

ตา... สวยด้วย Botox 😊

Pretty Eye....by Botox

Anuchit Poonyathalang, M.D.  
Ramathibodi Hospital, Mahidol University  
Department of Ophthalmology  
Bangkok Thailand

# Introduction

- Surgical procedures and **cosmetic procedures** especially **anti-aging** are trend towards **minimally invasive techniques**. Demands for cosmetic procedures that leave no scar and quicker return to normal activity are rising. (Short down time)
- Though traditional blepharoplasty and brow lift remain in the armamentarium of the facial cosmetic surgeon, minimally invasive procedures such as botox treatment can often achieve satisfactory results for patients.

# History



- In the 1820s, almost 200 years ago, the biological basis for food poisoning was not understood. *Dr. Justinus Kerner* studied improperly prepared blood sausages and stated that in the spoiled sausages, something he called “wurstgift” (German for sausage poison), responsible for the death of several dozen Germans.

His experiments led to a better understanding of the neurological symptoms of food-borne botulism (ptosis, dysphagia, muscle weakness, and, if left untreated, paralysis and respiratory failure).

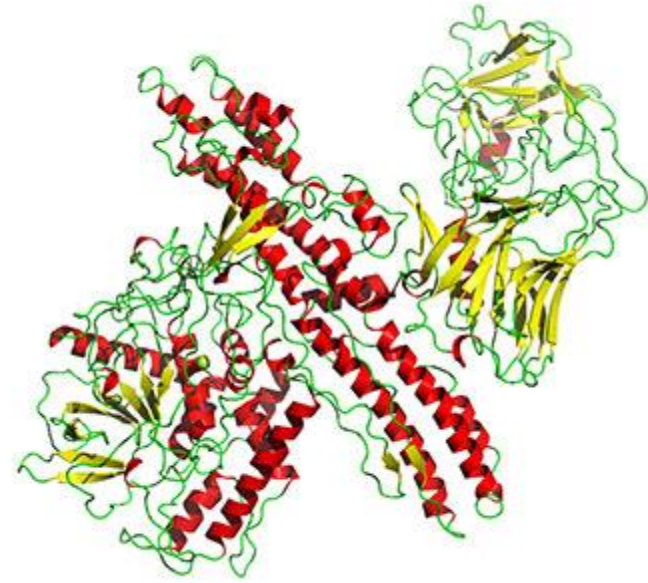
# History

- More than 70 years after Kerner's experiments, **Dr. Emile Pierre van Ermengem** of Belgium was asked to investigate an outbreak of botulism following a **funeral dinner where three people died and 23 were paralyzed**. Connection to a spore-forming bacterium he named *Bacillus botulinus* (now known as *Clostridium botulinum*), was found. Many scientific studies followed, and **7 strains** of botulinum toxin were identified (**A through G**).



# History

- In the early 1950s, Dr. Edward J. Schantz and his colleagues were able to purify botulinum toxin type A into crystalline form.
- In 1953, physiologist Dr. Vernon Brooks discovered that injecting small amounts into a hyperactive muscle blocked the release of acetylcholine from motor nerve endings, causing temporary “relaxation.”
- In the 1960s, ophthalmologist Dr. Alan B. Scott began injecting botulinum toxin type A into monkeys, theorizing its muscle-relaxing effects might help in the treatment of strabismus.



# ■ History

- In 1978, Scott received FDA approval to inject minute amounts of botulinum toxin into human volunteers.
- In the early 1980s, he published many studies including a 1981 paper in the Transactions of the American Ophthalmological Society that asserted botulinum toxin “appears to be a safe and useful therapy for strabismus.”
- Additional research went beyond ophthalmology such as temporary relief from facial, neck and shoulder spasms, even vocal cord spasms.



# History

- In 1988, **Allergan** acquired the rights to distribute Scott's batch of botulinum toxin type A (**Oculinum**) and a **year later**, the FDA approved botulinum toxin type A for the treatment of both strabismus and blepharospasm.
- Shortly thereafter, **Allergan** acquired **Scott's company** and **changed** the drug's name to "**Botox.**"



# Clinical conditions treated with BOTOX®



Strabismus



Cervical dystonia



Achalasia



Cerebral  
palsy



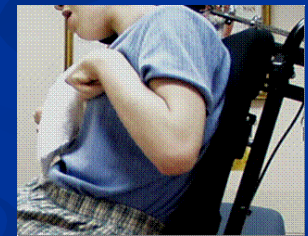
Blepharospasm



Hyperhidrosis



Glabellar Frown Lines



Spasticity

# History

- More uses, light- Bladder spasms, writer's cramp, excessive sweating, cerebral palsy in kids all were alleviated by the neurotoxin.
- But by far the most earth-shattering discovery came about by accident when Canadian ophthalmologist

Dr. Jean Carruthers noticed her blepharospasm patients were starting to lose their frown lines.

- In 1992, she and her dermatologist husband published a study in the Journal of Dermatologic Surgery and Oncology stating that though temporary, “Treatment with botulinum-A exotoxin is a simple, safe procedure” for the treatment of brow wrinkles.
- Dermatologists immediately took note (and took advantage of this “off-label” use) and by 1997, Botox use spiked so high the country’s supply temporary ran out.

# History

- In 2000, Botox got the FDA's nod for the treatment of cervical dystonia.
- In 2002, Botox Cosmetic got its official government go-ahead, greenlighting Allergan to begin a multi-million-dollar marketing campaign to boost its already healthy Botox sales, which had reached \$310 million by the end of 2001.
- Today, botulinum neurotoxin injection is the most commonly performed cosmetic procedure in the world.

