Facial Rejuvenation and the Medications that Make it Possible

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What we will cover...

- Botox:
  - Brief history
  - Clinical pharmacology
  - Product comparisons
  - Clinical indications, contraindications, and adverse reactions
- Dermal Fillers:
  - Brief history
  - Clinical pharmacology and Product comparisons
  - Clinical indications, contraindications and adverse reactions

I do not have any financial relationships to disclose.

Top Minimally-invasive Cosmetic Procedures

- Botulinum Toxin Type A (7.23 million procedures, up 2 percent from 2016)
- Soft Tissue Fillers (2.69 million procedures, up 3 percent from 2016)

American Society of Plastic Surgeons Statistics 2017

History of Botulinum Toxin

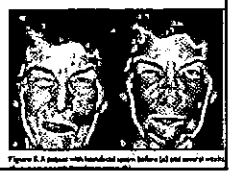
- Botulism first described in 1820
  - *Clostridium botulinum* bacterium produces a variety of neurotoxins causing paralysis by blockage of neurotransmitter release (acetylcholine) at the neuromuscular junction
  - Botulism causes widespread paralysis, ultimately may result in death due to respiratory failure.
    - Intoxication (death due to toxin effects), initially thought to be irreversible

History of Botox

- Dr. Alan Scott, an ophthalmologist, first used purified botulinum toxin type A
  - Dr. Scott founded Oculinum, Inc. to develop/test botulinum toxin A
- 1973: used on extraocular muscles of monkeys
- 1980: used on human test subjects to correct strabismus

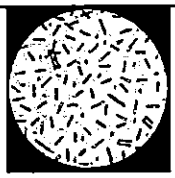
History Continued

- 1989: onabotulinumtoxinA is FDA approved for blepharospasm, strabismus and hemifacial spasm
- 1991 Allergan purchased, Inc. and renamed onabotulinumtoxin A as Botox
- 1992: Cosmetic applications of botox are first discussed (Alastair and Jean Carruthers)
  - blepharospasm patients had cosmetic side effects with relaxation of glabellar rhytids
- Botox is also approved for non-ophthalmic indications such as overactive bladder and migraine headaches



FDA approval

- 2002: Botox Cosmetic is approved for glabellar lines
- 2013: Botox Cosmetic is approved for lateral canthal lines
- 2017: Botox Cosmetic is approved for forehead lines
- FDA approves additional strains of botulinum toxin A:
  - abobotulinumtoxinA (Dysport) and incobutlinumtoxinA (Xeomin)
- FDA approves botulinum toxin B: RimabotulinumtoxinB (Myobloc)

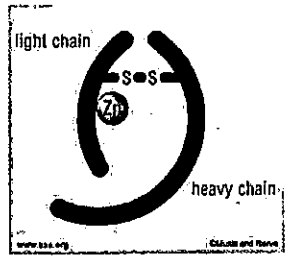


BOTOX

- The number 1 most common minimally invasive cosmetic procedure in the US
- Clostridium botulinum is the bacteria producing botulinum toxin. There are seven separate toxin serotypes: A-G.
- Only serotypes A and B are clinically used

Toxin Subtypes

- 7 subtypes of botulinum toxin (A-G)
- 5 of the subtypes affect the human nervous system (A, B and E-G)
- Botulinum toxin type A is considered the most potent subtype because is requires the least number of units and has the longest duration of action
- Each subtype has a heavy chain linked to a light chain with a single disulfide bond

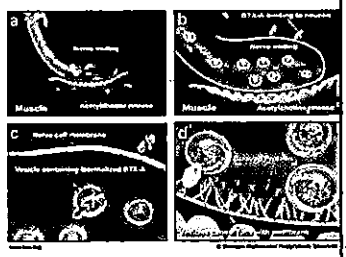


Botox Pharmacology

- The heavy chain binds and internalizes the toxin
- The light chain is responsible for internal blockade of neurotransmitter
- The subtypes differ based on where the light chain acts on the neuron's internal proteins to inhibit release of acetylcholine
  - The site of action is not know for all of the subtypes

