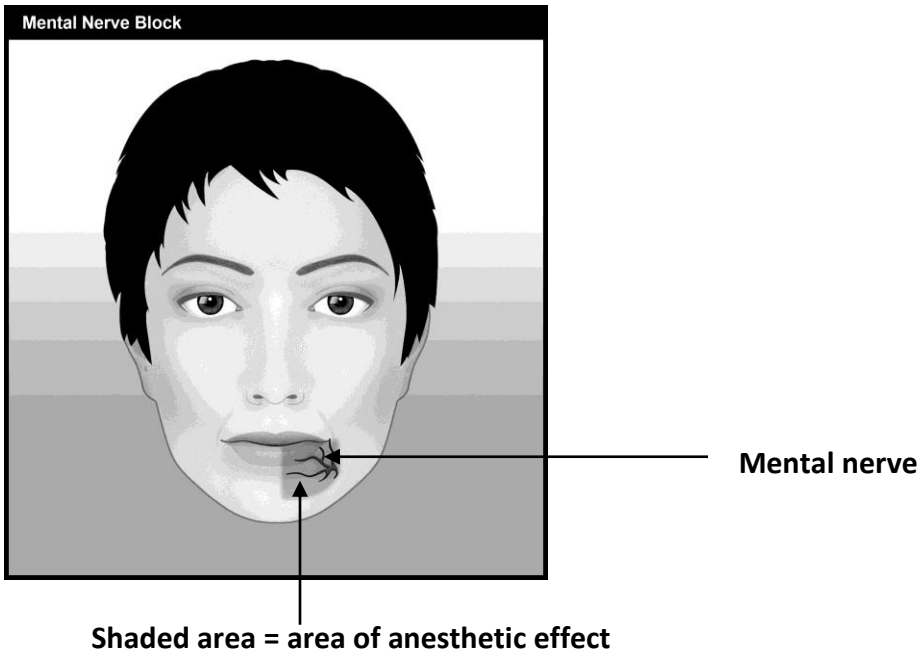





[3] Grekin RC, Auletta MJ. Local anesthesia in dermatologic surgery. *J Am Acad Dermatol* 1988;19(4):599−614.
[4] Gmyrek R. Local anesthesia and regional nerve block anesthesia. Available at: http://www.emedicine.com/derm/topic824.htm

## Mental Nerve Blocks

A mental nerve block innervates the lower lip and chin. Two techniques, an intraoral or an infiltrative injection, can be used. In either case, 1 to 3 mL of anesthetic is used.






Infraorbital and mental nerve blocks might not totally anesthetize the corners of the mouth and the area around the lips. Additional numbing options include:

- Mouth corner or "commissure block"
- Augmentative lip injections
- Infiltrative lip injections

## Mouth Corner or Commissure Block

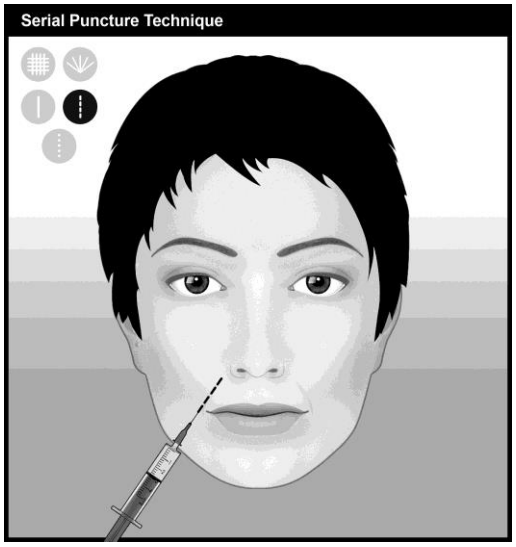
The technique used with a mouth corner or commissure block is to inject a small amount of anesthetic agent into the mucosa, lateral to the corner of the mouth. It is important not to inject too much volume because doing so can distort the anatomy, resulting in an unacceptable outcome.

