Botulinum Neuromodulators: Clinical Uses

Karol A Gutowski, MD, FACS
Disclosures

Merz Aesthetics- Advisory Board
AxcelRx Pharmaceuticals - Advisory Board
Suneva Medical - Instructor

Will discuss off-label uses
Will use brand names for ease of understanding
Will refer to BOTOX Cosmetic as BOTOX
Objectives & Level of Evidence

• Understand differences between botulinum toxin A (BoTN-A) products for cosmetic indications
• Apply neuromodulators into clinical practice

Level of Evidence
Mostly I - III
Some personal experience
BoTN-A Product Information

FDA Approved

• BOTOX Cosmetic – OnabotulinumtoxinA
  – VISTABEL, VISTABEX
• DYSPORT – AbobotulinumtoxinA
  – AZZALURE
• XEOMIN – IncobotulinumtoxinA
  – XEOMEEN, BOCOUTURE, NT201
BoTN-A Product Information

Not FDA Approved

• MYOBLOC - \textbf{Rima}botulinumtoxinB
• NEURONOX - Botulinum toxin A
  – MEDITOXIN, BOTULIFT
• REDUX - Botulinum toxin A
  – PROSIGNE, LANTOX
• RT001- Botulinum toxin A (Topical)
• RT002 - Botulinum toxin A
FDA Cosmetic Approval

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

• **DYSPORT** [Galderma]
  – 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
BoTN - A Mechanism of Action

- 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, and 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.

**Mechanism of Action**

*Types A and B bind to distinct acceptors*
- Botulinum Type A cleaves SNAP-25
- Botulinum Type B cleaves synaptobrevin (VAMP)
## Product Comparison

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<sup>*</sup>HSA = Human Serum Albumin

<sup>x</sup>Protein concentration based on a 100U vial.
BoTN-A Molecule

BoTN-A

BoTN-A + Accessory Proteins

Hemagglutinin Proteins

Non-Hemagglutinin Protein
BoTN-A Protein Comparison

**BOTOX**
- Ethanol Precipitation and Crystallization
  - ~900 kD

**DYSPORT**
- Ion Exchange
  - ~500 kD
  - ~300 kD

**XEOMIN**
- Ion Exchange and pH Change
  - 150 kD
  - No Accessory Proteins
# Pivotal Study Doses

<table>
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<th>BotN-A</th>
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<th>Glabella</th>
<th>Duration</th>
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<td>4u/0.1 cc</td>
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Dilution and dosage may vary as determined by clinician

Adjusting dose to target muscle mass may improve outcome and duration
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*Dilution and dosage may vary as determined by clinician*

Adjusting dose to target muscle mass may improve outcome and duration
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
DYSPORT Dose Response

Efficacy and Safety of Botulinum Toxin Type A in the Treatment of Lateral Crow's Feet: Double-Blind, Placebo-Controlled, Dose-Ranging Study

Benjamin Ascher, MD,*, Berthold J. Rzany, MD, ScM,† and Rajiv Grover, BSc, MB, BS, MD, FRCS (Plast)‡

30U & 45U better than 15U
DYSPORT Dose Response

Patient satisfaction similar at all doses
DYSPORT Dose Response

Older patients less likely to respond
XEOMIN Pivotal Studies

15% - 25% of patients maintain 2-Grade improvement at 3 months.
XEOMIN Phase 3 Post Hoc Analysis

- Issue of 1 vs 2 point clinical response
- 20u divided in 5 glabella sites
- Response no worse (or better) than Botox

Efficacy of IncobotulinumtoxinA for Treatment of Glabellar Frown Lines: A Post Hoc Pooled Analysis of 2 Randomized, Placebo-Controlled, Phase 3 Trials

Derek Jones, MD,* Jean Carruthers, MD,† Rhoda S. Narins, MD,‡ William P. Coleman, III, MD,§ Laura Harrington, PhD,‖ Fredric S. Brandt, MD,¶ and Joel L. Cohen, MD*
A Prospective Rater- and Subject-Blinded Study Comparing the Efficacy of IncobotulinumtoxinA and OnabotulinumtoxinA to Treat Crow's Feet: A Clinical Crossover Evaluation

Gabriele Muti, MD,* and Laura Harrington, PhD†
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.