Mechanism of Action

- 1. Binding: toxin (heavy chain) binds irreversibly to presynaptic neurons of neuromuscular junction
- 2. Internalization: toxin is internalized through receptor-mediated endocytosis. The heavy and light chains dissociate and the light chain translocates to the cytoplasm
- 3. Blocking: the toxin light chain disables the protein responsible for acetylcholine release, leading to target muscle paralysis

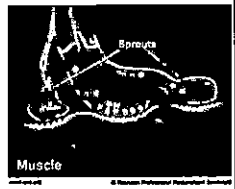


Dosing and Reversibility

- Botulism is a lethal disease, caused by neurotoxin binding to neurons that innervate the diaphragm. This would lead to respiratory distress.
- The lethal dose in humans is 2800-3500 units (glabella is usually 20 units)
- The effect of the toxin is temporary and varies depending on toxin type
- Neurons recover functioning by resprouting
  - functional neuronal sprouts connect with muscle fibers to resume muscle function (up to 3yrs after treatment)
  - eventually, the original nerve terminal does resume functioning, and the sprouts regress

Onset and Duration of Effect

- It takes approximately 3-4 days to see clinical effects
- It takes approximately 3-4 days for the toxin molecule to bind to the motor nerve terminal, internalize and block acetylcholine release
- The effects last 3-4 months
- It takes 3-4 months for new sprouts to grow (regenerate) and develop a functional connection at the myoneural junction
  - This is not dependent on the continued presence of botox at the nerve terminal



Toxin Type A and B

Preparation	Botox/Botox Cosmetic OnabotulinumtoxinA	Dysport AbobotulinumtoxinA	Xeomin IncobotulinumtoxinA	Myobloc RimabotulinumtoxinB
Manufacturer	Allergan Inc.	Ipsen Biopharm and Galderma Laboratories	Merz Pharma Inc.	Solstice Neurosciences Inc.
Use	• Blepharospasm/ hemifacial spasm • Strabismus • Cervical dystonia • Overactive bladder • Urinary incontinence • Chronic migraine • Spasticity • Axillary hyperhidrosis • Glabellar lines • Lateral canthal lines	• Cervical dystonia • Spasticity • Glabellar lines	• Cervical dystonia • Spasticity • Blepharospasm • Glabellar lines	• Cervical dystonia
Storage	2-8°C	2-8°C	20-25°C 2-C -20° to -10°C	2-8°C
Dose Equivalent Units	1	2-3	1	30-50

OnabotulinumtoxinA (Botox/Botox Cosmetic)

- Botox: 100 or 200 unit vials
- Botox Cosmetic: 100 or 50 unit vials
- Freeze-dried, require refrigeration
- Medication vial contains: neurotoxin, human albumin, sodium chloride
- Reconstitution: add sterile, preservative-free sodium chloride
- Can also use preservative containing, bacteriostatic NS for less pain (benzyl alcohol)

OnabotulinumtoxinA (Botox/Botox Cosmetic)

- Various dilutions (2.5-10 units per 0.1ml)
  - Commonly 4-5 units per 0.1ml
- Toxin is fragile, do not shake, may denature protein and make it ineffective
- manufacturer: use product within 24hours of reconstitution
- Research leading to 2015 consensus statement American Society for Dermatologic Surgery:
  - no decreased effectiveness or risk of contamination after proper reconstitution and storage for 4weeks

AbobotulinumtoxinA (Dysport)

- 300 or 500 unit vials, refrigerated
- Vial contains: 0.125mg human albumin, 2.5mg lactose and purified botulinum toxin A
- Same process for reconstitution and storage
- Not interchangeable, but estimated 2-3 units of Dysport are equivalent to 1 unit of Botox
- Faster onset, more diffusion, possible shorter duration of action