Lidocaine 1% with or without epinephrine is often used. Infraorbital and mental nerve blocks might not completely anesthetize the corners of the mouth or the area around the entire lip. To prevent this, the addition of a small amount of local anesthesia injected just lateral to the corner of the mouth will reduce pain. In addition, augmentative injections to the lip and/or infiltrative lip injections can help reduce discomfort.

**Injection Techniques with Soft Tissue Fillers**

The four basic injection techniques used for injecting soft tissue fillers are serial puncture, linear threading, fanning, and cross-hatching. As experience with fillers has increased, injectors have developed a variety of different injection techniques, including what is referred to as *ferning*.[5] The basic injection techniques are described in more detail below. It is important to note that although these techniques have most often been described for injecting HA fillers, they are universal and apply to most products.

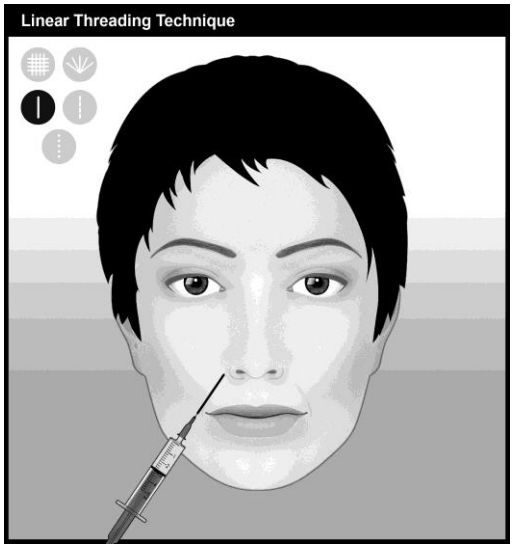
Serial Puncture**:**
The serial puncture technique involves multiple, closely spaced injections along fine lines, wrinkles, or folds. The injections should be made close together so that the injected material will merge into a smooth, continuous line, which lifts the wrinkle or fold. Some physicians find it helpful to slightly pull the skin away and out from the injection area while injecting. No spaces should remain between the serially injected materials.






Linear Threading**:**
The linear threading technique involves fully inserting the needle into the middle of the wrinkle or fold and injecting the filler as “threads.” This is most commonly done while the needle is slowly removed along the length of the facial defect (retrograde); however, some physicians have chosen to modify this technique by using the “push ahead” method (anterograde), which involves injecting while the needle is inserted. Physicians have reported less bruising with the anterograde technique.

[5] van Eijk T, Braun M. A novel method to inject hyaluronic acid: the fern pattern technique. *J Drugs Dermatol*. 2007;6(8):805−808.



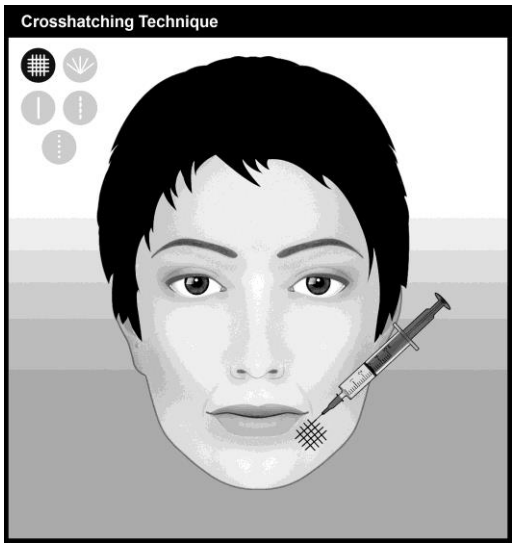



Fanning:

With the fanning technique, the needle is inserted in a manner like that used with the linear threading technique. However, immediately before the needle is withdrawn, the direction is changed, and a new line is injected (without withdrawing the needle tip from the skin). The fanning pattern of lines should be evenly spaced in a progressive, clockwise, or counterclockwise direction so that the contour is evenly filled and shaped. Fanning minimizes the number of puncture sites when treating larger areas.