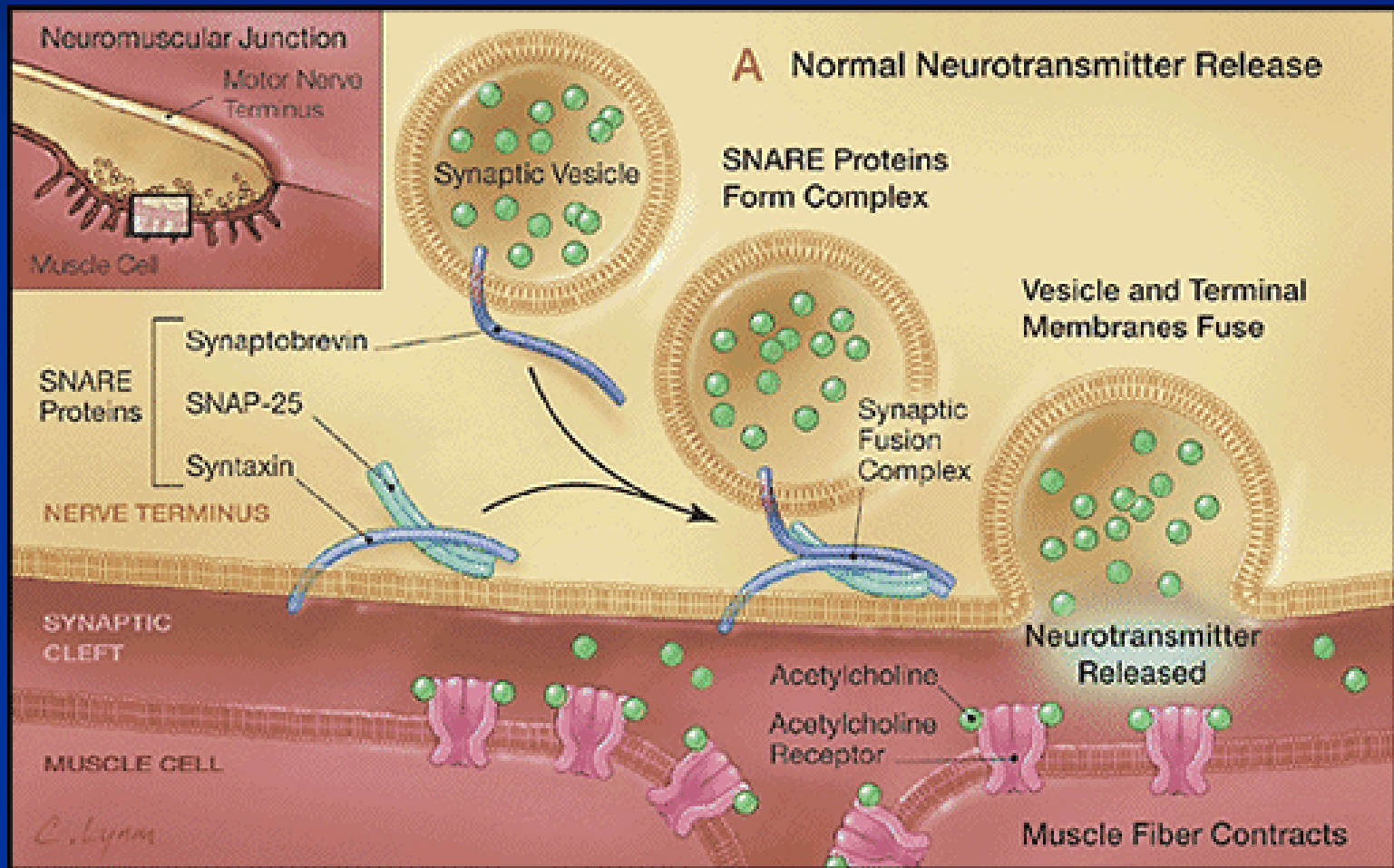
# Mechanism of Action

- Botulinum toxin exerts its effects by **paralyzing skeletal muscle**.
- The pharmacological site of action is at the **neuromuscular synapse**.
- The **presynaptic** neuromuscular nerve ending contains **membranous vesicles** prepared to release its **stored neurotransmitter, acetylcholine**.

# Mechanism of Action

- Neuronal stimulation initiates a cascade of events that leads to the fusion of the neurotransmitter-containing vesicle with the nerve membrane.
- This process is facilitated by a group of proteins comprising the SNARE complex.
- The **membrane fusion** results in the **release of acetylcholine into the synaptic cleft by a process of exocytosis**.
- The acetylcholine diffuses and eventually **binds to receptors** on the muscle, **leading to muscle contraction**.

# Mechanism of Action



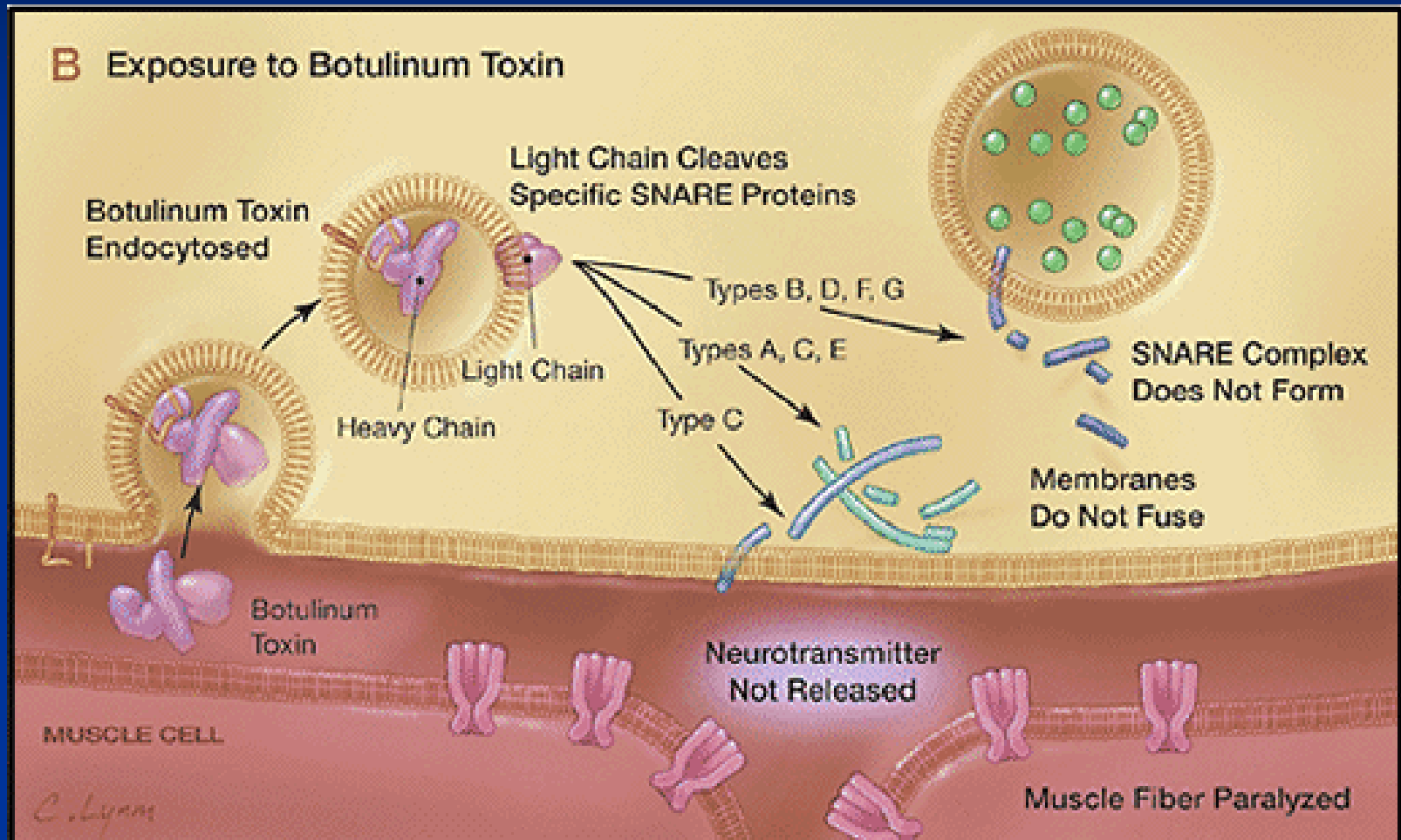
# Mechanism of Action

- Botulinumtoxin A (BOTOX) consists of a heavy chain of 100-kilodalton and a light chain of 50-kilodalton making up the 150-kilodalton core type A molecule.
- The BOTOX **core molecule enters the nerve cell by a process of receptor-mediated endocytosis**, mediated by the heavy chain.
- The **light chain** is released into the cytoplasm of the nerve terminal where it begins to cleave one of the SNARE proteins.

# Mechanism of Action

- In motor neurons, the **light chain of the BOTOX core molecule** blocks the release of **acetylcholine** by cleaving SNAP-25, which is an essential component of the SNARE complex. When **acetylcholine cannot be released, muscle contraction cannot occur.**
- The toxin does not appear to affect the conduction of electrical signals along the nerve fiber or the synthesis or storage of acetylcholine.

# Mechanism of Action



# Applications

- The cosmetic use of botulinum toxin is well-studied for the treatment of glabellar frown lines, horizontal forehead rhytids, and lateral canthal lines (crow's feet).
- Currently, contouring of the jawline, the neck, and the melolabial fold are being used.
- This talk will focus on the three more widely studied applications.

# Glabellar Frown Lines

- Glabellar frown lines are the **most common** reason for cosmetic injection of botulinum toxin.

