Botulinum Toxins: Pluses and Minuses

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Disclosure Information

- In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Purpose

- Discuss FDA-approved botulinum toxin preparations.
- Compare the available toxins.
- Pluses and minuses, side effects.
- Other considerations.

Introduction

- There are seven known botulinum neurotoxins (BoNT A-G).
  - Note: BoNT-D does not affect humans.
- Only two are FDA-approved for use in humans (BoNT-A and BoNT-B).

Bilyk JR, Yen MT, Bradley EA, et al. Ophthalmology 2018;125:1459-1467.
Samizadeh S, De Boulle K. Clin Cosmetic Invest Dermatol2018;11:273-287.

Introduction

- BoNT appears to have an affinity for hyperactive nerve terminals.
- In general, after injection:
  - Paresis in 2-5 days.
  - Maximum effect in 5-6 weeks.
  - Duration 2-5 months.
  - NB: Varies among formulations.
- Recovery from BoNT occurs in two stages:
  - Neuronal "sprouts" form that allow for neuronal function (?minor effect).
  - Recovery of the original terminals and regression of the sprouts (?major effect).

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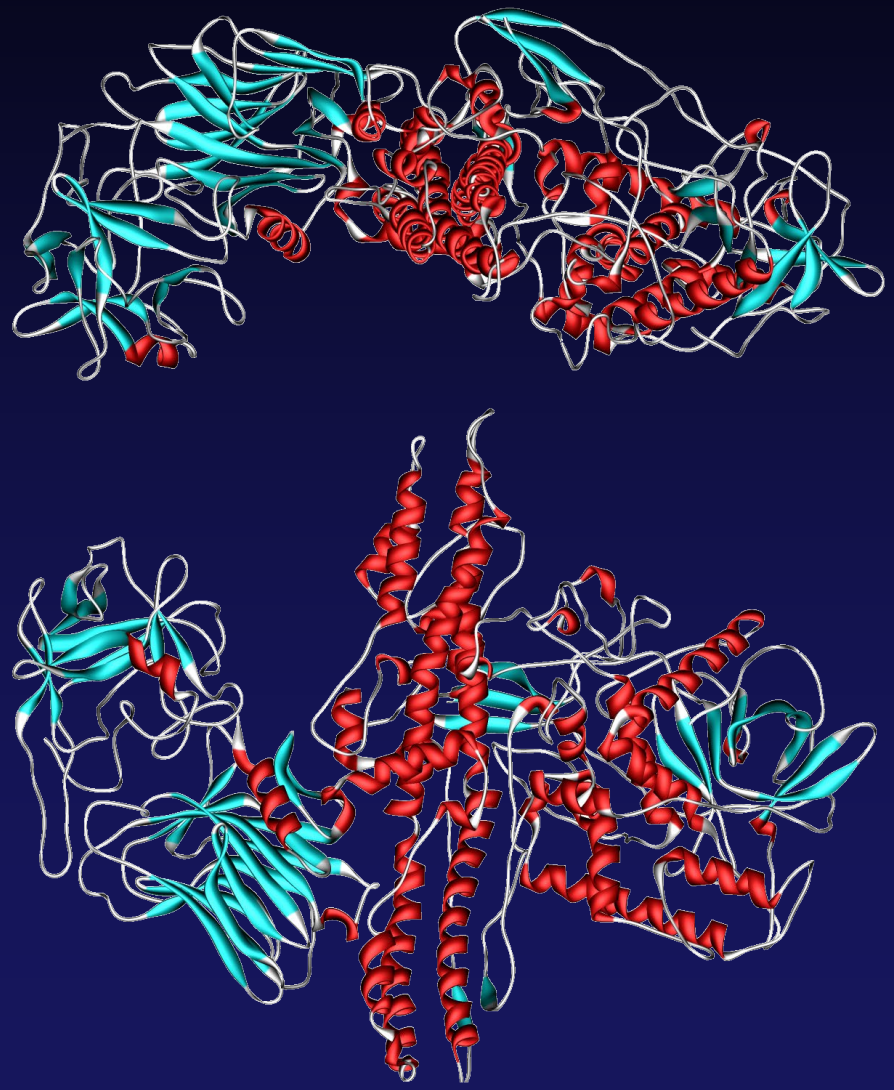
Botulinum Toxin



- The heavy and light chains are attached by a very fragile disulfide bond that is crucial to toxin efficacy.
- This bond is susceptible to environmental factors (temperature, etc).