Cross-hatching:

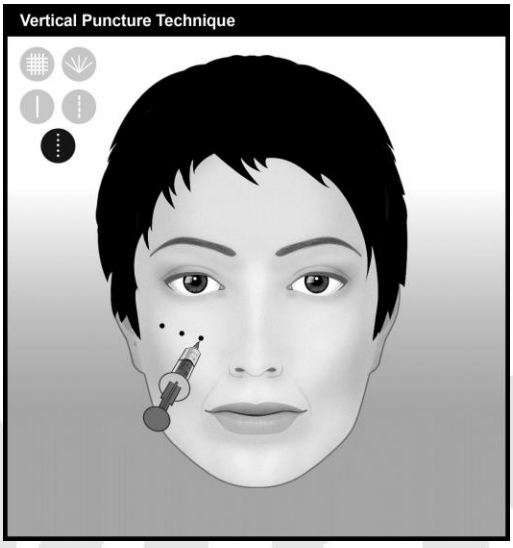
With the cross-hatching technique, the needle is inserted in a manner like that used with the linear threading technique. However, a series of threads are injected approximately 5 mm apart. A new series of threads are then injected at right angles to the others. This technique is often used when building support, such as in the oral commissure area.






Vertical Puncture

The approval of Juvéderm® Voluma XC has added a newer injection technique known as vertical puncture. Voluma is indicated for deep (subcutaneous and/or superperiosteal) injection for cheek augmentation. In this case, the deep vertical puncture technique can help to deliver small aliquots over a large area.



Use of Blunt Tip Cannulas

The use of blunt tip cannulas for certain injections has increased dramatically over the last few years. Due to the nature of a blunt tip vs. a sharp needle, these devices can produce less trauma to the tissues and decrease the risk for blood vessel rupture. The result is less bruising and less pain[6]. In addition, the use of blunt tip cannulas allows the clinician to treat larger areas with fewer injection points.

Blunt tip cannulas come in many sizes and are available from a variety of companies.

Massage:

Most injectors apply light massage after the product is injected to ensure it is in the correct plane and to smooth out any lumps or bumps.

## Avoiding and Managing Complications

Three of the most common reactions associated with HA soft tissue fillers are:

- Redness: Varies greatly by patient
- Bruising: Varies by patient. Avoiding blood vessels can help reduce bruising as can having patients avoid aspirin, ibuprofen, and other products known to cause bleeding.
- Swelling: Varies by patient but can be affected by the product and the injection skill and technique of the physician

Potential adverse events associated with fillers can also be generally categorized as the following:

- Injection and/or technique-related, including:
    - Asymmetry
    - Blanching
    - Bruising
    - Erythema and edema
    - Infection
    - Needle marks
    - Nodules, lumps, overcorrection, Tyndall effect
    - Vascular events
- Product-related, including allergic reactions and granulomas

[6] Fulton J., et al. (2012). Filler injections with the blunt-tip microcannula. *J Drugs Dermatol*. 2012:11(9 Supple): 1098-1103.

Injector- and/or technique-related complications can be greatly reduced with adequate knowledge and training. It is important that your patient understand the difference between complications, which can occur any time a needle is inserted into the face vs. adverse events.

Asymmetry more often occurs with less experienced injectors, although it can happen with experienced injectors, too. The anatomy can become distorted with injectable lidocaine, which can cause an asymmetrical result. It is important to schedule a follow-up appointment with your patient (2 weeks) so you can review the outcomes and do a touch-up if necessary. The follow-up visit is also a good time to get feedback from your patient, which can help to reinforce a positive injector-patient relationship.

