1 **Botulinum toxin:**
**Getting started with cosmetic treatment**

Suzanne K. Freitag, M.D.
Director, Ophthalmic Plastic Surgery Service
Massachusetts Eye and Ear Infirmary
Harvard Medical School

2

I have no financial disclosures.

3 **Learning Objectives**

- To understand facial aging changes
- To review anatomy of facial muscles of expression
- To understand the history and uses of botulinum toxin
- To review product reconstitution and injection technique
- To review the newest products on the market

4 **The Aging Face**

- Prominent facial lines can be misinterpreted as
  - anger
  - anxiety
  - fatigue
  - sadness

5 **The Aging Face**

- Causative factors
  - Chronic gravitational pull
  - Volumetric loss of fat
  - Actinic damage
  - Hyperfunctional lines

6 **The Aging Face**

- Hyperfunctional lines are the result of underlying muscle contraction
  - Glabellar lines
  - Forehead “furrows”

- "Crow's feet"
- Perioral "lipstick lines"
- Platysmal bands

7 **The Aging Face**

8 **The Aging Face**

- Treat the underlying pathophysiology
  - For hyperfunctional lines, treat the muscles

9 **What is Botulinum toxin ?**

- Produced by anaerobic gram negative rod bacterium *Clostridium botulinum*
- Most toxic poison known to man
- Exotoxin liberated from bacteria in culture
  - Purified, freeze-dried
- Eight sub-types
  - A, B, C1, C2, D, E, F, G

10 **What is Botulinum toxin ?**

- Mechanism of action
  - Binds to receptor in pre-synaptic neuromuscular endplate
  - Enters nerve via endocytosis
  - Prevents release of acetylcholine
  - Results in TEMPORARY PARALYSIS
    - Resolves as nerve regenerates new endplates

11 **History of Botulinum toxin**

- Early 1970's
  - Dr. A. Scott (ophthalmologist) - first clinical use of botulinum toxin - in strabismus
- mid 1980's
  - Dr. Caruthers - "father" of cosmetic Botox
  - Observes wrinkle-free glabella after blepharospasm treatment

12 **History of Botulinum toxin**

- 1989
  - FDA approval for strabismus, blepharospasm, hemifacial spasm
- 1990
  - NIH consensus recommendation for use in dystonias
- 2002

- FDA approval for glabellar lines

13 **Uses of Botulinum toxin**
- Spastic disorders
  - BEB, HFS, Parkinson's, MS, CP, traumatic brain injury, post-CVA, dysphonia
- Dystonic disorders
  - Cervical dystonia, torticollis, etc
- Strabismus
- Hyperhidrosis
  - Axilla, palms

14 **Uses of Botulinum toxin**
- Cosmetic
  - Forehead furrows, glabellar folds, crows feet, mentalis, lips, nasal flare, platysmal bands
- Miscellaneous uses
  - Headache, TMJ, constipation, low back pain

15 **Dilution and Storage**
- "Botox" produced by Allergan in US
- Each Botox (botulinum toxin A) vial contains
  - Approx. 100 Units freeze-dried toxin
  - 0.5 mg human albumin
  - 0.9 mg sodium chloride
- Kept refrigerated until reconstituted

16

17 **Dilution and Storage**
- 1 Unit toxin = LD (50) for a group of female Swiss Webster mice
  - LD (50) is the estimated lethal dose for 50% of individuals
- For humans, LD (50) = 40 U/kg or 2500-3000 U for a 70-kg man

18 **Dilution and Storage**
- Diluent
  - Manufacturer recommends NON-preserved saline
    - Concern that preservative deactivates toxin
  - Many physicians use preserved saline
    - 0.9% benzyl alcohol

- Better buffered, so less pain on injection
- Safer to use at a later time

19 **Dilution and Storage**

- Botulinum toxin is FRAGILE
  - Add diluent SLOWLY to bottle
  - SWIRL vial to mix, don't shake
  - Alcohol swabbed onto cap should evaporate prior to needle insertion

20 **Dilution and Storage**

- What is the best dilution ?
  - Manufacturer provides table up to 8 mL
  - Most physicians use 2 to 4 mL per vial
  - Example of calculation
    - 100 Unit vial/2 mL saline = 5 U/0.1 mL

21 **Dilution and Storage**

- High concentration (low volume)
  - Precise placement of toxin
  - Less diffusion into surrounding tissues
  - Greater duration of effect
- Lower concentration (high volume)
  - Encourages toxin spread
    - Desirable in some areas
  - Shorter duration of effect

22 **Dilution and Storage**

- Once reconstituted, Botox must be refrigerated
  - Package insert recommends use within 4 hours
  - Actual effectiveness is longer
  - CONTROVERSIAL

23 **Dilution and Storage**

- Longevity studies with variable results
  - 44% loss of activity in 12 hours
  - No loss of activity in 24 hours
  - No loss of potency at 30 days !!