BOTOX vs XEOMIN

A Prospective, Split-Face, Randomized, Double-Blind Study Comparing OnabotulinumtoxinA to IncobotulinumtoxinA for Upper Face Wrinkles

Ruth Hill Yeilding, M.D.
John P. Fezza, M.D.
Winter Park and Sarasota, Fla.

Background: The authors sought to compare the newest U.S. Food and Drug Administration-approved botulinum toxin type A product, incobotulinumtoxinA, to onabotulinumtoxinA for upper face wrinkles. This is the first prospec-

Statistically Significant
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

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<td>8</td>
<td>94% (29/31)</td>
<td>77% (24/31)</td>
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<td>12</td>
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<tr>
<td>16</td>
<td>53% (16/30)</td>
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P = .04

Lowe, J Am Acad Dermatol 2006
A Quantitative Analysis of OnabotulinumtoxinA, AbobotulinumtoxinA, and IncobotulinumtoxinA: A Randomized, Double-Blind, Prospective Clinical Trial of Comparative Dynamic Strain Reduction

Anthony J. Wilson, M.D.
Brian Chang, B.S.
Anthony J. Taglianti, M.D.
Blanca C. Chin, M.D.
Catherine S. Chang, M.D.
Nancy Folsom, R.N.
Ivona Perecic, M.D., Ph.D.

Background: U.S. Food and Drug Administration–approved formulations of botulinum toxin include onabotulinumtoxinA (Botox; Allergan, Inc., Irvine, Calif.), abobotulinumtoxinA (Dysport; Galderma Pharma S.A., Lausanne, Switzerland), and incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany). This study uses digital image correlation to compare dynamic strain reduction between available neurotoxins.

Methods: Seventy-three treatment-naive female patients aged were random-
Muscle Strain Reduction

- **Botox**: 43.5%
- **Dysport**: 38.4%
- **Xeomin**: 25.3%

Day 90
“There is insufficient evidence demonstrating an increased duration of benefit of any one medication relative to its competitors”
Fields of Effect

Fields of Muscular and Anhidrotic Effects of 2 Botulinum Toxin-A Commercial Preparations: A Prospective, Double-Blind, Randomized, Multicenter Study

Doris Hexsel, MD, *‡ Mariana Soirefmann, MD, MS, *‡ Manoela D. Porto, MD, *
Carolina Siega, BSc, * Juliana Schilling-Souza, BPharm, *
and Ticiana C. Rodrigues, MD, PhD *‡

- DYSPORT greater anhidrotic effect than XEOMIN
- Similar muscular effects by EMG
Unique Characteristics

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
BoTN-A Nonresponders

Clinical resistance to three types of botulinum toxin type A in aesthetic medicine

Farid Stephan, MD, Maya Habre, MD, & Roland Tomb, MD, PhD
Faculty of Medicine, Saint Joseph University, Beirut, Lebanon

- True nonresponders are rare
- May have antibodies to BoTN-A
  - Presence of antibody ≠ no response
  - Absence of antibody ≠ response
- Antibodies may disappear over time
- May respond to BoTN-B (Myobloc)
  - Acts on synaptobrevin (not SNAP-25)
Zinc Supplementation to Increase Duration

- Double-blinded, placebo-controlled cross-over study
- Inclusion: “Hard to Treat” patients
- BOTOX, DYSPORT, XEOMIN

- BoTN-A is zinc dependent
- Phytates block zinc absorption
Zinc Supplementation to Increase Duration

- 92% of patients reported 30% increase in duration
- Older patients
  - Greater improvement
  - No increase in duration

- Zytase $40 per treatment
Can I Really Store BoTN-A for 4 Weeks?