Patient 4

Female

Glabellar

Before



After



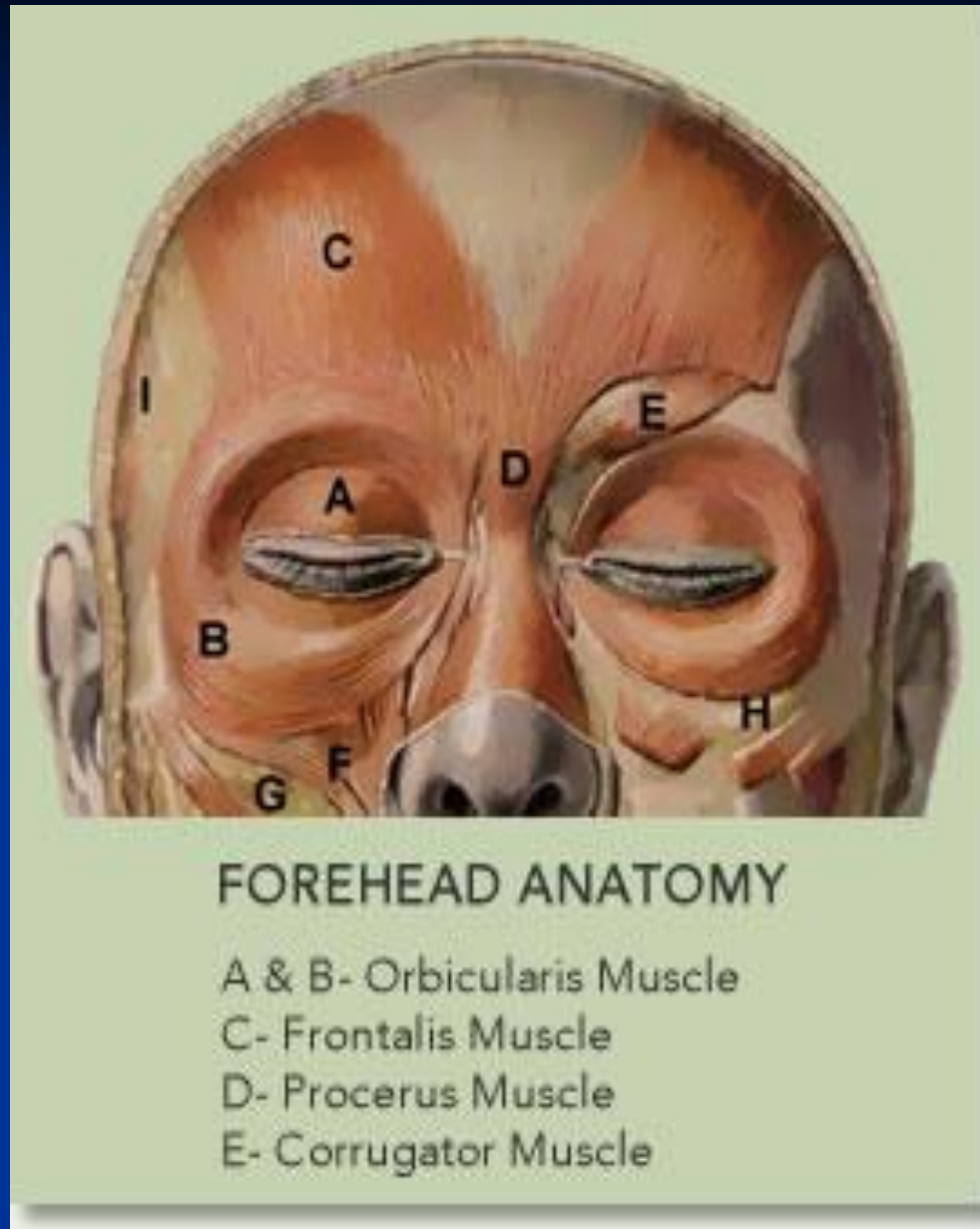
# Anatomy

- **Facial rhytides and folds** in this area result from action of the depressor muscles.
- The **corrugator superciliaris**, **medial orbital portion of the orbicularis oculi**, and **more horizontally oriented fibers of the depressor supercilii** produce the vertical lines of the glabella.



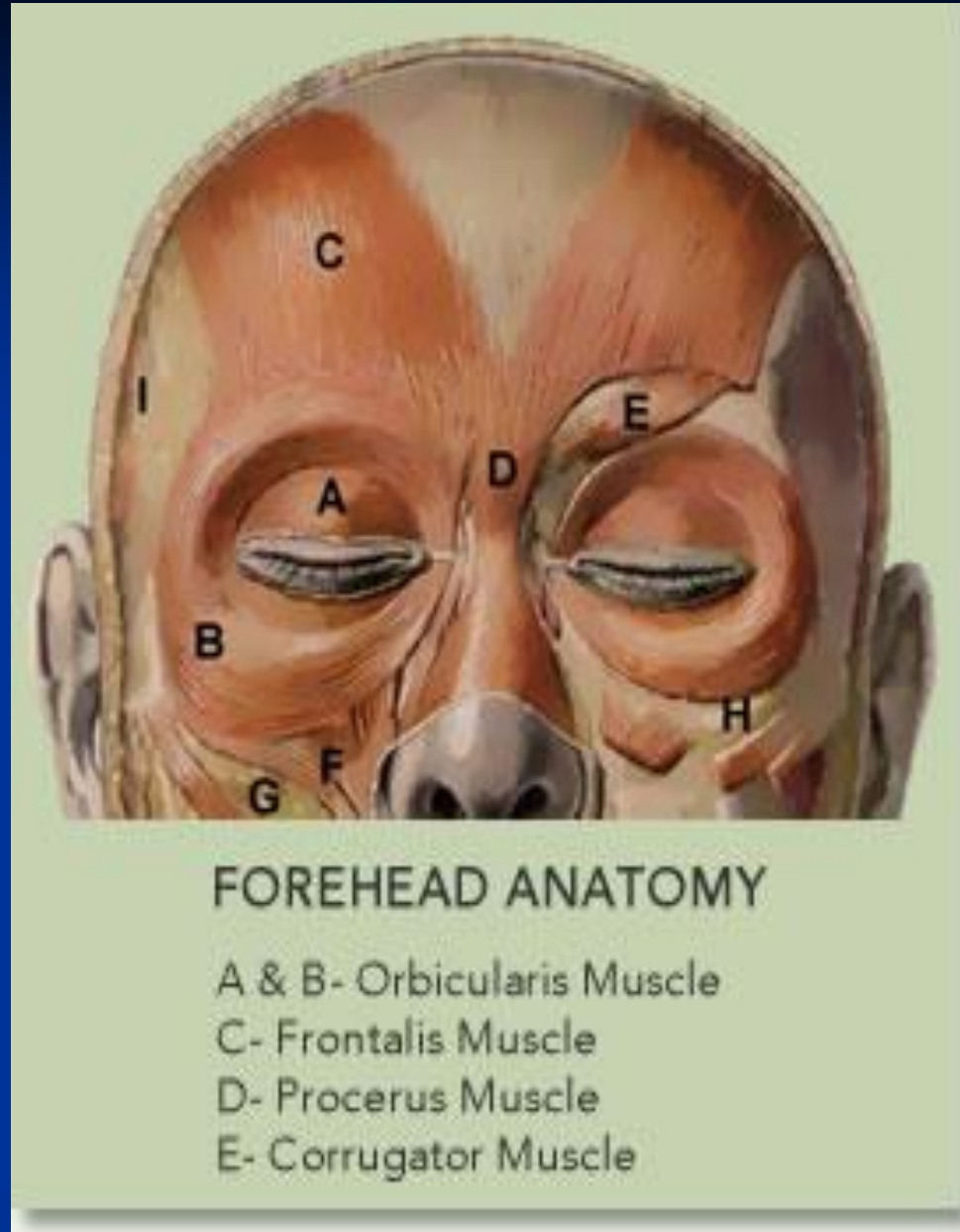
# Anatomy

- The **corrugator muscle (E)** is a brow adductor moving the eyebrow downward and medially.
- It **arises from the nasal bone** just above the rim of the orbit medially and extends laterally and upward, **inserting in the skin above the middle of the eyebrow**. It lies deep to the frontalis, procerus, and orbicularis oculi muscles.