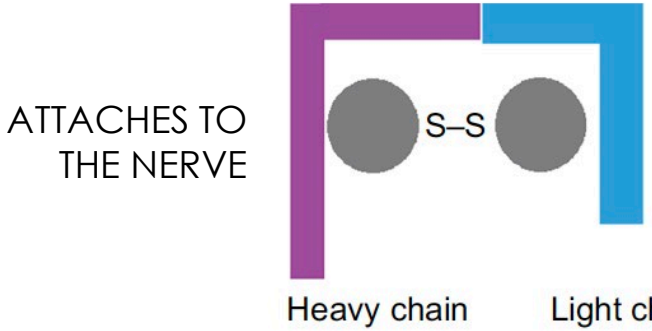
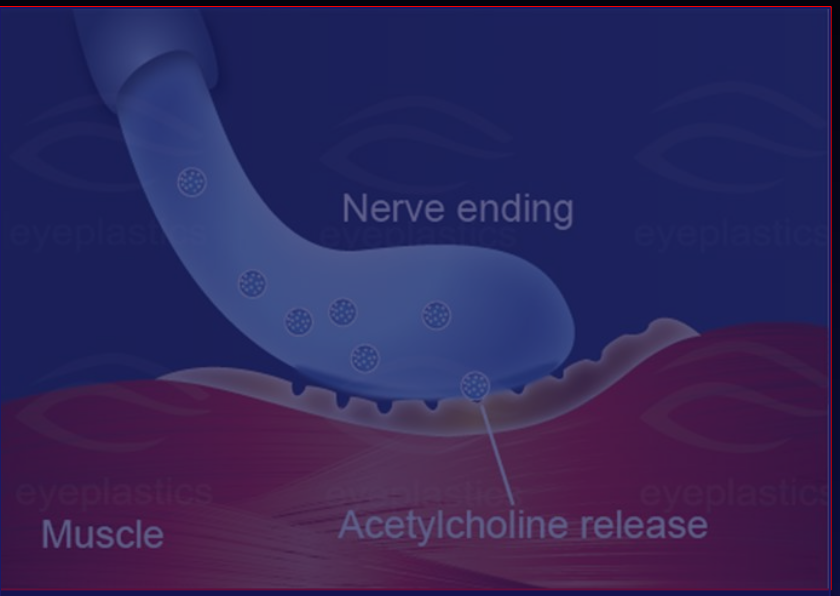
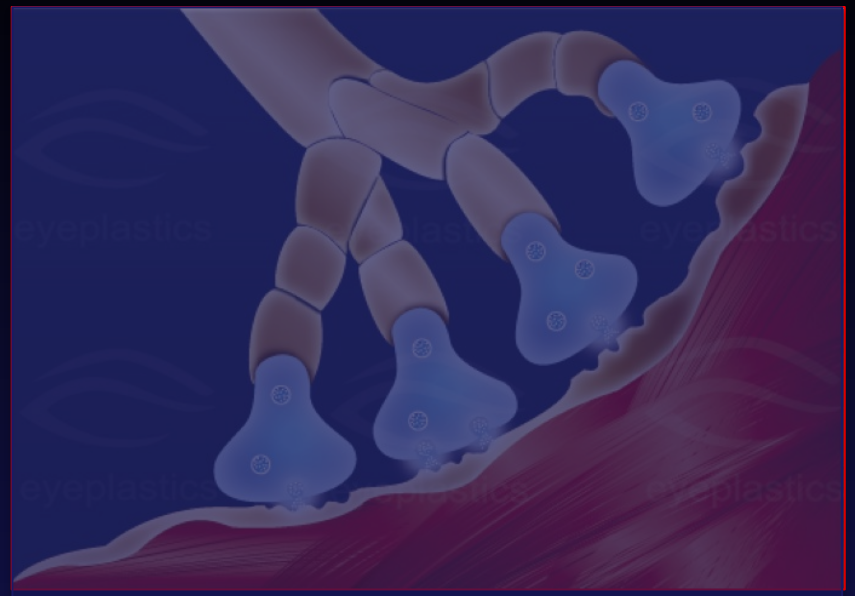


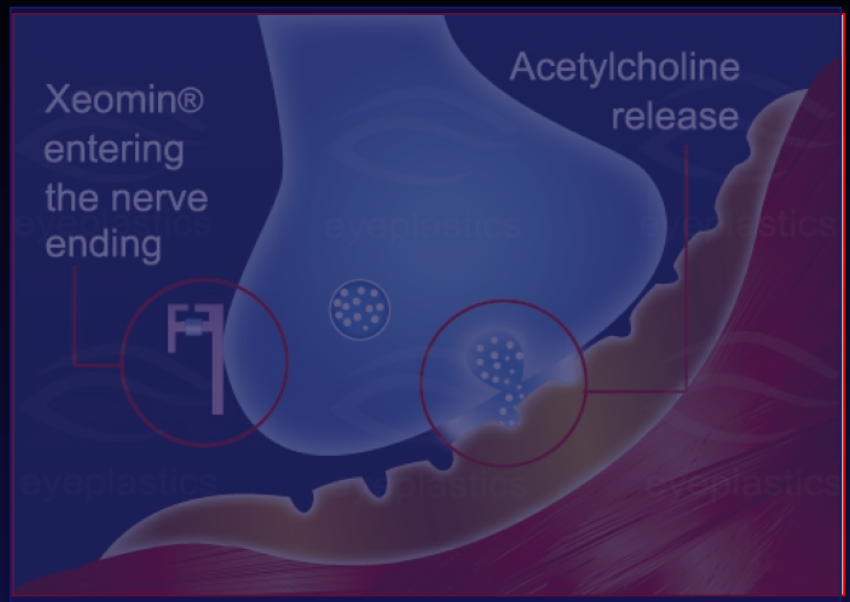
Figure 1 Botulinum neurotoxin consists of two amino acid chains connected by a disulfide bridge: a heavy amino acid chain with a molecular weight of 100 kDa and a light amino acid chain with a molecular weight of 50 kDa.[20]