- Literature review & 2 round Delphi process
- Can be refrigerated or refrozen for 4 weeks
- Can use on multiple patients (proper handling)
Selective eyebrow depressors cannot be targeted due to BoTN diffusion radius
BoTN-A 44 yo Twins Case Report

Regular BoTX-A injections every 4 to 6 months for 19 years

4 BoTX-A injections over 19 years

Regular BoTN-A treatments may prevent long-term skin changes
Personal Experience

- Fastest time to onset:  
  DYSPORT (1-3 days)
Personal Experience

- Fastest time to onset: DYSPORT (1-3 days)
- Duration: Equal
Personal Experience

- Fastest time to onset: DYSPORT (1-3 days)
- Duration: Equal
- Cost*: BOTOX > DYSPORT > XEOMIN

* Depends on dose & rebates
<table>
<thead>
<tr>
<th>Feature</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Pain</td>
<td>Same (technique?)</td>
</tr>
<tr>
<td>Spread</td>
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</tbody>
</table>

* Depends on dose & rebates
Personal Experience

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

* 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

• New products = new marketing opportunities
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
Although clinical trials have emphasized the efficacy of the drug with full doses, the frozen and nonmovement of the glabella and upper face including brows is nondesirous for most of our patients today. Thus, the full dosage of 20–30 units of onabotulinum/inciprotulin toxin or 50–60 units of abobotulinum toxin can be reduced to allow movement and expression. This makes it the physician’s responsibility to evaluate the patient at rest and with full movement of the upper facial units. This is accomplished with trial treatments.
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

• 1.0 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

Low injection volume limits diffusion (Glabella)
More product waste

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

Assume vial with 100 units of BOTOX

• 1.0 cc = 10 u/0.1 cc

• 2.0 cc = 5 u/0.1 cc

• 2.5 cc = 4 u/0.1 cc

• 4.0 cc = 2.5 u/0.1 cc

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)
Document the Treatment
Jenny Smith

10/2/14

None

Loved it!

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
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
Forehead

2 Units per Injection Site

16 to 20 units

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
Crow’s Feet & Laugh Lines
2 Units per Injection Site

2-3 injection sites per side
Crow’s Feet & Laugh Lines
Limitations due to Contributing Muscle Groups

Recognize contribution of zygomaticus muscles
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

3-5 injection sites
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

Smith, ASJ 2014
Masseter Hypertrophy
5-10 Units per Injection Site

Avoid medial injection to risorius muscle

Smith, ASJ 2014
Lip Corner Elevation
3 to 5 Units per Injection Site

Inject lateral to commissure to avoid central lip depression

*Smith, ASJ 2014*
Gummy Smile
4-5 Units per Injection Site

1 injection per side

Levator labii superioris alaeque nasi muscle
Other lip elevators

Smith, ASJ 2014
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
Platysmal Bands
4 Units per Injection Site

1 injection every 1-2 cm per side
Annoying Platysma

Loose Neck Skin
Annoying Platysma

Loose Neck Skin

After External Radiofrequency Skin Tightening
Annoying Platysma

Loose Neck Skin

After External Radiofrequency Skin Tightening
Annoying Platysma

Loose Neck Skin

Active Medial Platysmal Band
Annoying Platysma
Eyelid Ptosis Reversal

- Alpha-adrenergic agonist ophthalmic eye drops
  - Apraclonidine 0.5% (Iopidine)
  - Naphazoline (Naphcon)
  - Phenylephrine 2.5% (Myfrin)
- Stimulate Mueller’s muscle to elevate ptotic eyelid
  - Typical 2 mm of lid elevation
BoTN-A & the Four R’s

- **Relax** the muscle: BoTN-A
- **Refill** the face (volume): Fillers
- **Resurface** the skin: Lasers
  - Fractional CO$_2$
- **Relift** the tissue: Energy-based
  - Ultherapy
  - Neck laser-assisted liposuction
Aesthetic Uses of Neuromodulators: Current Uses and Future Directions

Michael S. Gart, MD
Karol A. Gutowski, MD
Chicago, Ill.

**Background:** The introduction of neuromodulators for aesthetic facial improvements greatly expanded the limits of nonsurgical facial rejuvenation. Although many current uses are considered “off-label,” the widespread acceptance and favorable safety profile of properly used botulinum toxins have made them one of the most common aesthetic treatments available.
All 3 type toxins act the same way
• Other 6 types (B-G) are not the same
• Complexing proteins dissociate at physiologic pH
Effects depend on kinetic relationship between BoTN-A & receptors
• Units are standard based on mouse LD$_{50}$ but not the same between 3 toxin types based on mg or number of molecules
• XEO:BTX is 1:1 but DYS:BTX may be 3:1 to 2:1
BoTN-A Clinical Postulates

The Use of Botulinum Neurotoxin Type A in Aesthetics: Key Clinical Postulates

Mark S. Nestor, MD, PhD, † Raymond E. Kleinfelder, DO, ‡ and Andy Pickett, PhD

• Muscle mass, age, gender affect BoTN-A response
• DYS has faster onset then BTX
• Dose affects time to onset & duration – to a point, then higher risk of adverse events
• Dilution affects results (in forehead)
• More injection points improve results (in forehead)
Botulinum Neuromodulators: What’s New?