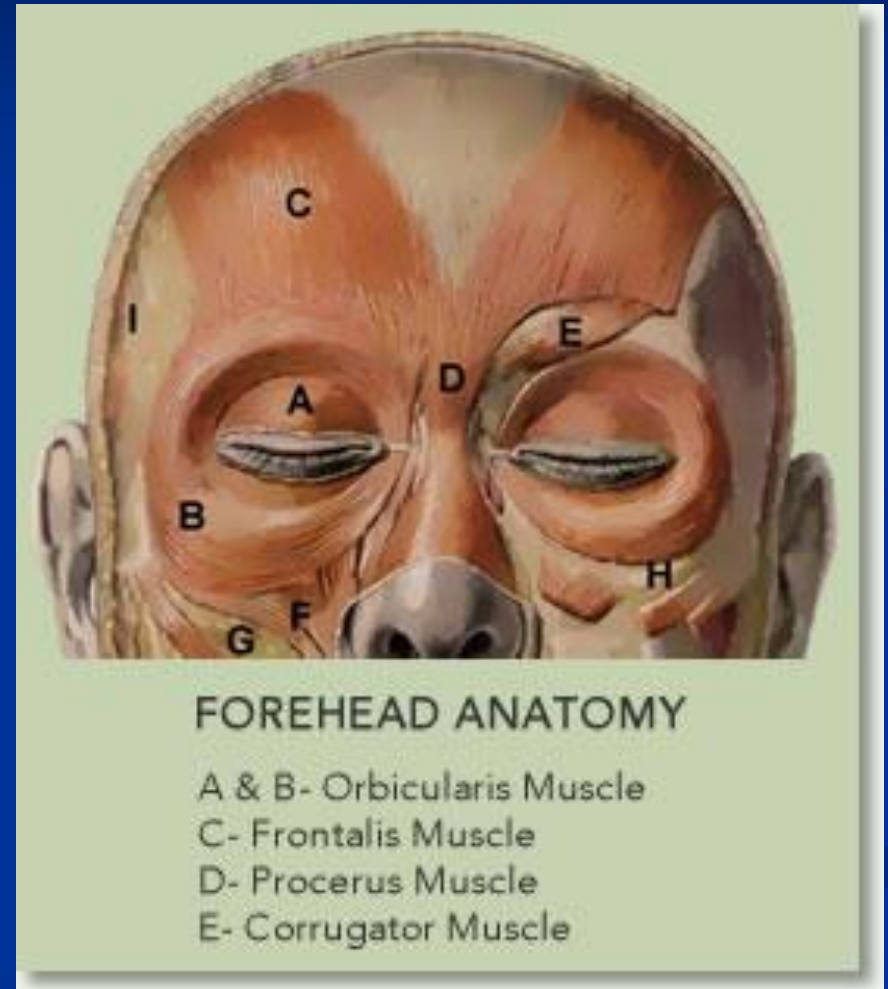
# Anatomy

- The medial fibers of the orbicularis oculi (A) originate from the medial orbital rim anterior to the origin of the corrugator.
- The fibers interdigitate with fibers of the frontalis, procerus, and corrugator muscles.



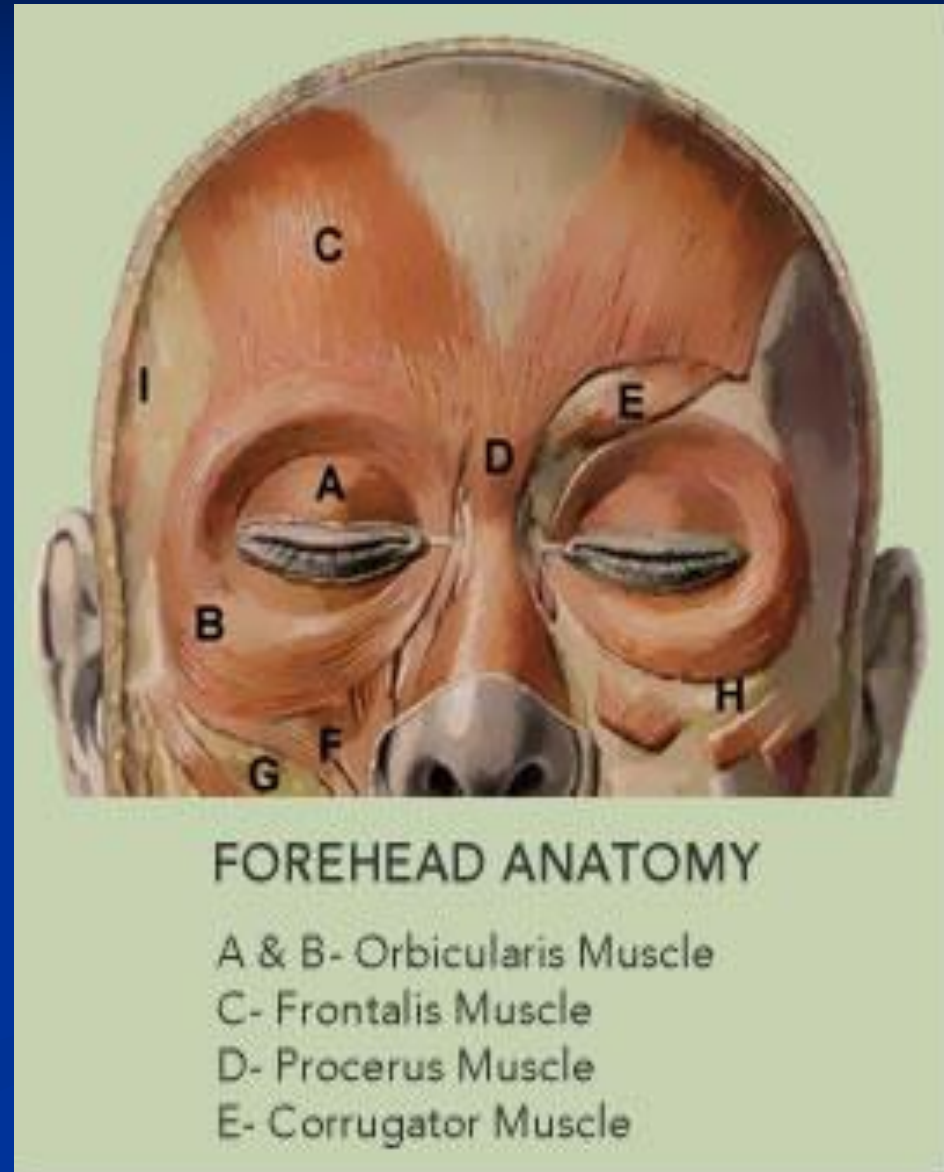
# Anatomy

- The depressor supercilii originates from the nasal process of the frontal bone and inserts into the skin at the medial aspect of the eyebrow.



# Anatomy

- The vertically oriented procerus muscle (D), which originates from the upper nasal cartilage and the lower nasal bone, produces the horizontal lines of the glabella and nasal root.
- It inserts into the skin between the brows and the frontal belly of the occipitofrontalis.
- Its fibers interdigitate with those of the orbicularis, frontalis, and corrugator muscles.



# Anatomy

- A **glabellar "spread test"** may be performed prior to injection by spreading the glabellar wrinkles apart with the thumb and index fingers.
- This may allow an **estimate of the expected benefit from botox injections**.
- Patients with **thick sebaceous skin** and deep dermal scarring that are not improved with **manual spreading** usually **respond poorly to botulinum toxin injections**.

# Technique

- Usually, 5 sites are injected with 4-6 units each for an average total dose of approximately 25 units.
- A 1998 dose/response study of 46 women receiving botulinum toxin for glabellar wrinkles found an effective starting dose from 2.5-4 units per injection site (12.5-20 U total).

# Technique

- In a 2007 double-blinded study, 70 patients were randomly assigned to treatment with 20 U botulinum toxin type A (BOTOX Cosmetic) or placebo, median glabellar line severity was significantly lower after botulinum toxin treatment compared to placebo.

# Technique

- Compared with placebo, botulinum toxin also resulted in **significantly superior patient** assessments and a greater proportion of patients considering they **looked younger than their current age**.

# Technique

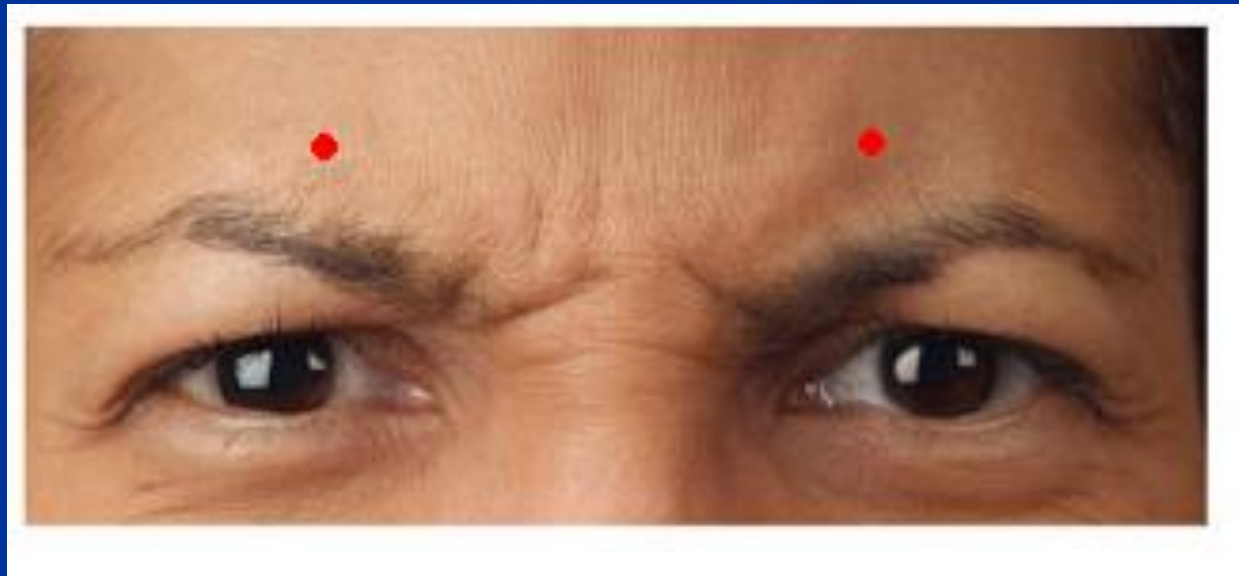
- In a 2005 study, 80 men were randomized to receive botulinum toxin type A. Results: The 40, 60, and 80 U doses of botulinum toxin type A were consistently more effective in reducing glabellar lines than the 20 U dose (duration, peak response rate, improvement from baseline).
- In addition, the participants reported a dose-dependent reduction in the ability to frown, improvement in their global assessment, and increased feelings of attractiveness, self-confidence, and satisfaction.
- The incidence of adverse events was not increased with higher doses. The authors concluded that male participants with glabellar rhytids benefit from starting doses of at least 40 units.

