Botulinum Neuromodulators: Clinical Data & Applications

Karol A Gutowski, MD, FACS
Disclosures

Angiotech/Quill - Advisory Board
Suneva Medical - Instructor
Viora - Speaker

Will discuss off-label uses
Will use brand names for ease of understanding
Will refer to BOTOX Cosmetic as BOTOX
BoTN-A Product Information

FDA Approved
• BOTOX Cosmetic - OnabotulinumtoxinA
• DYSPORT – AbobotulinumtoxinA
• XEOMIN – IncobotulinumtoxinA

Not FDA Approved
• MYOBLOC - RimabotulinumtoxinB
• NEURONOX - Botulinum toxin A
• RT001- Botulinum toxin A (Topical)
FDA Cosmetic Approval

• **BOTOX Cosmetic** * [Allergan]
  – Moderate to severe glabellar lines
  – Moderate to severe lateral canthal lines

• **DYSPORT** [Medicis/Valeant]
  – Moderate to severe glabellar lines

• **XEOMIN** [Merz Aesthetics]
  – Moderate to severe glabellar lines

• All for adults ≤ 65 years old
What FDA Wants You to Know

• Black Box Warning
  – Possibility of experiencing potentially life-threatening distant spread of toxin effect from injection site after local injection
  – Not reported in cosmetic uses

• Risk Evaluation and Mitigation Strategy (REMS)
  – *Medication Guide* to help patients understand risks & benefits

• Potency units are specific to each BoTN-A product
  – Doses or units cannot be compared or converted
BoTN-A Mechanism of Action

Block neuromuscular junction transmission by inhibiting acetyl choline release

• BoTN-A binds to cholinergic nerve terminals
• Internalized into nerve
• Light-chain translocated into nerve cytosol
• Enzymatic cleavage of SNAP-25 (essential for ACh release)
• Impulse transmission re-established by formation of new nerve endings
### Mechanism of Action

**Types A and B bind to distinct acceptors**

- Botulinum Type A cleaves SNAP-25
- Botulinum Type B cleaves synaptobrevin (VAMP)

A mechanism of action involves

- Block cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine from peripheral cholinergic nerve endings.
- Neurotoxin binding to cholinergic nerve terminals,
- Internalization of the neurotoxin into the nerve terminal,
- Translocation of the light chain part of the molecule into the cytosol of the nerve terminal,
- Enzymatic cleavage of SNAP25, a presynaptic target protein essential for the release of acetylcholine.

Impulse transmission is re-established by the formation of new nerve endings.
## Product Comparison

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BoTN-A Molecule

BoTN-A

BoTN-A + Accessory Proteins

Hemagglutinin Proteins

Non-Hemagglutinin Protein
BoTN-A Protein Comparison

**BOTOX**
- Ethanol Precipitation and Crystallization\(^1\)
- ~900 kD

**DYSPORT**
- Ion Exchange\(^2\)
- ~500 kD

**XEOMIN**
- Ion Exchange and pH Change\(^3,4\)
- ~300 kD
- 150 kD
- No Accessory Proteins
## Pivotal Study Doses

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*Dilution and dosage may vary as determined by clinician*

*Adjusting dose to target muscle mass may improve outcome and duration*
# Pivotal Study Doses

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BOTOX Pivotal Studies

50% of patients maintain improvement at 3 months
DYSPORT Pivotal Studies

40% - 50% of patients maintain 1-Grade improvement at 3 months

Improvement at every time point

GL-3 was a 6-month, single-dose, double-blind, multicenter, randomized, placebo-controlled study (N=300) to assess the safety and efficacy of 50 Units of Dysport vs placebo in subjects with moderate to severe glabellar lines at maximum frown. 60% (120/200) Dysport patients versus 0% treated with placebo met the primary endpoint.

Investigator and Subject Assessment of 1+ Grade Improvement in Glabellar Line Severity at Maximum Frown (Study GL-3)

Post-treatment Glabellar Line Severity of None or Mild with at Least a 1-Grade Improvement from Baseline

*p<0.001 for both investigator and subject assessments

GL-1 was a 6-month, single-dose, double-blind, multicenter, randomized, placebo-controlled study (N=150) to assess the safety and efficacy of 50 Units of Dysport vs placebo in subjects with moderate to severe glabellar lines at maximum frown. 55% percent (68/126) Dysport patients versus 0% treated with placebo met the primary endpoint.

