Nonsurgical Facial Rejuvenation: Botulinum Neuromodulators

Karol A Gutowski, MD, FACS

Disclosures

RTI Surgical - Advisor

Suneva Medical - Instructor

Angiotech/Surgical Specialties - Advisory Board

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* – **Ona**botulinumtoxin**A**
  - VISTABEL, VISTABEX
- DYSPORT – **Abo**botulinumtoxin**A**
  - AZZALURE
- XEOMIN – **Inco**botulinumtoxin**A**
  - XEOMEEN, BOCOUTURE, NT201

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

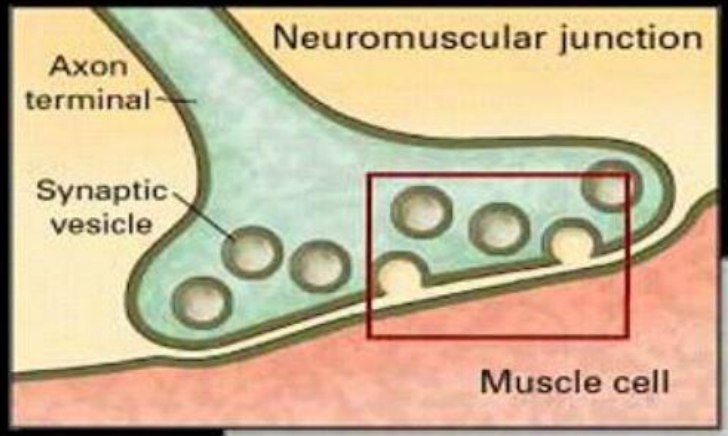
- BoTN-A binds to cholinergic nerve terminals
- Internalized into nerve
- Light-chain translocated into nerve cytosol
- Enzymatic cleavage of SNAP-25 (essential for ACh release)
- Impulse transmission re-established by formation of new nerve endings