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AS1 more dilution means more diffusion and less precision. More potent means need to be more precise with placement

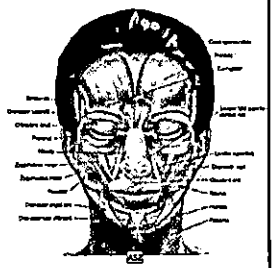
usually 1-2wks before discard
Amanda Salter, 11/8/2018

IncobotulinumtoxinA (Xeomin)

- 50, 100 or 200 unit vials
- Does not require refrigeration until reconstitution
- Vial contains: neurotoxin, 1mg human albumin, 4.7mg of sucrose
- Same process for reconstitution and storage
- Not interchangeable, but estimated 1 unit of Xeomin is equivalent to 1 unit of Botox
- More purified product, no complexing binding proteins, may decrease immunogenicity (less risk of antibody formation and allergy)

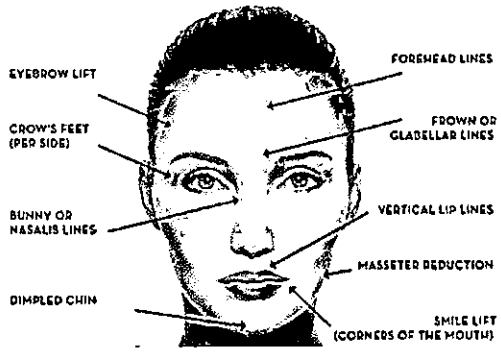
Cosmetic use of Botulinum Toxin Type A

- Botox treats dynamic lines (vs. static lines)
- In younger patients, botox can be preventative (30-50yo)
- Goal of providing a natural, not a frozen, appearance
- Consultation with patient: address individual concerns, facial asymmetry and realistic treatment results
- Can treat several areas of the face (know the muscles of facial anatomy and their actions)
  - many off-label indications
  - ice packs or topical numbing agent, 30-32g needle
  - post-treatment instructions very important!



FDA approved sites for Botox Cosmetic

- Botox® is FDA approved for use on the forehead lines, glabellar lines, and crow's feet
- Dysport® is FDA approved for use on glabellar (frown) lines
- Xeomin® is FDA approved for use on glabellar (frown) lines



...AND OFF LABEL USES

Botox

Absolute Contraindications for Botox:
prior allergic reaction
allergy to lactose, sucrose, saline, human albumin or eggs
active infection/inflammation at proposed site of injection
keloid scarring
pregnant or breast feeding (category C)

Relative contraindications:
Myasthenia gravis, autoimmune disease, muscular weakness or neurologic disorder (ALS, Eaton Lambert, Parkinsons)
Dry eye (depending on severity)
Ptosis (avoid frontalis injection, can still inject other sites)
Aminoglycosides, or other antibiotics
Penacillamine, aminoquinolones, quinine, calcium channel blockers, muscle relaxants
anti-coagulants (including herbal supplements)

Risks of Botox

1) Post treatment discomfort, swelling, redness, bruising or bleeding
2) Post treatment bacterial, viral and/or fungal infection requiring further treatments
3) Allergic reaction
4) Under correction (not enough effect) or over correction (too much effect)
5) Facial asymmetry (one side looks different than the other)
6) Paralysis of a nearby muscle leading to: droopy eyelid (in approximately 1-2% of injections, this usually lasts 2-3 weeks), double vision, inability to close eye, dry eye, difficulty whistling or drinking from a straw
7) Loss of vision, this is extremely rare, however, it can be caused by internal bleeding around the eyeball or needle stick injury
8) Permanent loss of muscle tone with repeated injection
9) Occasional numbness of the forehead lasting up to 2-3 weeks
10) Transient headache or flu-like symptoms may occur
11) Development of antibodies to Botox
12) Botox contains human-derived albumin and carries a theoretic ri of virus transmission. There have been no reports of disease transmission through Botox.