Blanching is whitening of the skin during the injection process. If you see blanching, you should immediately stop injecting and wait to see whether blood flow returns. Blanching occurs when the injection is too superficial or when blood vessels are compressed, which can happen if too much product is used. One way to treat blanching is to try to force the product lower through mechanical motion. If blanching continues, tissue viability can be compromised, causing necrosis. The only time blanching is acceptable is when correcting acne scars, in which case the blanching will disappear in 10 to 15 minutes.

Erythema and edema can occur as an allergic reaction to the HA filler. Swelling tends to occur more frequently in the lips and more often with first-time patients. Mechanical issues, such as injecting too fast or massaging too aggressively, can also cause swelling. It is also important to know whether a patient has allergies to latex to avoid a reaction to the anesthetic agent used. At times, it might be necessary to prescribe a steroid, such as a Medrol®.[7]

Infection is not a common adverse reaction associated with soft tissue fillers, but it is important to remember to minimize the possibility by ensuring that the patient's makeup is completely removed and by using proper technique.

Nodules, lumps, and overcorrection are most often the result of an improper injection technique and can be treated in several ways. First, it is important to let the patient know that HA fillers are not permanent, and time will resolve the problem. Massage might help disperse extra HA and smooth small lumps or bumps. If necessary, excess product can be removed by extrusion or by using hyaluronidase. Hyaluronidase is an enzyme that modifies the permeability of connective tissue through the hydrolysis of HA. Simply stated, hyaluronidase will break down excess HA filler when it is injected into the affected area. Many FDA-approved hyaluronidase products are available and the most popular products for use in an aesthetic practice are Vitrase®[8] and Hylenex®[9].


Hylenex®
recombinant
(hyaluronidase human injection)

[7] Medrol® is distributed by Pharmacia & Upjohn, Inc., a Division of Pfizer, Inc., New York, NY.
[8] Vitrase® is manufactured by Cardinal Health, Albuquerque, NM, and is distributed by ISTAPharmaceuticals, Inc., Irvine, CA.
[9] Hylenex is manufactured for and marketed by Halozyme Therapeutics, Inc., San Diego, CA 855-495-3639.

Hylenex® recombinant is a purified preparation of the enzyme recombinant human hyaluronidase. Vitrase® is a preparation of purified ovine testicular hyaluronidase, a protein enzyme. Skin test may be done prior to use of Vitrase®. Other hyaluronidase products include Wydase®, Hydase™ and Amphadase®; all prepared from purified bovine testicular hyaluronidase.

Vascular events, although not common, can occur and can be serious. It is important not to inject into an artery or to put pressure on the artery, which could constrict the blood supply. Doing so could cause ischemia which can lead to tissue hypoxia and necrosis; ultimately causing significant scarring. If you suspect an intravascular injection or you see a painful blanching, you should immediately stop injecting and follow the protocol below. **Do not use ice**, which could further reduce blood flow. Vascular adverse events are rare occurrences, but they do happen to the best of injectors, they are serious, and you should know how to treat them.

Treatment Recommendations for Vascular Compromise

As stated above, while vascular compromise is not common, most physicians will tell you that if you inject enough fillers, it WILL happen to you and you MUST be able to treat it to a successful outcome! First, you must recognize a vascular compromise. Pay attention to unusual blanching or a patient complaining of persistent pain. Trian your staff that any patient who calls complaining of pain after a filler treatment (the same day, the next or several days later) must immediately come to the office for evaluation. The faculty recommends you always have a **Filler CRASH Cart** ready which should contain:

- Hyaluronidase – Minimum of 600 units (in date!)
- Chewable aspirin
- Nitro paste
- Sildenafil 50 mg
- Cannulas
- Prednisone
- 2% lidocaine (acts as an anesthetic and dilates blood vessels)

Basic Protocol

- If you see blanching or a patient complains of excessive pain, **STOP INJECTING!!**
- Flood area with hyaluronidase – 300-600 units every 1-2 hrs. Do NOT discharge the patient until capillary refill is seen
- Warm compresses, every 10 minutes every 1-2 hours
- Vigorous massage, nerve block if necessary, no epinephrine
- Aspirin 325 mg under the tongue immediately and more thereafter (3-5 days)
- Oral prednisone 20-40 mg daily for 3-5 days
- Sildenafil 50 mg QD
- Nitro Paste – Topical, 2% - cover the affected area
- Hyperbaric Chamber (Know of an office that has one and use as related to the degree of compromise)

It is critical you follow the patient daily until there is improvement. Be sure to provide your contact info and clear, written instructions for at-home management.