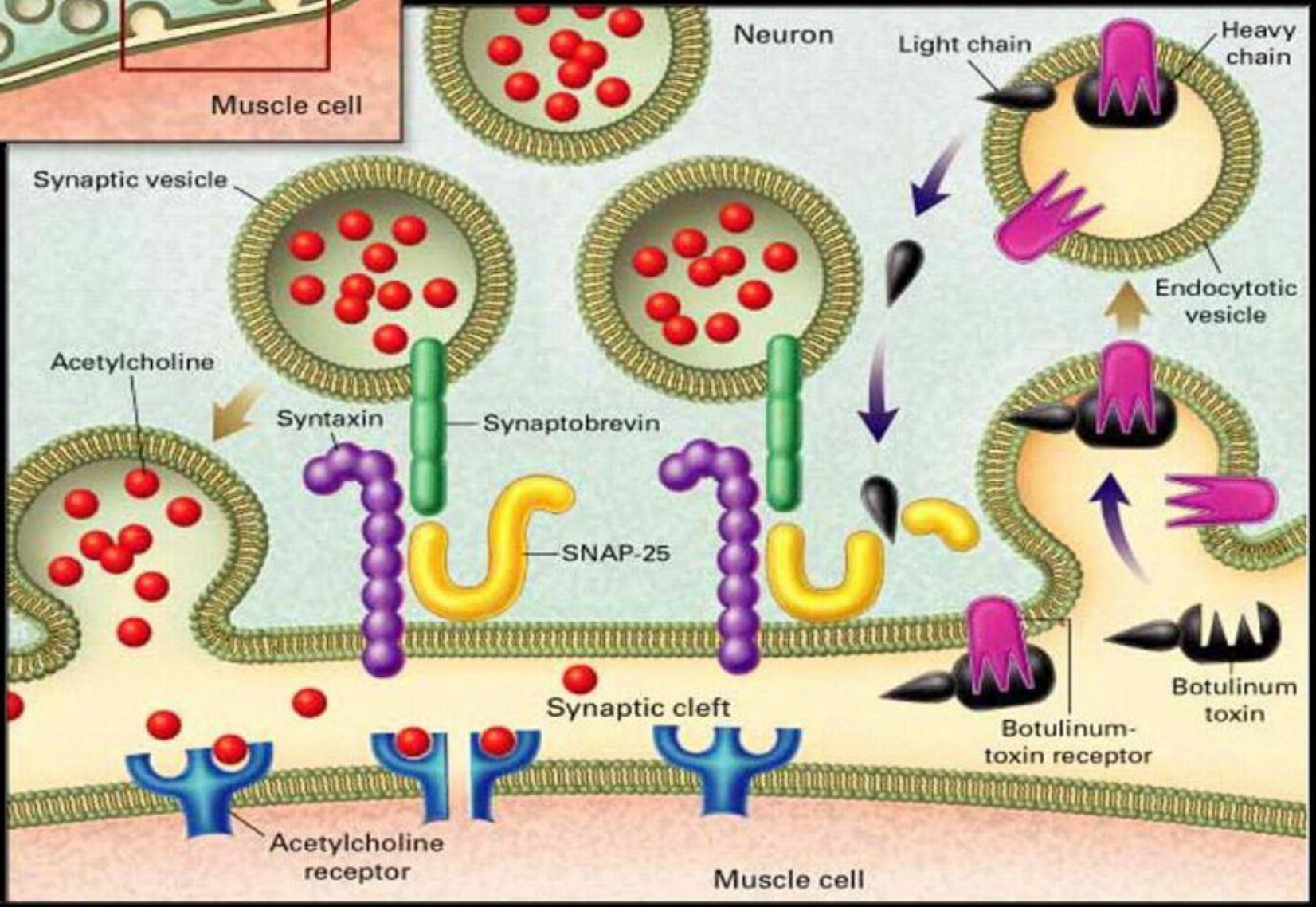
Mechanism of Action

Types A and B bind to distinct acceptors

Botulinum Type A cleaves SNAP-25

Botulinum Type B cleaves synaptobrevin (VAMP)





Hallett *NEJM* 1999;341 (2): 118

Product Comparison

	BOTOX® Cosmetic[1]	*DYSPORT®*[2]	*XEOMIN®*[3]
Non-Proprietary Name	**onabotulinumtoxinA**	**abobotulinumtoxinA**	**incobotulinumtoxinA**
First Approval	• 1989 (US)	• 1991 (UK)	• 2005 (Germany)
Serotype	• A	• A	• A
Strain	• Hall (Allergan)	• Hall¥	• Hall
Receptor/Target	• SV2/SNAP-25	• SV2/SNAP-25	• SV2/SNAP-25
Process	• Crystallization	• Chromatography	• Chromatography
Complex Size **Uniformity**	• ~900 kD* • Homogeneous	• ≤ 500 kD^ • Heterogenous	• 150 kD • Homogeneous
Excipients(Inactive ingredients) HAS = Human Serum Albumin	• HSA: 500 µg (100U vial) • Sodium chloride	• HSA:125 µg (300, 500U vial) • Lactose	• HSA: 1 mg (50, 100U vial) • Sucrose
Stabilization **Solubilization**	• Vacuum drying • Normal saline	• Lyophilization • Normal saline	• Lyophilization • Normal Saline
Unitage (U/Vial)	• 100, 200	• 300, 500	• 50, 100
Protein (ng/Vial)	• 5 (100U vial)	• 4.35¥ (500U vial)	• 0.6 (100U vial)

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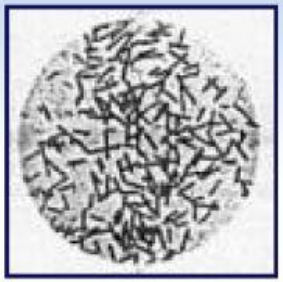
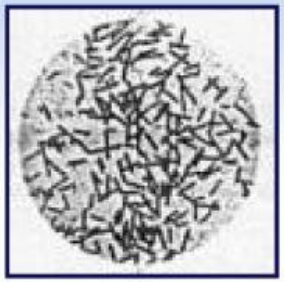
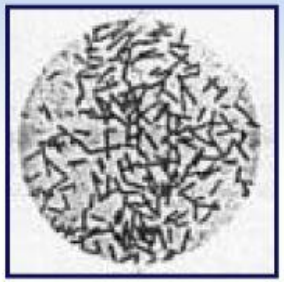
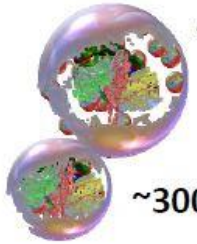
BoTN-A Protein Comparison