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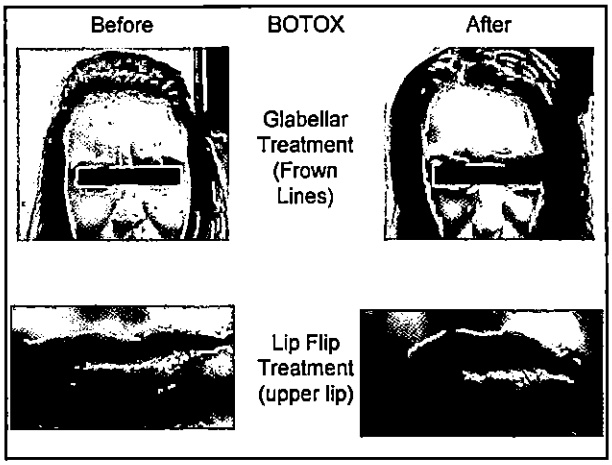
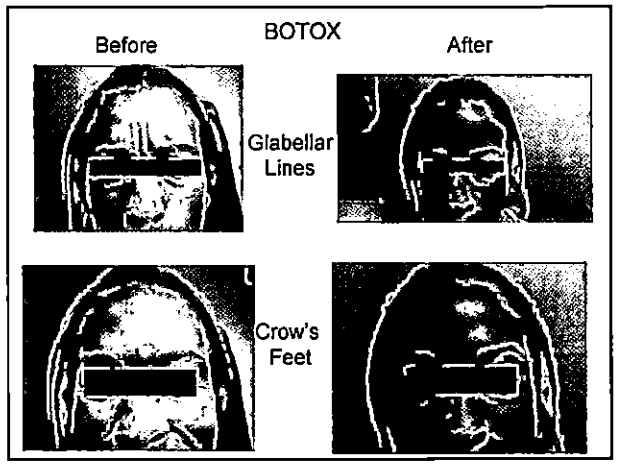
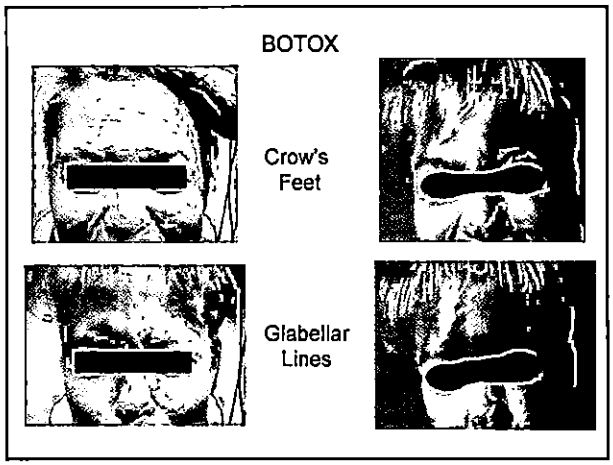
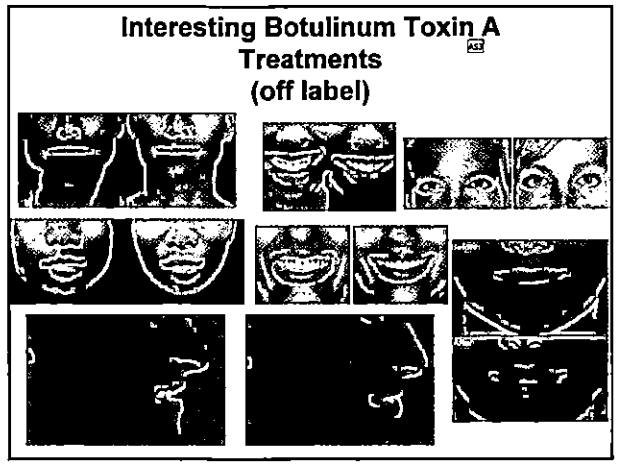
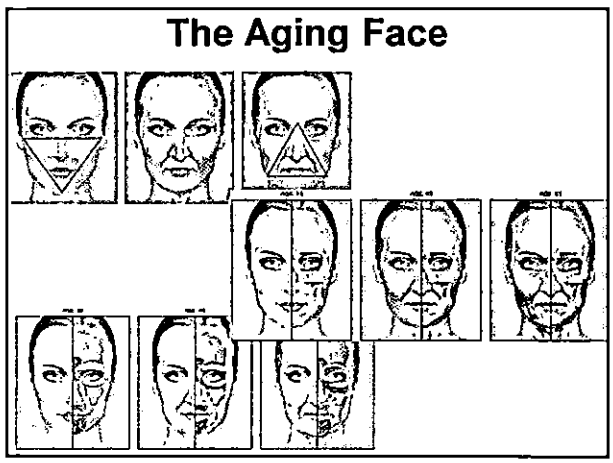
AS2 injection techniques, dosages etc are beyond the scope of the lecture
Amanda Salter, 11/8/2018