**Patient referred to the office 4 days post injection: already in tissue compromise**
**Photos courtesy of Miles Graivier, MD**

Treatment:

- 400 U Vitrase injected SQ in NL area
- 325 mg ASA
- Oral ASA – 80 mg BID x 5 day
- Started oral and topical antibiotics x 7 days
- Low pressure hyperbaric O2 therapy everyday x 5 days
- Later: IPL for residual capillaries

Tyndall Effect or "blue hue" is another technique-related problem that is caused by placing HA fillers too superficially. Although HA fillers are colorless gels, when the product is injected too superficially, the Tyndall phenomenon[10] results in a blue discoloration. This usually can be resolved through extrusion or by dissolving the filler with hyaluronidase.

Granulomas are different from lumps and nodules. They are an aggressive inflammatory response, which can occur several months to several years after injection. Borders are seldom defined, so it is difficult to excise them. Without treatment, granulomas can grow, persist, and then spontaneously disappear. Granulomas are seldom a problem associated with HA fillers, but they can occur. They generally respond well to antibiotic therapy. Some physicians treat with intralesional steroid injections.

Early inflammatory reactions from HA fillers typically respond well to oral steroids and/or antihistamines. In addition, topical steroids also might help alleviate symptoms. Intralesional steroid therapy is not recommended except in the rare case of granulomas.

[10] The Tyndall phenomenon is the visibility of floating particles in gases or liquids when illuminated by a ray of sunlight and viewed at right angles to the illuminating ray. http://www.stedmans.com/ accessed March 8, 2010.

One final note regarding complications and adverse events with filler products: know the source of your product. Although it might be tempting to purchase products at a discounted price from outside the United States, you might be putting yourself and your patients at risk. We are all familiar with the stories of imported Botox causing serious complications in patients. Keep in mind that your malpractice insurance provider will not cover you for complications from a product that is not purchased from a United States-approved manufacturer.

**Summary**

In summary, to maximize results with soft tissue fillers, it is important that the patient and the injector are thoroughly educated and understand the expected versus true complications of the product. The injector should thoroughly explain the treatment goals and be sure the patient understands any limitations to the procedure(s). If the injector uses adequate pain control and develops proper injection techniques, many complications can be avoided.

# COMBINATION THERAPY – PERFECTING RESULTS

**Combining Fillers and Neuromodulators for Optimal Results**

Regardless of what treatment a patient receives, successful outcomes typically stimulate interest in additional procedures. Patients can often benefit from combination or multimodal therapy. Once a thorough aesthetic analysis has been conducted, your understanding of the different products, including specific product injection techniques, will help you determine which product(s) will work best. Combining fillers and neuromodulators often produce enhanced results.

As you know, injecting botulinumtoxin A requires a different degree of knowledge and technique from those required for fillers. It is important to know whether you need to:

**RELAX or REFILL and/or REPLACE**

Botulinumtoxin A is usually used to *RELAX*:

- Glabellar
- Brow
- Lateral canthal area
- Depressor angularis oris
- Upper lip
- Platysma

Soft tissue fillers are usually used to *REVOLUMIZE/REJUVENATE*:

- Nasolabial folds
- Lips
- Deep glabellar area
- Tear troughs
- Malar area
- Oral commissures
- Mental area
- Jaw line

Various areas of the face might require different fillers for the best results. It might also be beneficial to combine or layer fillers in the same area of the face for optimum enhancement.