BOTOX	DYSPORT	XEOMIN
		
Ethanol Precipitation and Crystallization[1]	Ion Exchange[2]	Ion Exchange and pH Change[3,4]
		
~900 kD	~500 kD ~300 kD	150 kD
		No Accessory Proteins

Pivotal Study Doses

BoTN-A	Dilution	Glabella	Duration
BOTOX	4u/0.1 cc	4 u at 5 sites	3-4 months
DYSPORT	10u/0.08 cc	10 u at 5 sites	3-4 months
XEOMIN	4u/0.1 cc	4 u at 5 sites	3 months

Dilution and dosage may vary as determined by clinician

Adjusting dose to target muscle mass may improve outcome and duration

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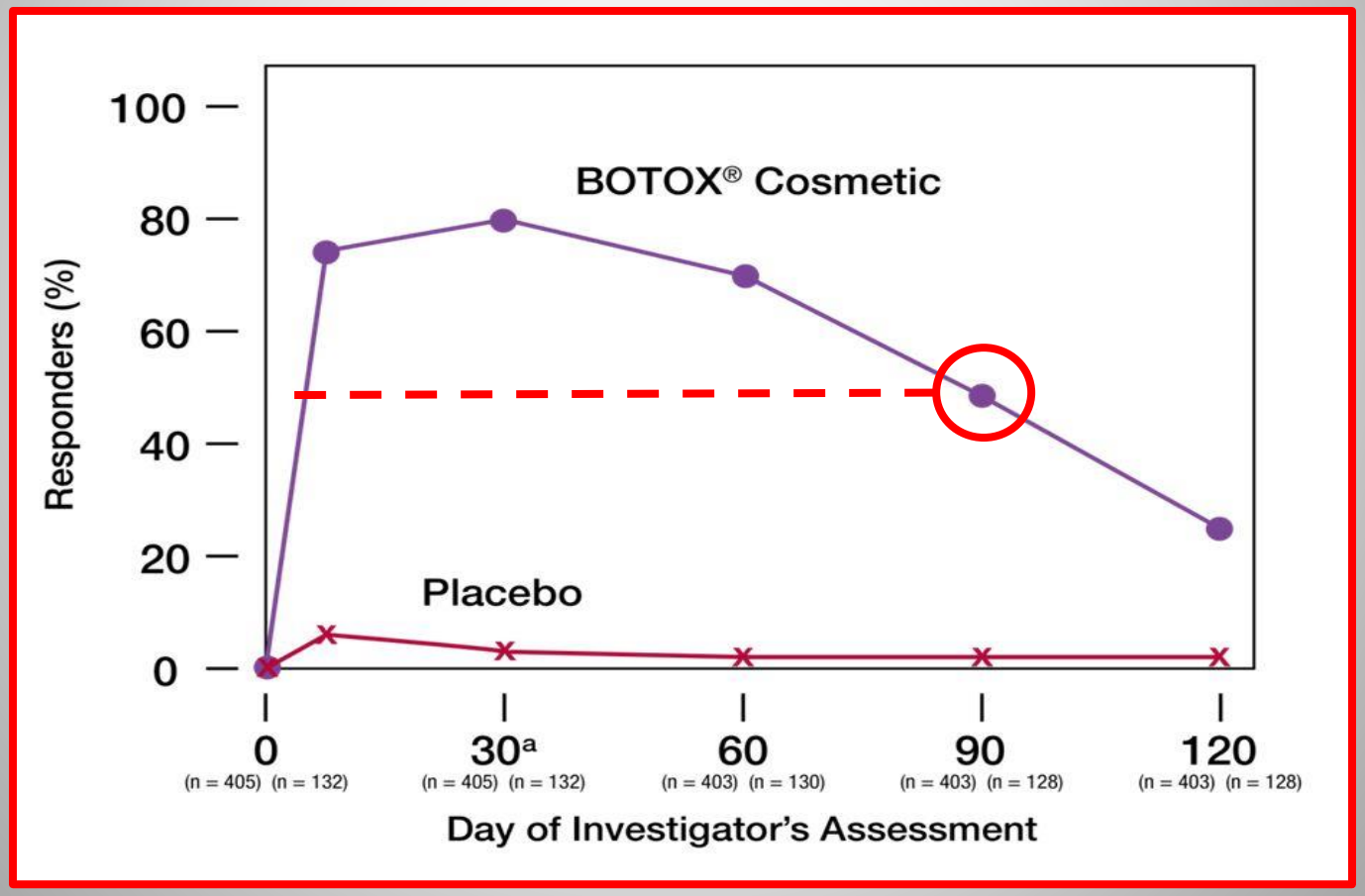
BOTOX Pivotal Studies