# Technique

- One site on each side is used to inject the corrugator
- One site on each side is used to inject the orbicularis oculi and depressor supercilii
- And one site is used to inject the procerus in the mid line.
- The patient is asked to frown and scowl, and the target muscles are palpated.

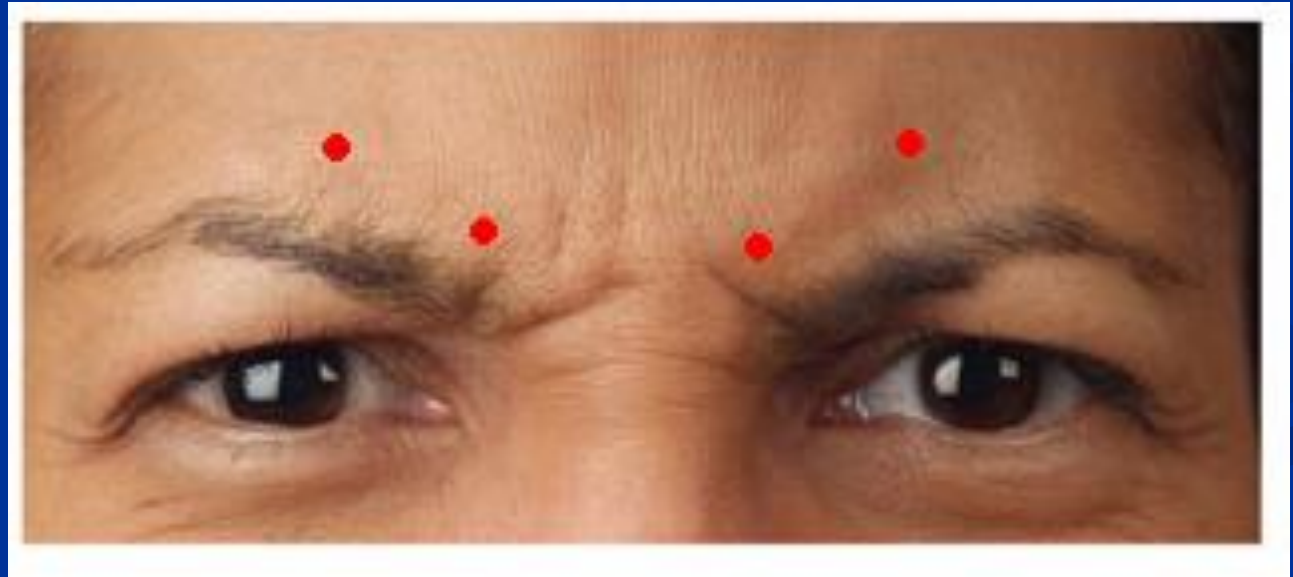
# Technique

- The needle is inserted at the origin of the corrugator fibers **just above the medial canthus** then advanced within the belly of the muscle upward and lateral as far as the medial third of the eyebrow, 1 cm superior to the orbital rim. **4-6 units** are injected as the needle is withdrawn.



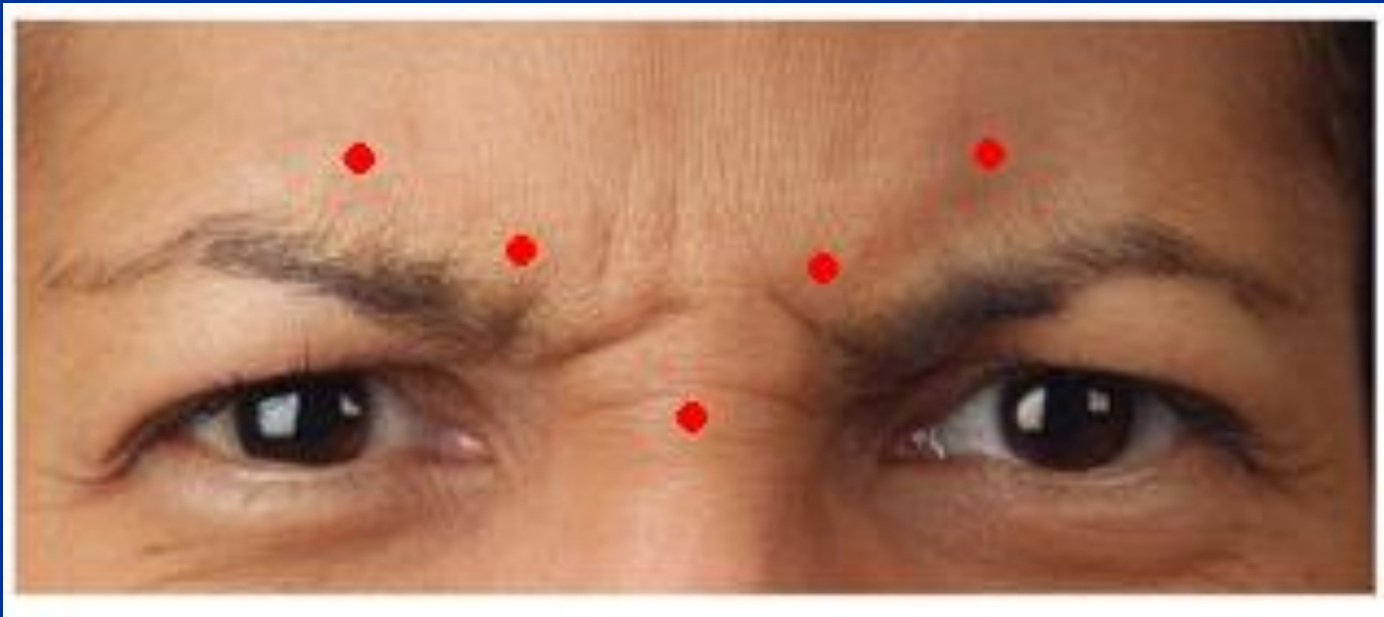
# Technique

- The next site is approximately **1 cm above the upper medial aspect of the supraorbital ridge**. The needle is advanced slightly in a vertical direction toward the hairline. **4-6 units** are injected into the orbicularis oculi and depressor supercilii as the needle is withdrawn.



# Technique

- The last injection is central into the belly of the procerus to eliminate the horizontal lines at the root of the nose. 4-6 units are injected at a point where 2 lines drawn at 45° from the medial aspect of the eyebrows converge in the center of the nasal root.