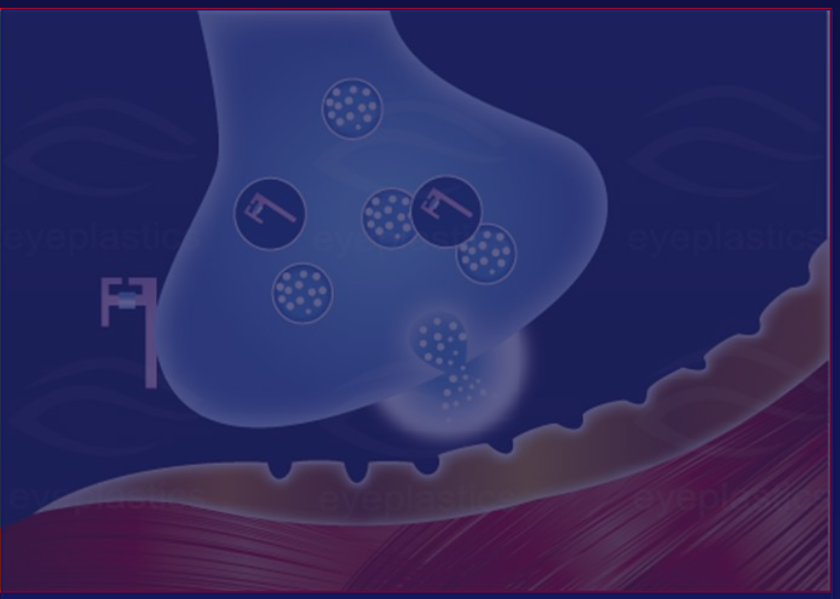
NORMAL NERVE-MUSCLE JUNCTION



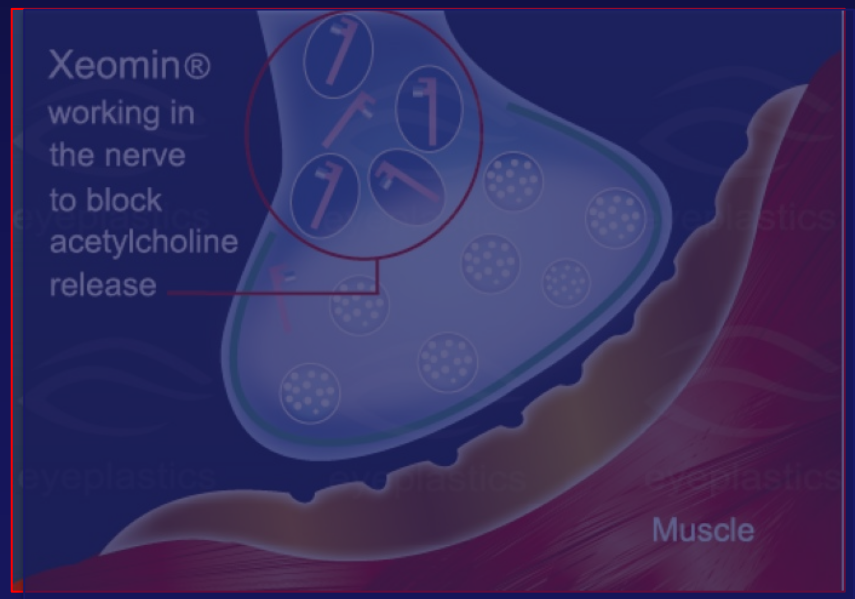
"HYPERACTIVE" NERVE TERMINAL



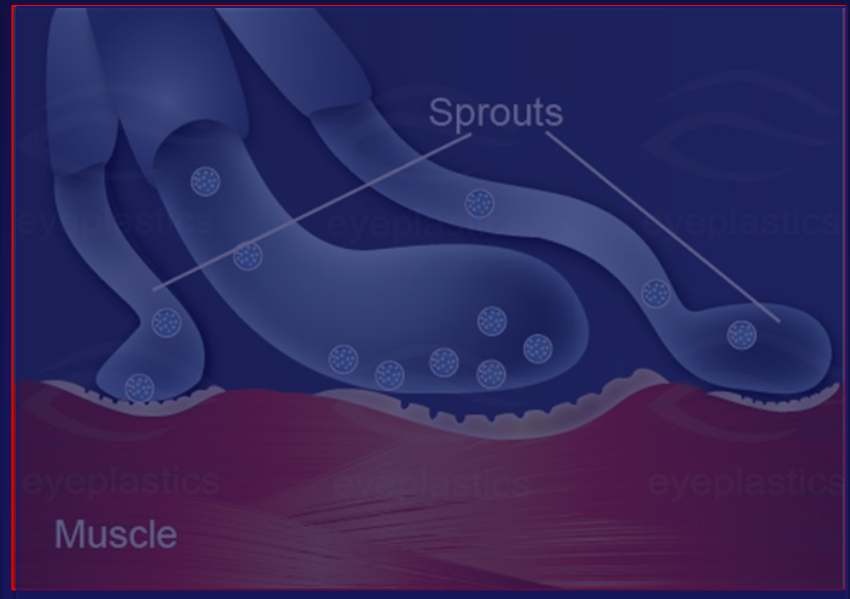
BoNT ATTACHMENT TO NERVE ENDING



BoNT ENTERING NERVE



BoNT BLOCKIN ACH RELEASE



NERVE "SPROUTS" FORMING

Variables Among Toxins

- Composition:
  - Toxin complex size.
  - Molecular weight.
  - Chemical properties.
  - Protein load (toxin + nontoxic accessory proteins).
- “Excipients” (other stuff in the bottle):
  - Sucrose, lactose, gelatin, serum albumin, dextran.
  - Buffering systems.
- Biologic properties.
  - Includes risk of antigenicity.
- Preparation:
  - Amount of neurotoxin (units).
  - pH
  - Storage before and after reconstitution.
- Indications.
- Geographic distribution.
- Insurance coverage.

Samizadeh S, De Boulle K. Clin Cosmetic Invest Dermatol2018;11:273-287.

Other Considerations

- Anatomy:
  - Specific muscle activity pattern.
  - Muscle architecture.
  - Thickness of epidermis and skin.
  - Fascial planes.
  - Eyelid anatomic planes.
  - AGE!

*NB: There has NEVER been a report of any deleterious CNS symptoms from BoNT injection. There is no evidence that BoNT is found in the bloodstream after usual injection doses for BEB or HFS.

- Injection techniques:
  - Dilutions/doses.
  - Volumes of injection.
  - Depth.
  - Number.
  - Pattern.
- Direct and indirect effects:
  - Direct: Neuromuscular junction, muscle atrophy.
  - Indirect: Retroaxonal transport into the central nervous system (e.g migraines).*