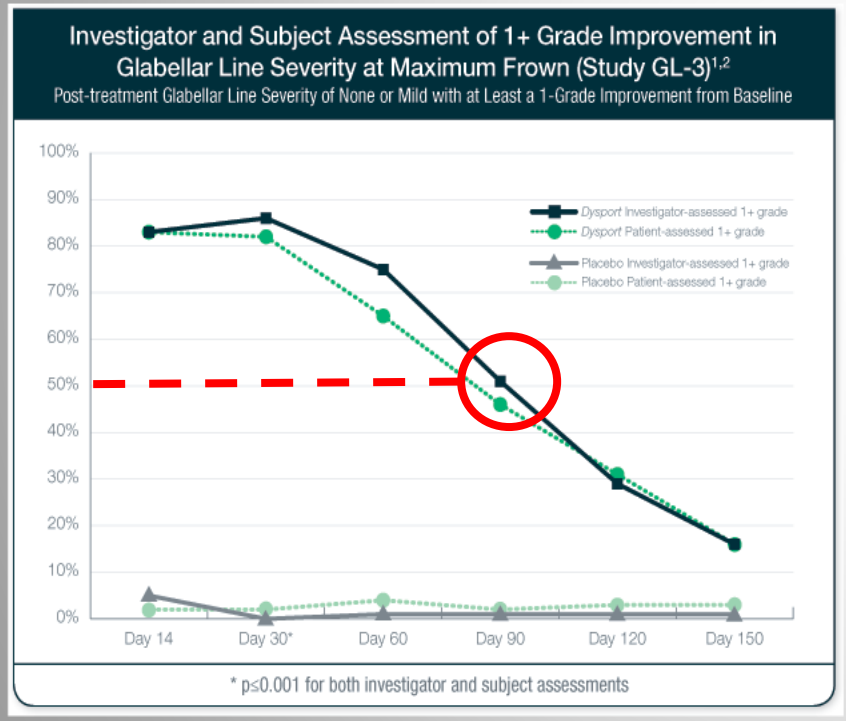
50% of patients maintain improvement at 3 months



DYSPORT Pivotal Studies

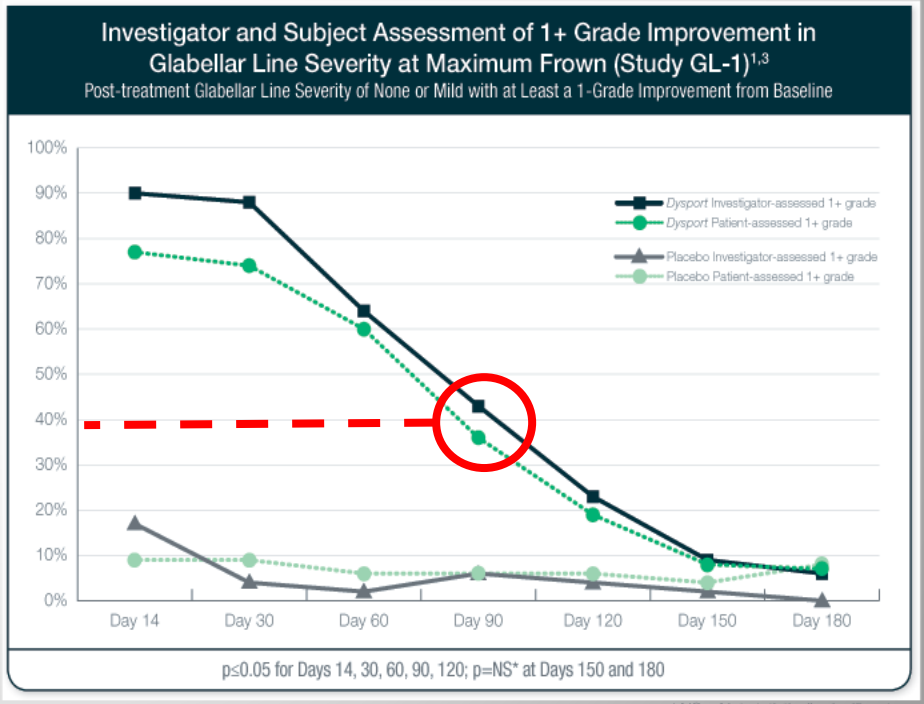
40% - 50% of patients maintain <u>1-Grade</u> improvement at 3 months