# Technique

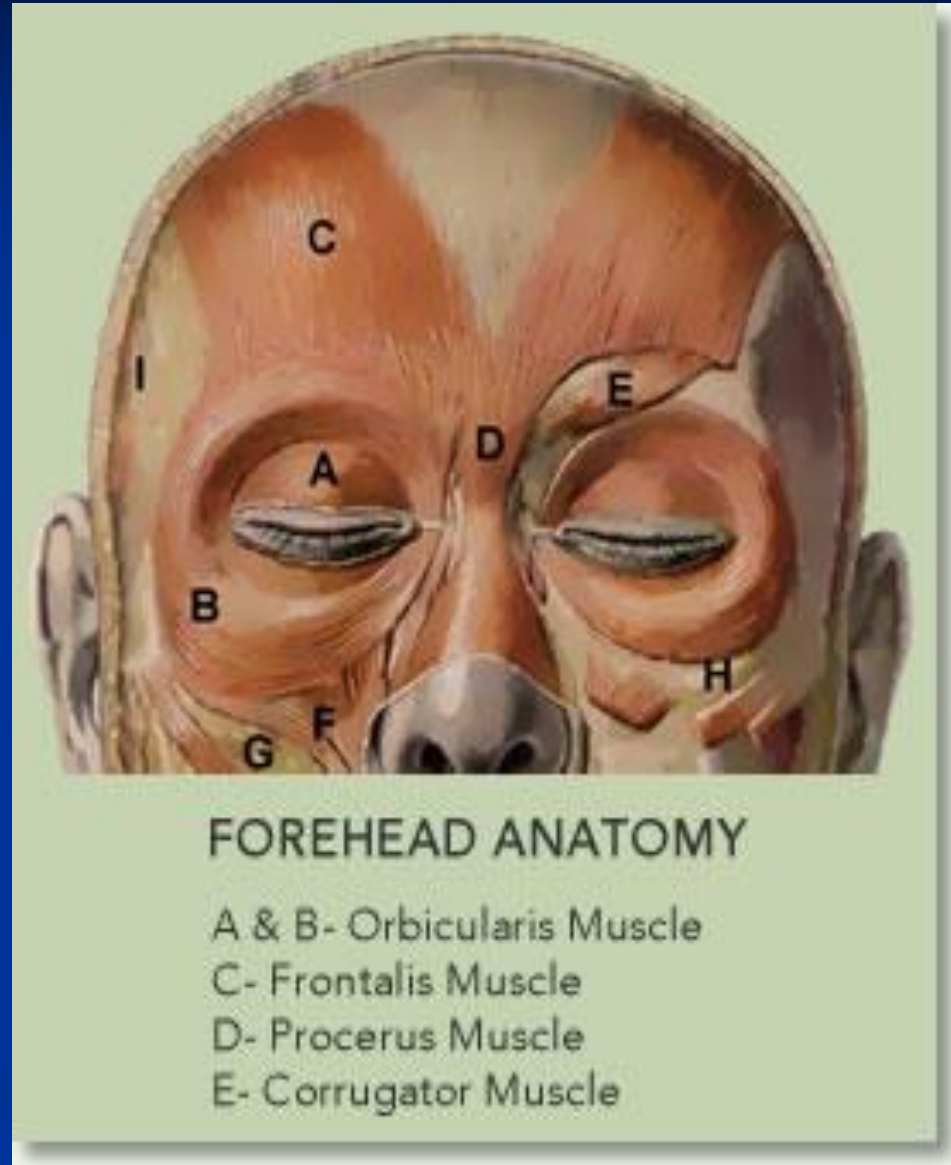
- To avoid resultant accentuation of eyebrow arching in men, an additional 4-6 units are injected 1 cm above the supraorbital prominence vertical to the mid point of the eyebrow.

# Horizontal Forehead Lines

- Performing botulinum toxin injections to treat horizontal forehead lines is relatively easy, and the result usually is quite satisfying.
- Treatment can be combined with injections for glabellar frown lines when appropriate.

# Anatomy

- Elevates eyebrows and the skin of the forehead, the **Frontalis (C) are oriented vertically**, and **wrinkles** of the forehead are oriented **horizontally**.
- originates on the galea aponeurotica near the coronal suture and inserts on the superciliary ridge of the frontal bone and skin of the brow, interdigitating with fibers of the brow depressors.

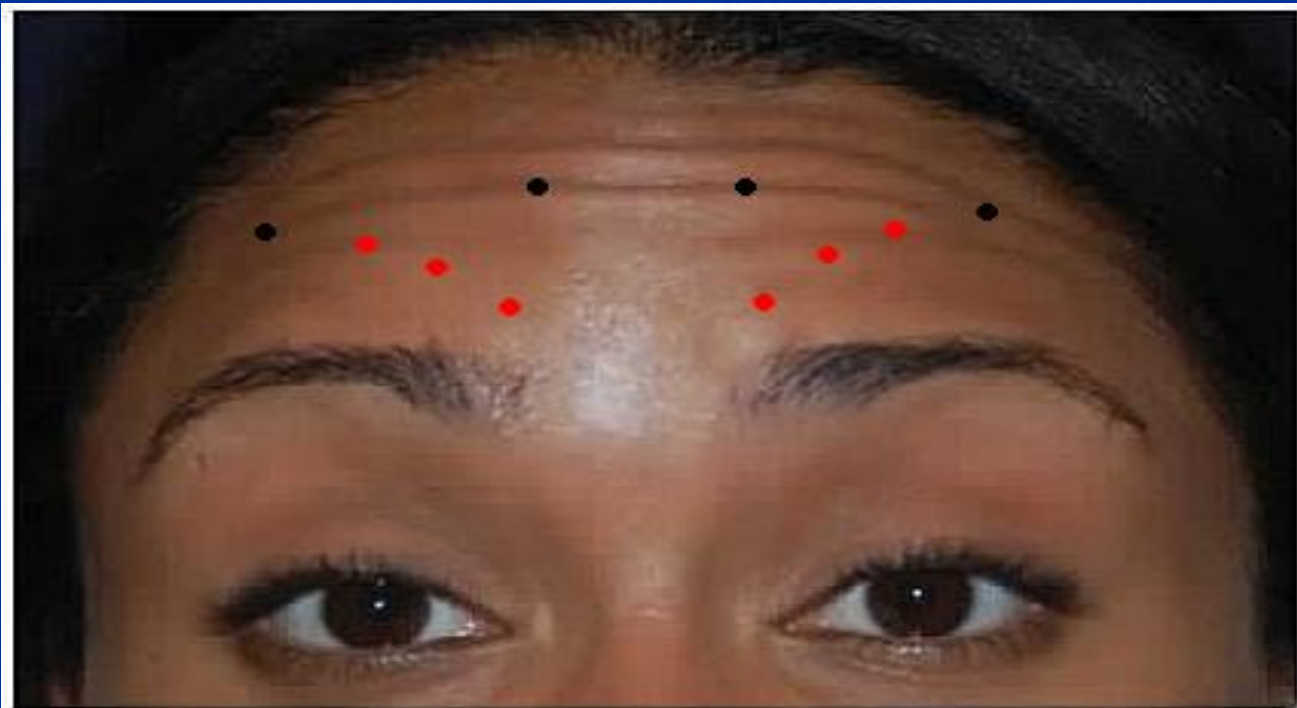


# Anatomy

- The medial fibers usually are more fibrous than the lateral fibers, thus requiring less toxin for paralysis.
- Total paralysis of the frontalis should be avoided, since this is likely to cause brow ptosis and loss of expression.
- Injection too close to the lateral eyebrow can cause lateral eyebrow ptosis.

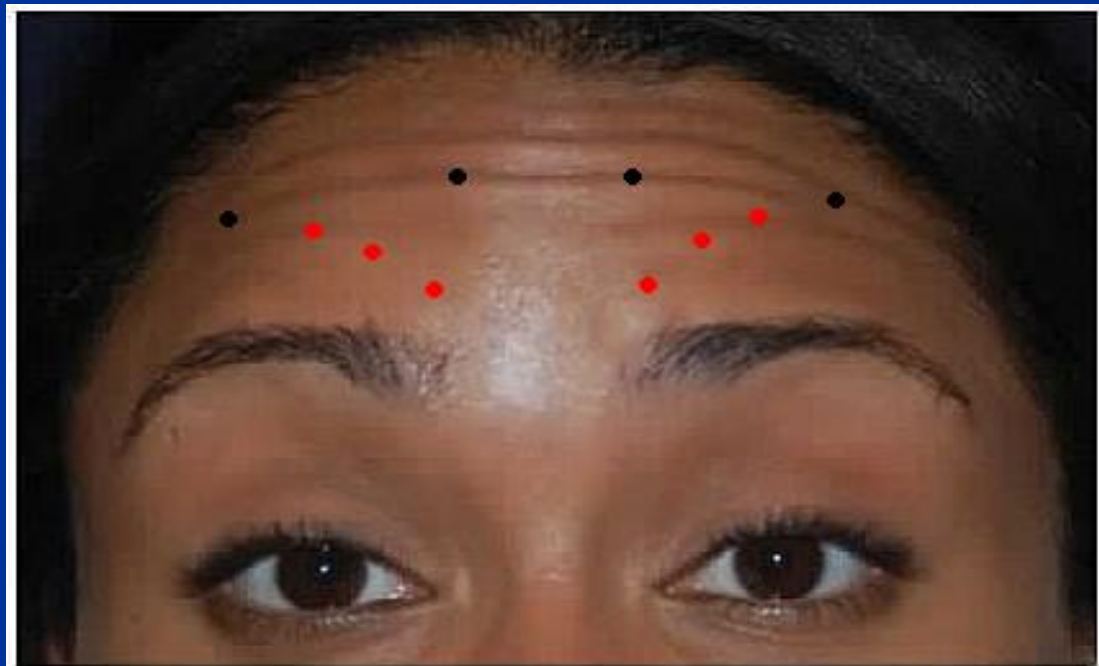
# Technique

- Multiple injections of small amounts of toxin create weakness without total paralysis. ( ● BLACK DOT)
- 3-5 sites on each side of the mid line are injected, usually using 2 units (1-3 U) per site.
- Sites are separated by 1-2 cm.