Often, combination treatments are required to achieve optimal correction. It is important to obtain the input of your plastic surgeon or core trained physician before initiating treatment for a patient you think would benefit from combination treatment. Considering that many of the techniques commonly used in combination therapy are off-label techniques, it is important to obtain informed consent and your physician's input. Combination injection can be accomplished in one setting or with a staged two-treatment protocol, depending on patient and doctor comfort. Typically, botulinumtoxin A would be injected first, in staged treatments, with the patient returning 2 to 4 weeks later for filler injection.

The typical combination injection techniques include:

- Botulinumtoxin A to the forehead and filler to temporal areas
- Botulinumtoxin A to the crow's feet and filler to the tear trough
- Botulinumtoxin A to the depressor anguli oris with filler to the perioral and marionette lines

There is room for creativity in the use of combination treatment, and patients should be allowed to be part of that creative process. If you have a patient who is receiving botulinumtoxin A and you think he or she might be a good candidate to receive fillers, the patient should be instructed to return in 2 to 4 weeks for reevaluation and potential filler treatment. This allows for optimal treatment of the patient and avoids the "Botox did not work for me" sentiment. Patient expectations ultimately must be understood, and a patient wanting rejuvenation might not get it from the use of neuromodulators alone.

It has become the norm to use hyaluronic acid (HA) fillers in combination with botulinumtoxin A to achieve enhanced results and a longer duration of effect. A study conducted by Carruthers and Carruthers[1] demonstrated enhanced longevity when combining Restylane® and BOTOX® Cosmetic. The objectives of the study were to compare the efficacy of botulinum toxin type A combined with intradermal non-animal stabilized hyaluronic acid (NASHA™) with the efficacy of NASHA™ alone in female patients with moderate to severe glabellar rhytides. Results demonstrated the medial time for return to pre-injection furrows:

- 18 weeks with Restylane® alone
- 32 weeks with Restylane® plus BOTOX® Cosmetic

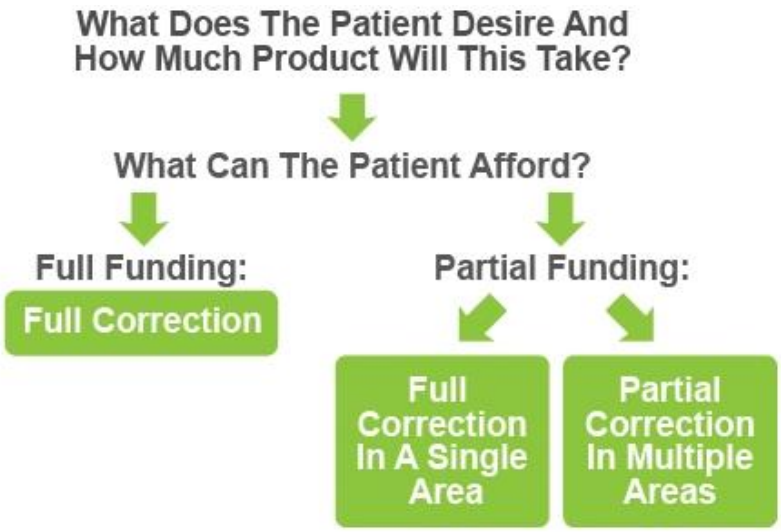
**Concept of Full Correction**

Results with soft tissue fillers are highly individual and are impacted by multiple factors including:

- Age
- Gender
- Patient goals
- Skin elasticity
- Genetics
- Treatment history (other facial treatments)
- Facial anatomy
- Depth and extent of defects
- Number, type, and location of areas to be treated
- Affordability

Experience has shown that two to three syringes of an HA filler might be required for *full correction* for typical aesthetic defects. You will find that a second or third syringe can make the difference between a good result and a great result. It is important that your patient understand that outstanding results require full correction and that, in most cases, full correction requires more than one syringe of product.