Two Simple Rules

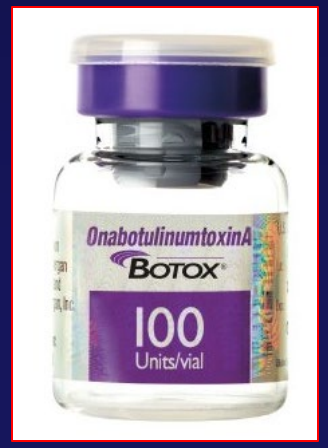
- Higher doses of BoNT result in higher efficacy *BUT* also result in higher "adverse events" (e.g. droopy eyelid, double vision, lagophthalmos, dry eye).
- Higher volumes of BoNT at each site result in more diffusion, with higher adverse events.
- The usual algorithm physicians use is:
  - Start at a lower dose and then increase as needed.
  - Use smallest volume (0.1cc) at each site.

Defazio G, Abbruzzese G, Girlanda P, et al. Arch Neurol 2002;59:418-420.
Triung D, Comella C, Fernandez HH, et al. Parkinsonism Relat Disord 2008;14:407-414.

The Toxins

Generic Name	Trade name (USA)	Manufacturer	FDA Approval	Storage
OnabotulinumtoxinA	Botox	Allergan, USA	1989	2-8°C
BobotulinumtoxinA	Dysport	Ipsen, France	2009	2-8°C
IncobotulinumtoxinA	Xeomin	Merz, Germany	2018	25°C (room temperature)
RimabotulinumtoxinB*	Myobloc	Solstice, USA	2019	2-8°C

*Higher incidence of autonomic side effects. Not often used for motor dystonias (BEB, HFS).



The Toxins: General Information

- All supplied in powder form.
- All need to be reconstituted with saline.
- Debate on preservative-free vs preserved saline:
  - No decrease in efficacy with preserved saline.
  - Preserved saline injections are less painful.
  - Most physicians use preserved saline.
- Shaking the bottle does NOT affect potency.
- Botox maintains potency for to 2-6 weeks after reconstitution with refrigeration.
- Xeomin maintains potency for at least 7 days at room temperature.