Karol A Gutowski, MD, FACS
Laser Transcutaneous Delivery

Prospective Randomized Controlled Study to Determine the Effect of Topical Application of Botulinum Toxin A for Crow's Feet After Treatment With Ablative Fractional CO₂ Laser

Bassel H. Mahmoud, MD, PhD, Christopher Burnett, MD, and David Ozog, MD*

- Dysport 100U to treatment area
- Improved lateral lines
Nabota (DWP450)

Comparative trial of a novel botulinum neurotoxin type A versus onabotulinumtoxinA in the treatment of glabellar lines: A multicenter, randomized, double-blind, active-controlled study

Chong Hyun Won¹, MD, PhD, Hyun Kyu Kim², MD, Beom Joon Kim², MD, PhD, Hoon Kang³, MD, PhD, Joon Pio Hong⁴, MD, PhD, Su-Young Lee⁵, BS, and Chung-Sei Kim⁵, PhD

Daewoong, Korea

- EVOSYAL in USA
- >98% pure (Botox 95% pure)
- 84% had onset within 2 days
- Similar adverse events profile
- In FDA approval process
Nabota (DWP450)
Chinese BoTN-A

- CBoTN-A (aka Hengli BoTN-A, HBoTN-A)
- Greater diffusion area than BOTOX
  - Based on forehead anhidrosis test
- Possible longer duration than BOTOX
- Glabella: 20U > duration than 10U
RT001: Topical BoTN-A

- Revance developed mechanism to allow transepidermal transfer of large molecules
- Supplied as lyophilized 150kD BoTN-A + proprietary peptide
- Reconstituted with poloxamer diluent
- Gels on contact with skin
- Removed after 30 min
RT001 Lateral Canthal Lines

- 45 patients in each arm
- ≥ 2 point improvement
- At 4 weeks
  - 44% ≥ 2 point improvement
  - 89% clinically relevant improvement
RT001: 4 Week Response

Investigator

Patient
RT001: Topical BoTN-A

- No related adverse events
- No evidence of spread beyond treatment area
- 13 clinical trials in 1400 patients
- In Phase 3 trials in USA
RT001: Topical BoTN-A

• Potential advantages in
  – Hyperhidrosis
  – Forehead
  – Lateral orbit
  – Platysma

• Less likely in
  – Lower ½ of face
RT001: Topical BoTN-A
Safety and Efficacy of RT002, an Injectable Botulinum Toxin Type A, forTreating Glabellar Lines: Results of a Phase 1/2, Open-Label, Sequential Dose-Escalation Study

Enrique Garcia-Murray, MD,* María Luisa Velasco Villasenor, MD,† Berenice Acevedo, MD,* Silvia Luna, MD,* Jane Lee, BS,‡ Jacob M. Waugh, MD,‡ and Carl S. Hornfeldt, PhD‡

• Less BoTN-A spread
• Allows greater injection
  – Possible longer duration?
• TransMTS Peptide
• Remains in targeted area
• Limits spread

• Response (Investigator & Patient)
  – 100% maintained at 6 months
  – 50% maintained ≥ 7 months
Neuromodulator Alternatives

ThermiRase
Radiofrequency nerve ablation
Neuromodulator Alternatives

Cryoneuromodulation
(Temporary neuropraxia)

- 20 patients
  - All showed immediate reduction in frontalis dynamic lines
- 75% continued 1 point reduction in wrinkle severity at 30 days
- 50% positive response at 60 days
- No severe adverse events

*AJ Burns ASAPS 2012*
Botulinum Neuromodulators: Clinical Uses

Karol A Gutowski, MD, FACS

DrGutowski.com ➔ For Physicians
Add Lori Filler Jelly Roll