- Potential problems arise with sterility
- Must consider using preserved saline

- Many practitioners limit use to 24 hours

24 **Contraindications**
- Neuromuscular junction disease
  - Myasthenia gravis, Eaton-Lambert
- Hypersensitivity to human albumin
- Pregnancy
  - Category C drug
    - "not established whether harmful"
- Breast feeding
  - Not known whether excreted

25 **Relative Contraindications**
- Recent use (2 weeks) aminoglycosides, penicillamine, quinine, Ca channel blocker
  - Can potentiate effects of toxin
- Anticoagulation
  - Ecchymosis and hematoma at injection sites

26 **Candidate Selection**
- Hyperfunctional lines
  - Due to action of underlying muscles
- "Spread test"
  - The ability to efface the lines by manually spreading surrounding skin
  - Predictive of favorable response to Botox

27 **Candidate Selection**
- Avoid patients with wrinkles in thick, sebaceous skin areas
  - Suggests dermal fibrosis to underlying muscles
  - Predictive of unfavorable response to Botox

28 **Muscular Anatomy**
- Frontalis
  - Origin: galea aponeurosis
  - Insertion: frontal bone & fibers of procerus, corrugator
  - Elevates brow
  - Horizontal forehead wrinkles

- Overtreatment: brow droop or ptosis

29 **Muscular anatomy**
- Corrugator supercilii
  - On frontal bone of upper medial orbit
  - Origin: frontal bone medial to brow
  - Insertion: dermis above middle third of brow
  - Brow adductor (down and medial)
  - Causes vertical glabellar crease

30 **Muscular anatomy**
- Procerus
  - Origin: lower nasal bone
  - Insertion: skin overlying nasal bridge
  - Causes “snout” contraction with horizontal nasal wrinkles

31 **Muscular anatomy**
- Orbicularis oculi
  - Origin: anterior aspect orbital rims
  - Insertion: medial and lateral canthal tendons
  - Closes eyes and depresses brow
  - Causes “crows feet” laterally

32 **Injection technique**
- Obtain written consent
- Cleanse areas with alcohol
- Ask patient to make facial expression to accentuate problem areas
- +/- marking pen
- Use 1/2 inch 30 gauge needle

33 **Injection technique**
- Inject into muscle, NOT the crease
  - Opposite of filler techniques
- Record injection sites and doses
- Photograph pre-injection & follow-up
- Err on side of injecting too little the first time
  - At 2 week exam, may reinject if needed

34 **Injection technique**
- Dosing
  - Individual thresholds and longevity of effect are highly

variable
- Approximate dosages
  - Frontalis: 5 to 25 U
  - Glabella: 5 to 20 U
  - Crows feet: 5 to 15 U

35 **Injection technique**
- Applying pressure immediately after injection may decrease ecchymosis
  - Will spread area of toxin effect
  - May or may not be desirable
- Effects reported as early as 24 to 48 hours
  - May take up to 7 days
- Effects last approx. 3 to 6 months

36 **Injection technique**
- Glabella
  - Inject into corrugator (deep)
    - May insert needle to bone and pull back
  - Into procerus if horizontal line

37 **Injection technique**
- Forehead
  - Stay at least 2 cm above brow
  - Caution lateral to pupils
    - Avoid brow ptosis
  - Inject intramuscularly in alternating pattern above and below crease

38 **Injection technique**
- Crows feet
  - Ask patient to squint to localize lines
  - Alternate along lines
  - Stay lateral to orbital rim
  - Inject into orbicularis
    - Just deep to skin
  - About 10 U each side

39 **Botox as adjuvent therapy**
- Endoscopic brow lift PLUS Botox

- Decrease corrugator and procerus action
- Allows healing to new position more securely
- Laser-resurfacing PLUS Botox
  - Prevents reappearance of lines if underlying muscles are paralyzed during healing
- Filler injection PLUS Botox
  - Implanted material not compressed by muscle contraction

40 **Complications**

- FDA reports 16 deaths from botulinum toxin, 4 in kids <18 YO
  - In cervical dystonia injections
    - Respiratory muscle paralysis
    - Aspiration pneumonia
- Localized reactions (common)
  - Pain, bruising, hematoma, edema, erythema
  - May pretreat with EMLA or ice

41 **Complications**

- Inadvertent spread of toxin
  - Temporary weakness of adjacent muscles
  - Lid or brow ptosis, ectropion, corneal exposure, lagophthalmos, diplopia, epiphora
  - Ways to avoid
    - Don't massage, inject low volumes, avoid injection near orbital rim

42 **Complications**

- Mild ptosis may be treated with alpha-adrenergic agonist eyedrop
  - Apraclonidine 0.5% (Iopidine)
  - Causes Muller's muscle contraction
  - Gives 1-2 mm upper lid lift

43 **Antibodies to Botox**

- Botulinum toxin is an antigenic protein
- Patients receiving repetitive, high-dose injections may develop antibodies
- These IgG's block/neutralize Botox
  - Causes resistance to treatment effect
  - Do NOT cause hypersensitivity reactions

44 **Botulinum Products Available**
- Botox (type A) – Allergan, USA
- Dysport (type A) – made in Ireland, FDA approved in USA
- Botulinum toxin type A from Lanzhou Inst. in China
- Neuronox (type A) by Medy Tox in South Korea began in 2009

45 **Another Botulinum toxin product available**
- Xeomin
  - Manufactured by Merz in Greensboro, NC
  - FDA approved in 2010
    - cervical dystonia and blepharospasm
  - An isolate of active toxin
    - Without non-toxic accessory proteins
    - "low protein load"

46 **Botulinum toxin Type B**
- Myobloc
  - FDA approved 2000 for cervical dystonia
- Unique immunologic profile
  - Effective for patients with antibodies to typeA
- Treatment effective for 12 to 14 weeks
- More diffusion of toxin to adjacent tissues
  - High rate of undesired regional effects

47 **Before and After**

48 **Before and After**

49 **Before and After**