“Dose Equivalence”

- QUICK FACT: All three BoNT preparations (Botox, Xeomin, Dysport)are effective.
- The debate is really about conversion factors between BoNTs.
- Objective: Different number of molecules in “one unit” in each preparation.
- Subjective:
  - Efficacy and comparisons between BoNTs are difficult because of inherent subjectivity.
  - Most studies depend on a variety of “scoring scales”

What Does “One Unit” Mean?

How Do You Rate the Toxins?

- "BEB Rating Scales":
  - Clinical (doctors): Jankovic.
  - Activities of daily living (patients): BSDI.
  - Global activity: Secondary outcomes.

Albanese A, Sorbo FD, Comella C, et al. Mov Disord 2013;28:874-883.
Wabbels B, Jost WH, Roggenkämper P. J neual Transm (Vieena) 2011;118:925-943.
Jankovic J, Kenney C, Graefe S, et al. Mov Disord 2009;24:407-413.

Easy Rule

- Botox:Xeomin – 1:1-1.2
  - Verified by numerous studies.

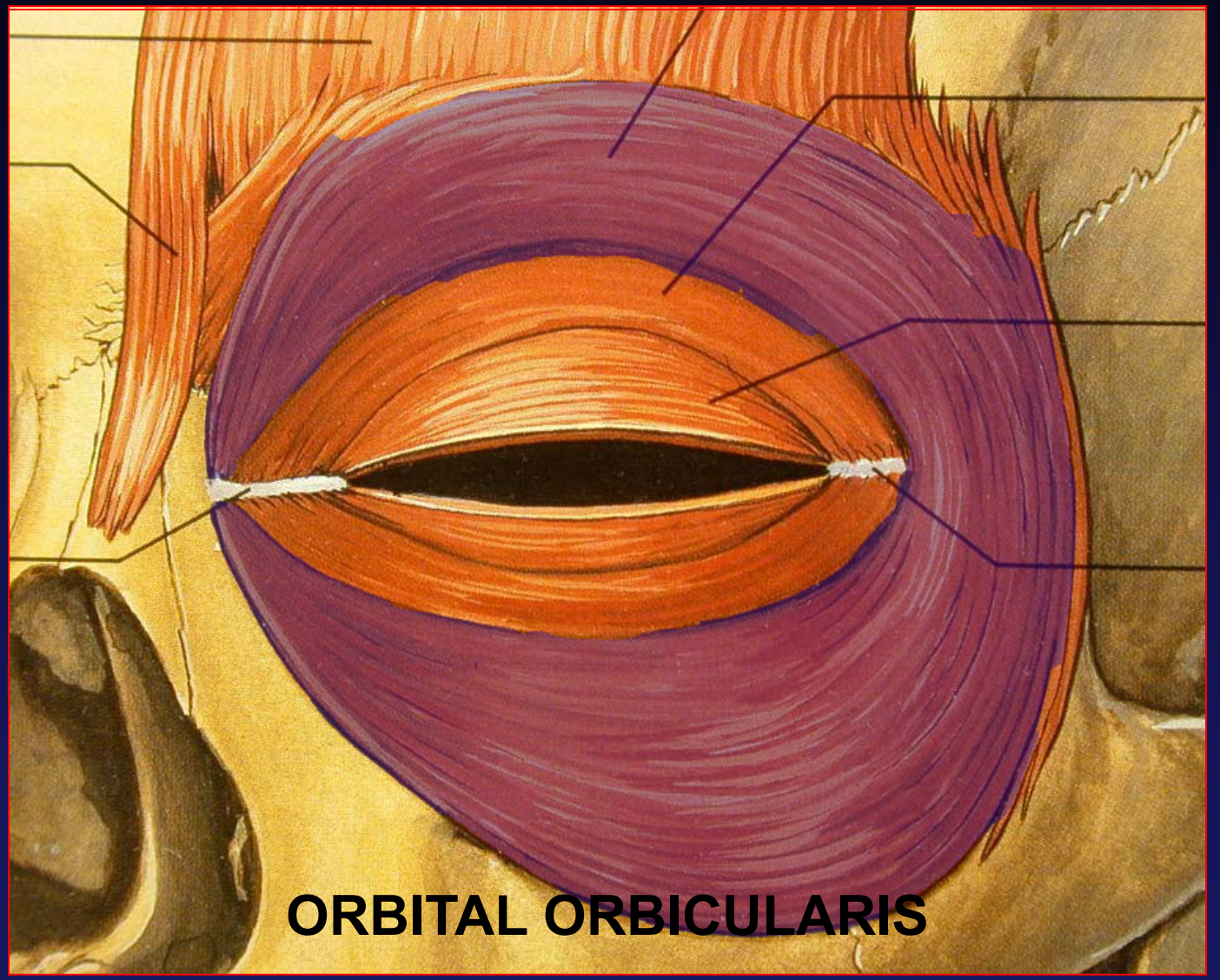
Scaglione F. Toxins (Basel) 2016;865.