# Technique

- The initial injection site is approximately 1 cm above the eyebrow directly above the medial canthus.
- Additional sites • diverge laterally and upward to the hairline in a "V" configuration, often for a total of 3 sites.
- Additional sites can be added in the mid line or more laterally depending on individual and clinical response.



# Technique

- Injections of the upper face and periocular region usually are performed with the patient seated.
- The patient is asked to remain upright for 2-3 hours to prevent spread of toxin through the orbital septum.

# Lateral Canthal Lines (crow's feet)

- Aging and photodamage cause much of the wrinkling in this area.
- However, the component of hyperfunctional contraction of the lateral aspect of the orbicularis oculi is targeted for improvement with botulinum toxin injections.



# Anatomy

- The lateral fibers of the orbicularis oculi are arranged in a circular pattern around the eye. Contraction of these fibers produces wrinkles that extend radially from the region of the lateral canthus.



# Technique

- 3 or 4 subcutaneous injections ,approximately 1 cm lateral to the lateral orbital rim using 2-3 units per injection site ( total of 6-12 U per side).
- Sites are spaced 0.5-1 cm apart in a vertical line or slightly curving arch. Doses that are too high or injections that are too medial can lead to eyelid ptosis or diplopia.



# Technique

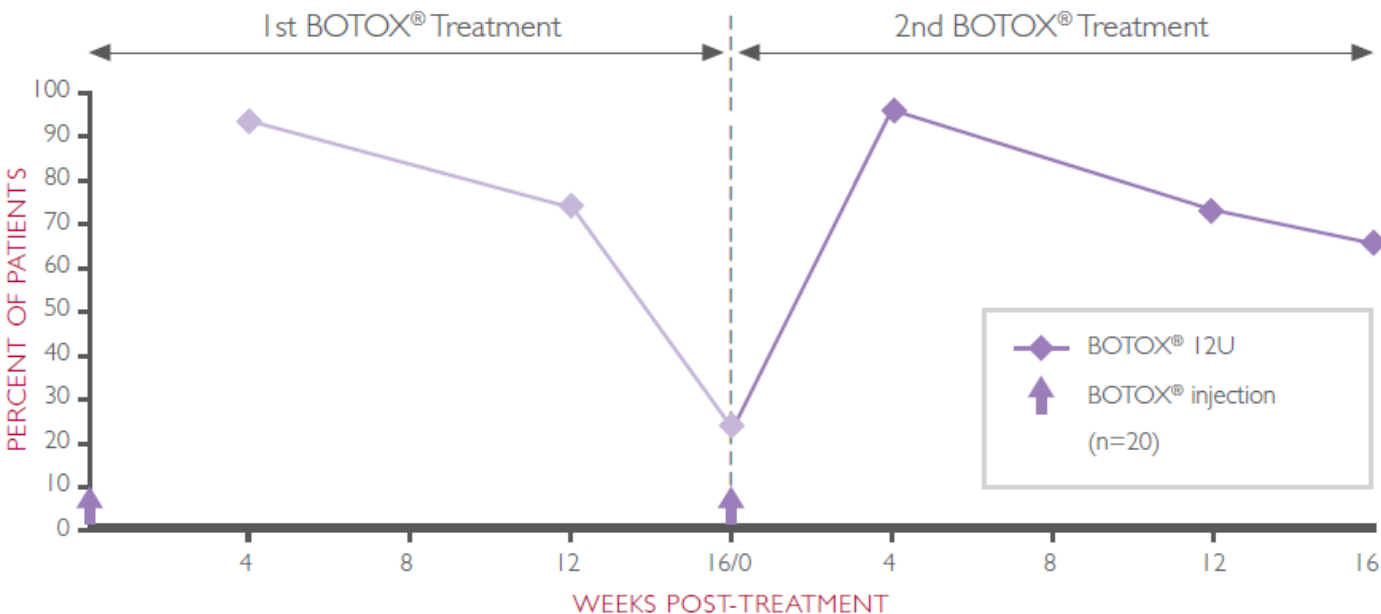
- A 2002 study showed doses of 6, 12 or 18 units of botulinum toxin delivered to the lateral orbicularis were significantly superior to placebo, but with no clear dose-response relationship.
- 2005, showed a dose-dependent effect for efficacy, with higher doses having an increased magnitude and duration of effect.
- Few adverse events incidence were reported, with no statistically significant differences between BTX-A and placebo.
- They suggested 12 U per side as the most appropriate dose.

# Technique

- In a recent 2009 placebo-controlled study, 15, 30, or 45 U of botulinum toxin or placebo were injected unilaterally.
- A clear dose-response effect was seen with 30 and 45 U delivering a more durable benefit at 12 weeks.
- These results suggest that higher doses than previously used are optimal for lateral canthal lines.

# BOTOX<sup>®</sup> treatment efficacy: Results improve with repeated use in crow's feet

Percentage of patients with at least 1-point improvement in crow's feet at maximum contraction compared with placebo



The effect of 2<sup>nd</sup> injection of the same dose were sustained for longer duration than the first injection

# Contraindications !!!

- Known hypersensitivity to any ingredient in the formulation
- Disorders of neuromuscular junction
  - Myasthenia gravis
  - Eaton Lambert syndrome
- Presence of infection at the proposed injection site

# Precautions<sup>1</sup>

- Do not use dosage recommendation and potency units of other botulinum toxin products when using BOTOX<sup>®</sup>
- Peripheral motor neuropathic diseases or neuro-muscular junctional disorders
- Use with aminoglycosides, e.g. gentamycin, streptomycin, penicillamine, quinine, and **calcium channel blockers** or drugs interfering with neuro-muscular transmission
- Disorders of muscle weakness: Multiple sclerosis, Amyotrophic lateral sclerosis
- Injection :Procedure-related injury
- During pregnancy –lactation active nursing should be avoided
- Glaucoma clients at risk of angle closure glaucoma
- Unrealistic client expectations

# Adverse Effects

- Generalized reactions that have **idiosyncratically** from botox injections include **nausea, fatigue, malaise, flulike symptoms, and rashes at sites distant from the injection.**
- However, a large 2009 meta-analysis of 5 placebo-controlled studies showed that acne, injection site pruritus, oral herpes, rash, lower respiratory tract infection, dental caries, and eye pain were significantly more common in placebo-treated patients compared with botulinum toxin-treated participants.
- In addition, there were **no symptoms of weakness remote to the injection site or related to the central nervous system.**

# Adverse Effects

- Sequelae that can occur at any **site** due to percutaneous **injection** of botox include **pain, edema, erythema,**
- Topical anesthetics such as ***EMLA cream*** before injection, and the use of **30 / 31-gauge needles.**
- A **2005** single-center, double-blind, randomized study demonstrated a **statistically significant reduction in procedural pain** in participants **pretreated with *lidocaine 4%*.**
- However, a 2006 study showed that pretreatment with **topical *betacaine*** followed by skin cooling seems to **have a deleterious impact on BOTOX effect without a significantly reduction in injection discomfort.**

# Adverse Effects

- Pinching the skin and the underlying muscle, slowly inserting the needle bevel up through the opening of a pilo sebaceous unit, and slowly injecting the solution will also help to diminish discomfort.
- Ice applied immediately after injection will further reduce the pain as well as the edema and erythema associated with an IM injection.

# Adverse Effects

- Ecchymosis can be minimized by avoiding aspirin, aspirin-containing products, and NSAIDs for 7 to 10 days before injection.
- Bruising occurs most frequently in older patients taking aspirin and in middle-aged persons taking vitamin E.
- Limiting the number of injections and applying postinjection digital pressure without manipulation will also assist in reducing bruising.

# Adverse Effects

- While the onset of **headaches** has been initiated with **botox** injections, Treatment : over-the-counter **analgesics**.
- It is, **however**, more common for patients to report that **chronic tension headaches** have improved following injections of **botulinum toxin**.