Investigator and Subject Assessment of 1+ Grade Improvement in Glabellar Line Severity at Maximum Frown (Study GL-1)

Post-treatment Glabellar Line Severity of None or Mild with at Least a 1-Grade Improvement from Baseline

*p<0.05 for Days 14, 30, 60, 90, 120; p=NS* at Days 150 and 180

NS = Not statistically significant
15% - 25% of patients maintain 2-Grade improvement at 3 months.
BOTOX vs DYSPORT Dose

For cervical dystonia and blepharospasm

Mean Dose by Drug and Condition

Overall Mean Dose Ratio = 4.5 : 1

Patients within Each Ratio Group

Dose Ratio of Dysport® to BOTOX®
BOTOX vs DYSPORT Duration

Duration From a Double-Blind, Randomized, Parallel-Group Study

Incidence of at least 1-grade improvement from baseline in glabellar line severity at maximum contraction

Weeks

<table>
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<th>Patients (%)</th>
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<th>12</th>
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<td>BOTOX® Cosmetic (20 Units) (n = 31)</td>
<td>94% (29/31)</td>
<td>77% (24/31)</td>
<td>53% (16/30)</td>
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<td>Dysport® (50 Units) (n = 31)</td>
<td>97% (29/30)</td>
<td>59% (17/29)</td>
<td>28% (8/29)</td>
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P = .04

Lowe, J Am Acad Dermatol 2006
BOTOX vs XEOMIN Dose

Meta-analysis established 1:1 dose effectiveness but not duration

Relative Potency of IncobotulinumtoxinA vs OnabotulinumtoxinA
A Meta-Analysis of Key Evidence

Ravi Jandhyala MSc MBBS MRCS
Banbury Face Clinic, The Jandhyala Institute, Banbury, UK Consultant Pharmaceutical Physician, Medical Director, Latralis

ABSTRACT

Botulinum neurotoxin-A (BoNT-A) has become widely used in aesthetic applications over the past 20 years with several formulations now available. Although widely assumed to be equipotent, recent claims that the original commercial formulation, onabotulinumtoxinA (Botox®/Vistabel®, Allergan UK, Marlow, UK) is more potent than incobotulinumtoxinA (Bocouture®/Xeomin®, Merz Pharma, UK) have raised concerns that clinicians may be persuaded to increase doses to the potential detriment of their patients. To investigate this further, a review of the clinical evidence for the commercially available cosmetic formulations of BoNT-A was undertaken alongside a meta-analysis, carried out using mixed treatment analysis (MTA) methodology, of the available clinical data in the aesthetic setting. This demonstrated that at a dose of 24 units, there was a 94% likelihood that incobotulinumtoxinA was more effective than onabotulinumtoxinA in achieving a response as defined in the included studies; however, the scale of this advantage was not clinically meaningful. Of 11 clinical and preclinical studies identified comparing incobotulinumtoxinA and onabotulinumtoxinA directly, the weight of evidence suggested that there was no difference in the relative potency of the two products. As such, clinicians should continue to consider the formulations to be equipotent until such time that compelling clinical evidence to the contrary becomes available.

**DYSPORT**

- Don’t use in cow’s milk allergy
- May have greater diffusion area
  - Significant clinical effect?
  - Dilution and injection technique?
- May have more injection pain
  - Not significant clinical effect
  - Dilution and injection technique

**XEOMIN**

- Unreconstituted can store at room temperature
BoTN-A Resistance & Accessory Proteins

- Some patients develop less effect or nonresponse
- May be due to development of antibodies (Ab)
  - BoTN-A Ab very rare in cosmetic uses
  - Some secondary nonresponders don’t have measured Ab
  - Some patients have measured Ab and still respond
- XEOMIN has no accessory proteins
  - May induce less Ab formation
  - But accessory protein Ab may not effect BoTN-A itself
  - Antibodies directly against BoTN-A may effect result
Personal Experience

- Fastest time to onset: DYSPORT (1-3 days)
- Shortest duration: XEOMIN?
- Cost*: BOTOX > DYSPORT > XEOMIN
- Pain: Same (technique?)
- Spread: Same (dilution & technique?)

* Depends on dose & rebates
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- Dose: 1BOTOX = 1XEOMIN = 2 or 3DYSPORT

* Depends on dose & rebates
Personal Experience

• Accessory proteins  Do they matter?
• Interchangeable  Maybe (more similar than different)
• Split face  Not much difference
• Patient cross-over  Not much difference
• BOTOX non-responders  It’s the same molecule but worth a try?
In Your Practice

- Consider your overall BoTN-A usage
  - Other product lines & rewards programs
  - Time to educate patients
  - High volume users may allow for 2 or 3 products
  - Low volume users may have more product waste

- What are patients demanding?