Improvement at every time point[2]



GL-3 was a 5-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.[1] 60% (120/200 *Dysport* patients versus 0% treated with placebo) met the primary endpoint.

Improvement demonstrated for up to 4 months[3]



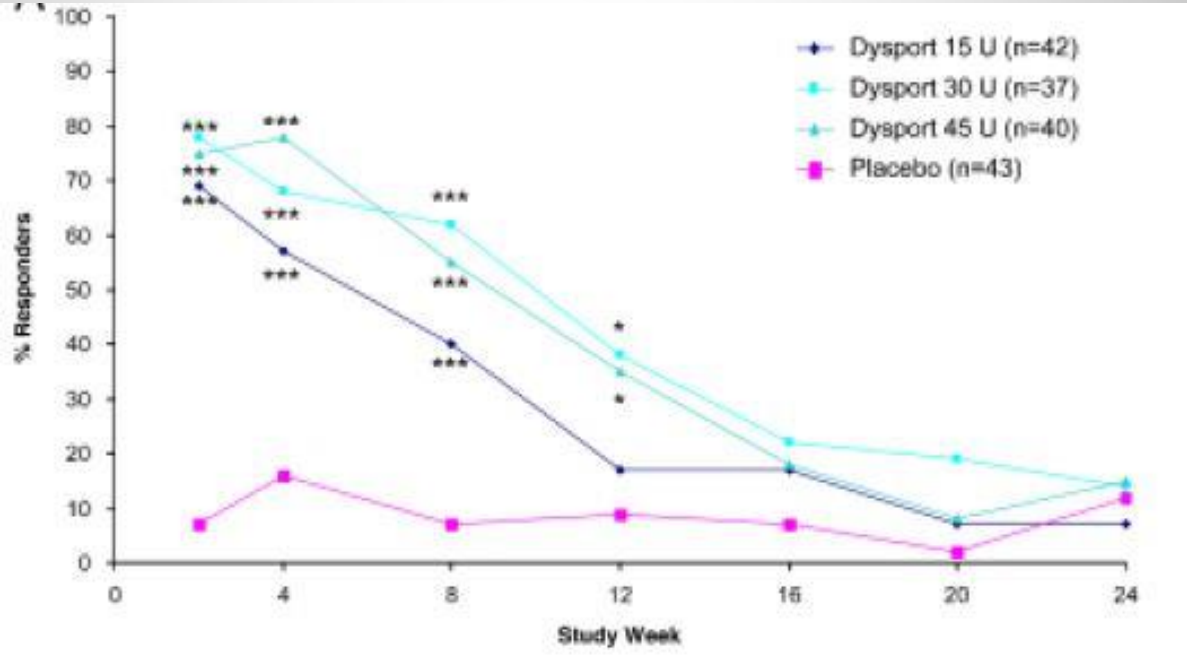
* NS = Not statistically significant

GL-1 was a 6-month, single-dose, double-blind, multicenter, randomized, placebo-controlled study (N=158) to assess the safety and efficacy of 50 Units of *Dysport* vs placebo in subjects with moderate to severe glabellar lines at maximum frown.[1] 55% percent (58/105 *Dysport* patients versus 0% treated with placebo) met the primary endpoint.