More Complicated

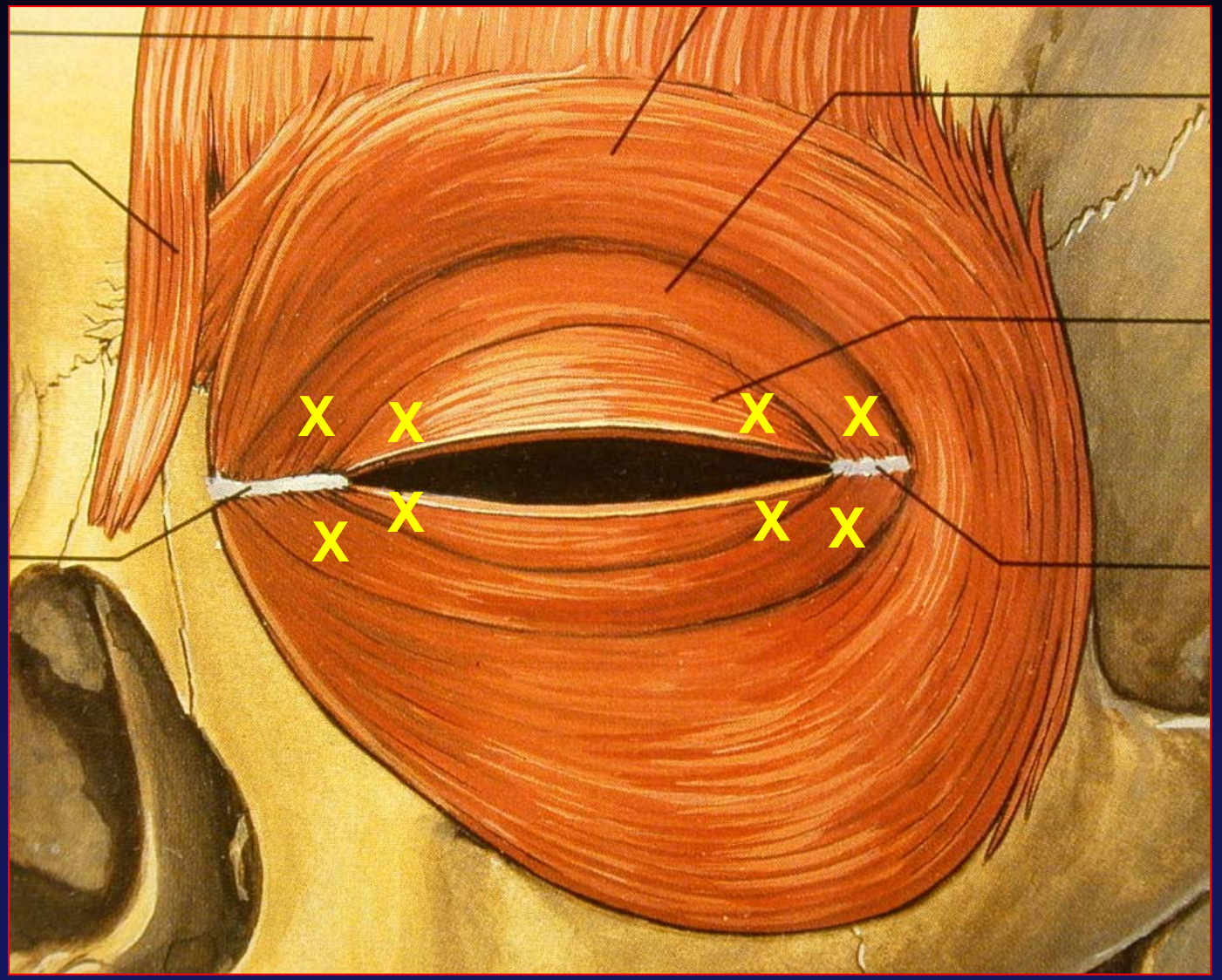
- Botox/Xeomin:Dysport = 1:3-4 *BUT*
  - Ranges from 1:1-11.
  - Dysport may also have a wider "spread" than Botox or Xeomin.
- Botox:Myobloc = 1:24-100.
- General rule: It's easier to switch between Botox and Xeomin than Dysport. Don't use Myobloc.
  - Underdose.
  - Overdose.
  - Adverse events.

Scaglione F. Toxins (Basel) 2016;865.
Sampaio C, Ferreira JJ, Simoes F, et al. Mov Disord 1997;12(6):1013-1018.
Dashtipour K, Chen JJ, Espay AJ, et al. Mov Disord Clin Pract 2016:3:109-115.

Where You Are Injected Matters



Where You Are Injected Matters



86% effective

96% effective, longer duration, fewer AEs.

Çakmur R, Ozturk V, Uzunel F, et al. J Neurol 2002;249:64-68.