# Adverse Effects

- The most common complication in treatment of the glabellar complex is ptosis of the upper eyelid.
- This is caused by diffusion of the toxin through the orbital septum, where it affects the levator palpebrae muscle.



# Adverse Effects

- To avoid ptosis, injections should not cross the midpupillary line, and should be 1 cm above the eyebrow.
- Digital pressure at the border of the supraorbital ridge while injecting the corrugator also reduces the potential for extravasation.
- Patients often are instructed to remain in an upright position for 3-4 hours following injection and to avoid manual manipulation of the area.
- Active contraction of the muscles under treatment may increase the uptake of toxin and decrease its diffusion.

# Adverse Effects

- Ptosis can be treated with apraclonidine 0.5% eyedrops, an alpha<sub>2</sub>-adrenergic agonist that causes contraction of Müller muscles
- Apraclonidine is contraindicated in patients with documented hypersensitivity.
- Phenylephrine (Neo-Synephrine) 2.5% can be used when apraclonidine is not available.
- Neo-Synephrine is contraindicated in patients with narrow-angle glaucoma and in patients with aneurysms.

# Adverse Effects

- The most significant complication of treatment of the frontalis is **brow ptosis**.
- **Injections** in the forehead **should always be above the lowest fold** produced when the subject is asked to elevate their forehead (frontalis).
- If the **patient has a low eyebrow**, treatment of the forehead lines should be avoided, or limited to that portion of the forehead **4.0 cm or more above the brow**.

# Adverse Effects

- An equally esthetically unfavorable outcome is the brow that assumes a quizzical or “cockeyed” appearance.
- The central brow then becomes lowered and the lateral brow is pulled upward.
- The treatment is to inject a small amount of botox into the fibers of the lateral forehead that are pulling upward.
- However, only a small amount of Botox is required, as overcompensation can cause hooded brow that partially covers the eye.



# Adverse Effects

- The most common complications in the “crow’s feet” area are **bruising, diplopia, ectropion and an asymmetric smile** due to injection of zygomaticus major.
- If severe lower lid weakness occurs, an exposure keratitis may result. Treatment is symptomatic.
- These complications are avoided **by injecting at least 1 cm outside the bony orbit or 1.5 cm lateral to the lateral canthus**, not injecting medial to a vertical line through the lateral canthus and **not injecting close to the inferior margin of the zygoma**.
- Violating these boundaries has on occasion also resulted in **diplopia** due to medial migration of Botox and resultant **paralysis of the lateral rectus** muscle.

# Adverse Effects

- It should be noted that, even though **serious adverse events** have not been seen with the use of licensed products, the same is not true with the use of unlicensed preparations.
- A **case series of 4 patients** with symptoms consistent with naturally occurring botulism was **published in 2006**.
- All case-patients had been injected with a highly concentrated, **unlicensed preparation of botulinum toxin A** and may have received doses **2857 times the estimated human lethal dose by injection**.
- **Serum toxin levels** in 3 of the 4 case-patients were equivalent to **21 to 43 times the estimated human lethal dose**. These laboratory-confirmed cases of botulism demonstrate that clinical use of **unlicensed botulinum toxin A can result in severe, life-threatening illness**.

# Antibodies

- An estimated 5-15% of patients injected serially with botulinum toxin develop secondary nonresponsiveness from the production of neutralizing antibodies.
- Risk factors associated with the development of neutralizing antibodies include injection of more than 200 units per session and repeat or booster injections given within 1 month of treatment.

# Antibodies

- When a patient loses his or her response, serum can be tested for neutralizing antibodies, although this rarely is performed outside research settings.
- Alternatively, a patient's physiologic response can be evaluated with a single injection of 15 units into the frontalis on one side.

# Antibodies

- Limited information is available as to whether neutralizing antibodies resolve over time and, consequently, whether attempts at reinjection should be made after a prolonged period.
- Using the lowest dose of toxin necessary to achieve the desired clinical effect and avoiding reinjection within 1 month appear prudent in an effort to keep antibody formation as low and unlikely as possible.

# Conclusion

- Botulinum injections have become widely popular for combating the effects of aging.
- Aging patients will continue to seek out the procedure.
- Knowledge of optimal treatment patterns and adverse effects will allow physicians to safely and effectively deliver this therapy.

# Bibliography

- Chad Simon, M.D.Vicente Resto, M.D., Ph.D.University of Texas Medical Branch
- Department of Otolaryngology Grand Rounds Presentation February 25, 2010
- Sbastian Torres, Mark Hamilton, Elena Sanches<sup>4</sup>, Polina Starovatova<sup>3</sup>, Elena
- Neutralizing antibodies to botulinum neurotoxin type A in aesthetic medicine: five case reports Dove Press: Clinical, Cosmetic and Investigational Dermatology 17 Dec 2013
- [Northington ME](#), [Huang CC](#). Dry eyes and superficial punctate keratitis: a complication of treatment of glabellar dynamic rhytides with botulinum exotoxin A. Dermatol Surg. 2004 Dec;30(12 Pt 2):1515-7.
- [Brin MF](#), [Boodhoo TI](#), [Pogoda JM](#), [James LM](#), [Demos G](#), [Terashima Y](#), [Gu J](#), [Eadie N](#), [Bowen BL](#). Safety and tolerability of onabotulinumtoxinA in the treatment of facial lines: a meta-analysis of individual patient data from global clinical registration studies in 1678 participants. J Am Acad Dermatol. 2009 Dec;61(6):961-70.e1-11. Epub 2009 Sep 9.
- [Ascher B](#), [Rzany BJ](#), [Grover R](#). Efficacy and safety of botulinum toxin type A in the treatment of lateral crow's feet: double-blind, placebo-controlled, dose-ranging study. Dermatol Surg. 2009 Oct;35(10):1478-86. Epub 2009 Jul 20.
- [Lowe NJ](#), [Lask G](#), [Yamauchi P](#), [Moore D](#). Bilateral, double-blind, randomized comparison of 3 doses of botulinum toxin type A and placebo in patients with crow's feet. J Am Acad Dermatol. 2002 Dec;47(6):834-40.
- [Fagien S](#), [Cox SE](#), [Finn JC](#), [Werschler WP](#), [Kowalski JW](#). Patient-reported outcomes with botulinum toxin type A treatment of glabellar rhytids: a double-blind, randomized, placebo-controlled study. Dermatol Surg. 2007 Jan;33(1 Spec No.):S2-9.
- [Carruthers A](#), [Carruthers J](#). Prospective, double-blind, randomized, parallel-group, dose-ranging study of botulinum toxin type A in men with glabellar rhytids. Dermatol Surg. 2005 Oct;31(10):1297-303.

# Bibliography

- Chertow DS, Tan ET, Maslanka SE, Schulte J, Bresnitz EA, Weisman RS, Bernstein J, Marcus SM, Kumar S, Malecki J, Sobel J, Braden CR. Botulism in 4 adults following cosmetic injections with an unlicensed, highly concentrated botulinum preparation. JAMA. 2006 Nov 22;296(20):2476-9.
- Sami MS, Soparkar CN, Patrinely JR, Hollier LM, Hollier LH. Efficacy of botulinum toxin type a after topical anesthesia. Ophthal Plast Reconstr Surg. 2006 Nov-Dec;22(6):448-52.
- Carruthers A, Carruthers J. Single-center, double-blind, randomized study to evaluate the efficacy of 4% lidocaine cream versus vehicle cream during botulinum toxin type A treatments. Dermatol Surg. 2005 Dec;31(12):1655-9.
- Ascher B, Zakine B, Kestemont P, Baspeyras M, Bougara A, Santini J. A multicenter, randomized, double blind, placebo-controlled study of efficacy and safety of three doses of botulinum toxin A in the treatment of glabellar lines. J Am Acad Dermatol. 2004;51:223-233.
- Rzany B, Ascher B, Fratila A, Monheit GD, Talarico S, Sterry W. Efficacy and safety of 3- and 5-injection patterns (30 and 50 U) of botulinum toxin A (Dysport) for the treatment of wrinkles in the glabella and the central forehead region. Arch Dermatol. 2006 Mar;142(3):320-6.
- Klein A.W. Contraindications and complications with the use of botulinum toxin. Clin Dermatol. 2004;22:66-75.
- Lowe NJ, Ascher B, Heckmann M, Kumar C, Fraczek S, Eadie N; Botox Facial Aesthetics Study Team. Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of botulinum toxin type A in subjects with crow's feet. Dermatol Surg. 2005 Mar;31(3):257-62.