Dermal Fillers

- What is dermal filler?
  - Injectable gel dermal filler is a medical aesthetic treatment that helps to fill in wrinkles and add volume, resulting in a smoother appearance. The results are subtle, immediate, and long-lasting.
- Dermal fillers can help by adding volume to desired areas on the face, resulting in an overall lifted look to reduce a drawn and sagging appearance.
- Dermal fillers can address early signs of aging and can be used on their own, or in complement with Botox.
- Several different filler compositions:
  - Hyaluronic acid (HA), Calcium hydroxylapatite (CaHA), Polymethylmethacrylate (PMMA), Poly-L Lactic Acid (PLLA)

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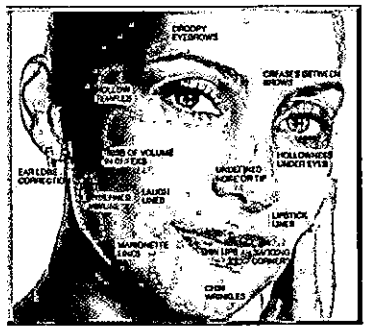
AS3 masseter muscle hypertrophy and facial contouring, gummy smile correction, nasal tip lift, brow lift, lip lift
Amanda Salter, 11/9/2018

FDA Approval of Dermal Fillers

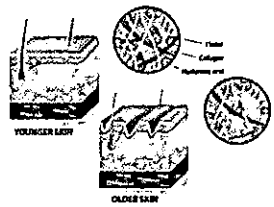
- 1981 FDA first approved bovine collagen filler
  - Use limited by short duration and potential for allergic reaction
- 2003 FDA first approves HA (Restylane) and human collagen facial fillers
- 2004 FDA approves more HA fillers and PLLA (Sculptra)
- 2006 FDA approves additional HA filler (Juvederm), PMMA (Bellafill), and CaHA (Radiesse)
- 2008 FDA approves HA + lidocaine filler
- Multiple other approvals not listed here...



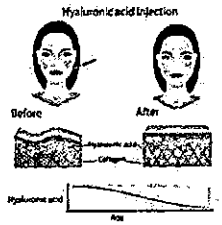
FDA approved for
- Cheeks
- Lips
- Laugh lines
- Marionette lines

Hyaluronic Acid Fillers

- HA is a polysaccharide normally found in the connective tissues of the body
  - Original products were made from animals (rooster combs)
  - Now synthetic, cross-linked hyaluronic acid, can come premixed with lidocaine
  - Injected in deep dermis, superficial subcutaneous tissue or preperiosteal planes
  - If too superficial get Tyndall effect: bluish appearance of product seen through the skin due to the particles scattering blue light
  - Considered a safer fillers due to the ability to reverse effects with hyaluronidase
  - Can last from 6-24 months depending on type of filler



Hyaluronic Acid Fillers



RESTYLANE

RESTYLANE