How Old You Are Matters

- Older patients (>65yrs) required less BoNT than younger patients.
- Probably due to loss of muscle mass with age.
- Less muscle mass = Less BoNT needed.

Cillino S, Raimondi G, Guepratte N, et al. Eye (London) 2010:24:600-607.

Adverse Events

Table 2. Summary of Adverse Events Reported*

Adverse Event	Botox (%)	Dysport† (%)	Xeomin (%)	Meditoxin (%)	Placebo (%)
Ptosis	4.5–29.4[2,6,17,23,33,44]	13–58[22]	6.1–18.9[6,44,45]	6.4[33]	5.9[45]
Diplopia	0–8.6[2,17,23]	10–16[22]	NR	NR	NR
Facial weakness‡	3–11[17,23]	NR	NR	NR	NR
Ecchymosis	8.6–22.6[2,44]	NR	2.7[45]–27.3[44]	NR	2.9[45]
Dry eye/eye burning	0–2.7[2,6,33]	3[22]	0.7–18.9[6,44,45]	7.6[33]	11.8[45]
Mouth droop	1.7[2]	NR	NR	NR	NR
Photophobia	0–3.4[2,6]	NR	1.4[6]	NR	NR
Blurred vision	0–3.2[2,6]	23–42[22]	1.4–5.4[45]	NR	5.9[45]
Epiphora	0–0.6[2,23]	6–17[22]	2.7[45]	NR	2.9[45]

NR = not recorded.
*An additional 24 patients who received onabotulinumtoxinA (oBTX-A) for treatment of entropion were not included in this review.
†Data from Truong et al[22] are listed as a range of dose-related adverse events.
‡In patients with hemifacial spasm.