[1] Carruthers J, Carruthers A. A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivative compared with the derivative and BTX-A. *Dermatol Surg* 2003;29(8):802–809.




A frank discussion with your patient will help you understand their financial commitment for facial rejuvenation. Many times, first-time patients are reluctant to invest in what you believe is necessary to achieve full correction. It can be helpful to have photos that will show them the difference between full and partial correction.

In summary, combination therapy has been shown to enhance the longevity of both treatments and allows for development of more individualized treatment plans.

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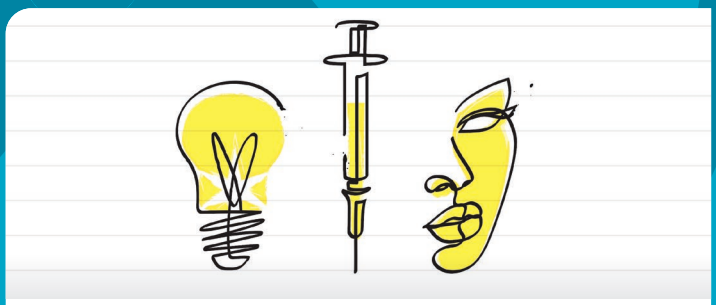


## What You Need 2 Know…. When Injecting Dermal Fillers

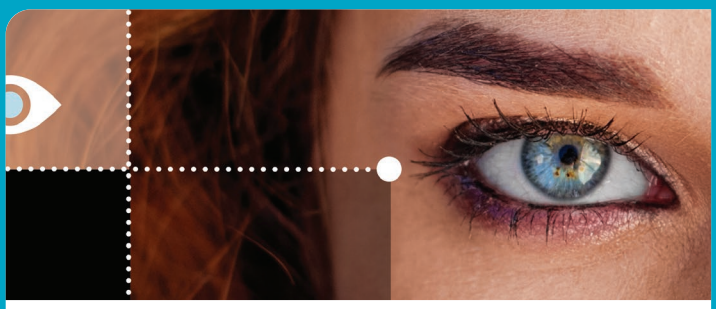
Online CME Series

This CME Series focuses on the use of dermal fillers and their role in facial anatomy, rheology, cannulas, and safety. In this series, you will find informative lectures and a faculty Q&A discussion.

## Aesthetic Moments

Online CME Series

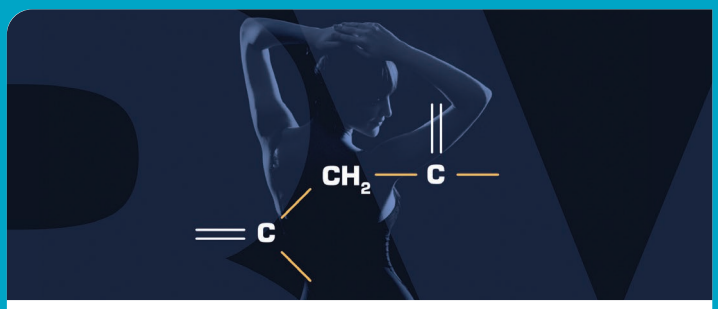
This CME series features discussions with stellar faculty G. Jackie Yee, MD, Arthur Swift, MD, Michael Kane MD, and Shino Bay Aguilera, DO. The faculty discuss tips and techniques when injecting in the upper, mid and lower face.



## Novel Approaches for Treating the Periorbital Area with HA Fillers

Online CME Series

This CME series takes a close look at options for rejuvenating the periorbital area with HA fillers. The faculty will review the anatomy of this area and then delve into different ways to treat and/or camouflage prolapsed fat pads. A review of safety and patient demos are included.




## Beyond Volume: Hyperdilute CaHA

Online CME Series

This CME series focuses on the use of hyperdilute biostimulatory fillers and their role in improving skin quality and firmness. In this series, you will find informative lectures, a lively faculty Q&A discussion and a variety of injection demonstrations by 6 different and highly skilled physicians.

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