- Patient perceived superiority or inferiority of product

- Consider XEOMIN for touch-ups (cost & duration)

- New products = new marketing opportunities
Applications
Observe Patient During Conversation

• Watch for expressions & muscle movements during a normal conversation
• More appropriate initially than treating exaggerated or extreme movements
Patient Education

• Explain what it can & what it can’t improve
• Introduce the “4 R’s”
  – Relax, Resurface, Refill, then Relift
New Patients

- Informed consent & “off-label” use
- Photo documentation
- Start with lowest doses needed
- Need for 2 week follow up visit
Product Dilutions

Assume vial with 100 units of BOTOX

- 1.0cc = 10u/0.1 cc
  
  Low injection volume limits diffusion (Glabella)
  More product waste

- 2.0 cc = 5u/0.1 cc

- 2.5 cc = 4u/0.1 cc

- 4.0 cc = 2.5u/0.1cc

  High injection volume increases diffusion (Forehead)
  Less product waste
Injection

Assume vial with 100 units of BOTOX

- 1.0 cc = 10u/0.1 cc

- 2.0 cc = 5u/0.1 cc

- 2.5 cc = 4u/0.1 cc

- 4.0 cc = 2.5u/0.1cc

0.3 cc insulin syringe with fixed 31G needle
Needle dulls after a few injections

1.0 cc syringe with removable 32G needle
(Less discomfort than 30G needle)
Injectable Product Worksheet

Patient: Jenny Smith  Date: 10/2/14  Injector: Karol A. Gutowski, MD

Allergy & Medical Update: None

Results after last injection: Loved it!

Neuromodulator

- Xeomin 100 U (1 ml), then, dilute 3:15 = 4 U/ml
- Dysport 10 U (0.1 ml)
- Xeomin 100 U (1 ml), then, dilute 3:15 = 4 U/ml
- Botox 100 U (0.5 ml)
- Xeomin 10 U (0.1 ml)
- Dysport 10 U (0.1 ml)
- Xeomin 100 U (1 ml), then, dilute 3:15 = 4 U/ml

Filler or Stimulator

- Artefill [A]
- Restylane [R]
- Bellafill [B]
- Pequal [P]
- Juvederm Ultra [U]
- Radiesse [R]
- Juvederm Ultra Plus [VP]
- Voluma [V]
- Sculptra [S]
- Xymansion [X]

Injection

- 32G Needle
- 27G Microcannula

Anesthetic

- 1:100,000 Lidocaine at injection sites
- Nerve block
- Topical
- Ice

Complications: None

Treatment outcomes:

Place Product Stickers Here

C 32 1578
Voluma 13-578

Additional Notes

F = 2u x 6 = 12u
Malar = 0.5 cc per side
May need more in 2 weeks
Injection Sites
Assume Botox Units & First Treatment
Bunny Lines
2 Units per Injection Site

2-4 injection sites

Procerus muscle
Nasalis muscles
Upper Lip Lines
2 Units per Injection Site

1-2 injection sites per side
Forehead
2 Units per Injection Site

3-5 injection sites per side
Avoid lower 1/3
Forehead
2 Units per Injection Site

3-5 injection sites per side
Avoid lower 1/3
Crow’s Feet & Laugh Lines
2 Units per Injection Site

2-3 injection sites per side
Lateral Brow Lift
2 Units per Injection Site

1 injection site per side
Glabella
4-5 Units per Injection Site

3 injection sites
Glabella
4-5 Units per Injection Site

5 injection sites
(More likely in men)
Masseter Hypertrophy
5-10 Units per Injection Site

2-3 injection sites per side
Lip Corner Elevation
3 to 5 Units per Injection Site

1 injection per side

Depressor anguli oris muscle
Gummy Smile
4-5 Units per Injection Site

1 injection per side

Levator labii superioris alaeque nasi muscle
Other lip elevators
Chin Dimples
4-5 Units per Injection Site

1 injection per side

Mentalis muscle
Platysmal Bands
4 Units per Injection Site

1 injection every 1-2 cm per side
Eyelid Ptosis Reversal

• Alpha-adrenergic agonist ophthalmic eye drops
  – Apraclonidine 0.5% (Iopidine)
  – Naphazoline (Naphcon)
  – Phenylephrine 2.5% (Myfrin)

• Stimulate Mueller’s muscle elevate ptotic eyelid
  – Typical 2 mm of lid elevation
Botulinum Neuromodulators: Clinical Data & Applications

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