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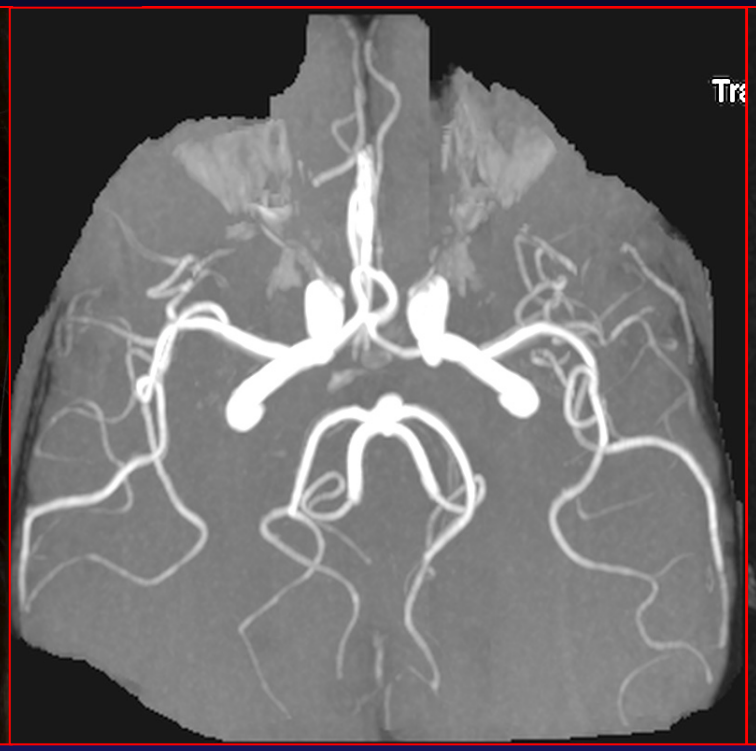
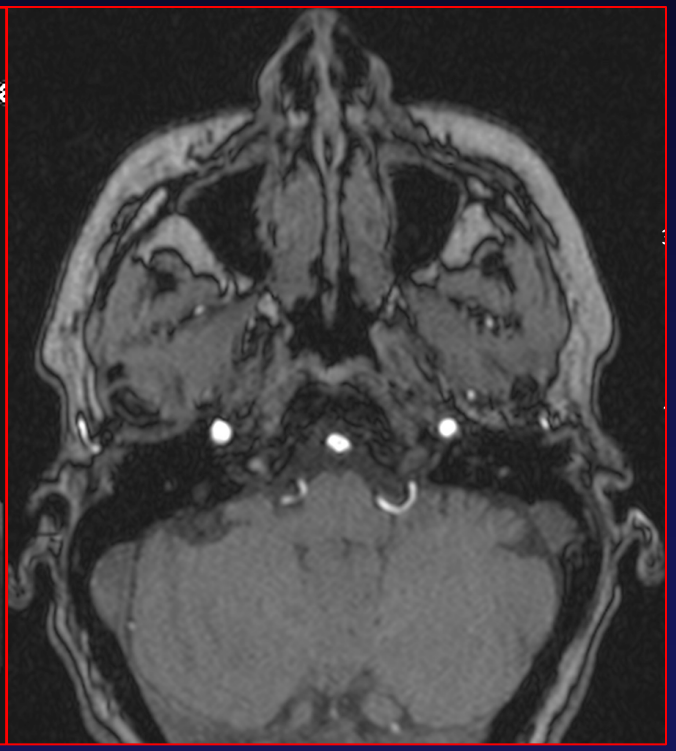
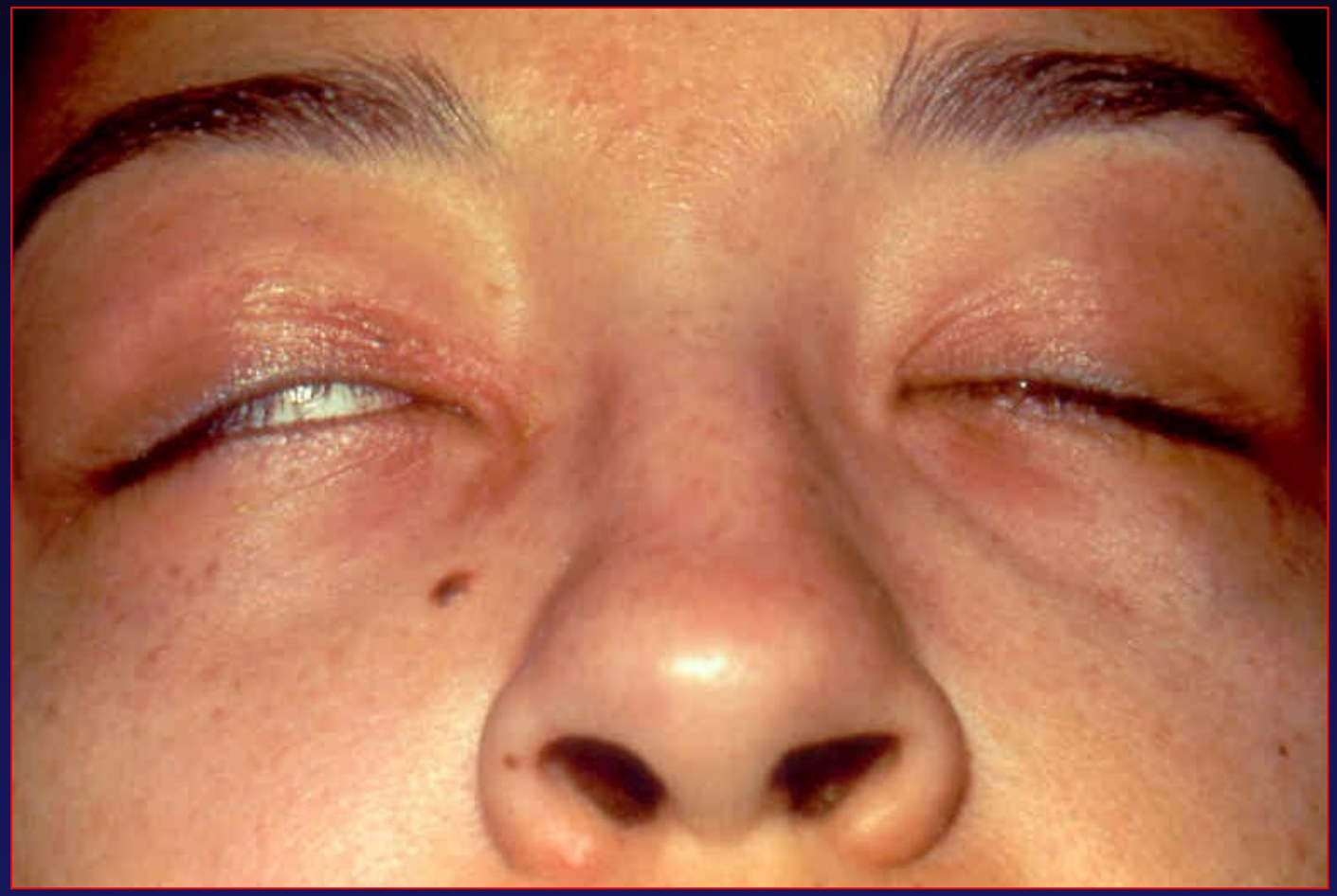
Ptosis





Worsening Dry Eye Symptoms



- Lagophthalmos.
- Incomplete blink.

How About "Antigenicity"?

- All BoNTs contain nonhuman complexing proteins.
- These may behave like antigens and provoke a antibody response by the body's immune system, either directly against the BoNT ("neutralizing") or one of the other proteins ("nonneutralizing") or both.
- May increase with repeated injections or with more frequent injections (<2 months apart).
- A much bigger concern when large volumes of BoNT are injected (torticollis vs BEB/HFS).

Summary

- All 3 BoNT are effective in BEB/HFS.
- Conversion is much easier with Botox and Xeomin than with Dysport.
- Other considerations:
  - Dose, dilution, frequency.
  - Location on lids/face.
  - Age.

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