Dysport Dose Response

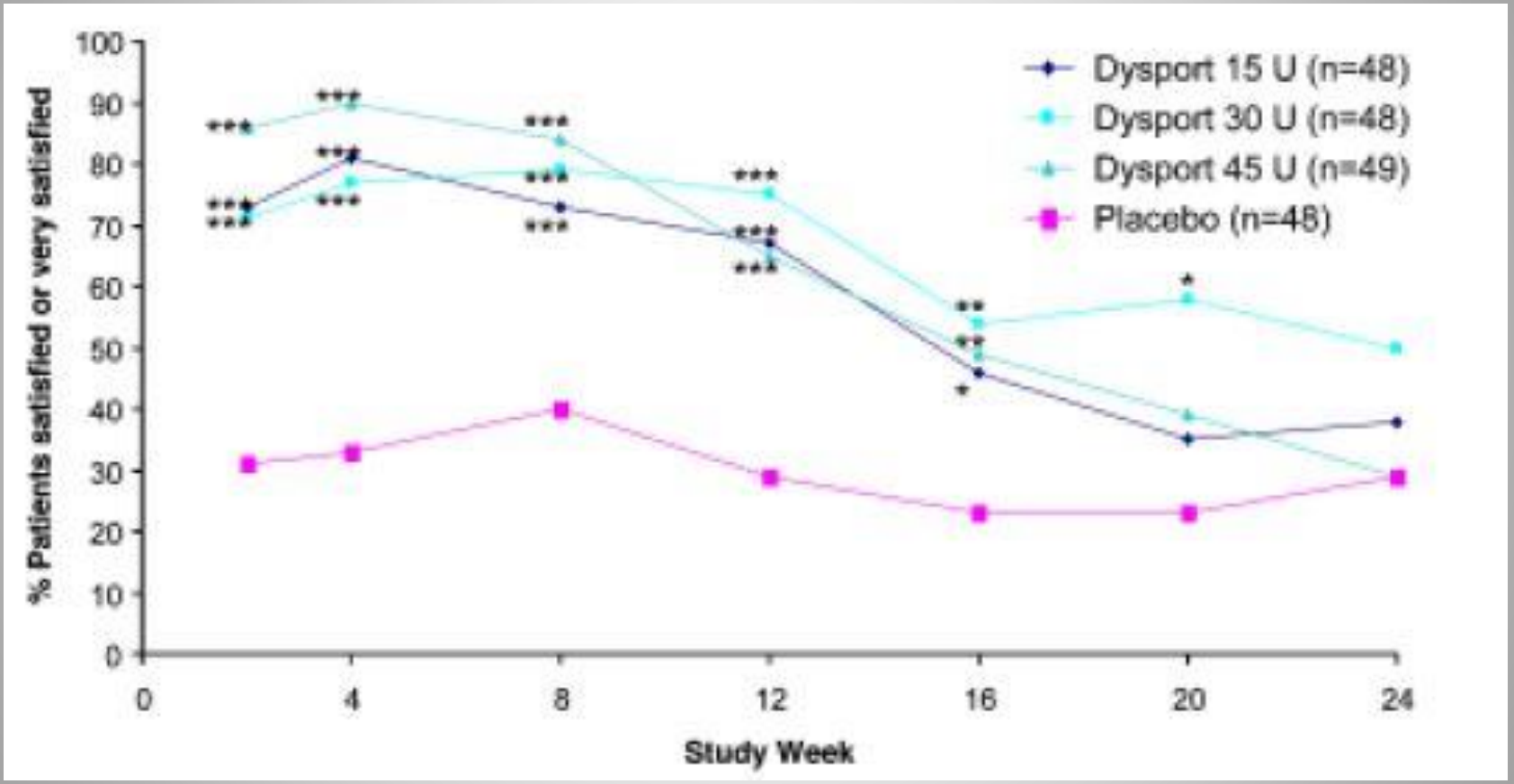
Efficacy and Safety of Botulinum Toxin Type A in the Treatment of Lateral Crow's Feet: Double-Blind, Placebo-Controlled, Dose-Ranging Study

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



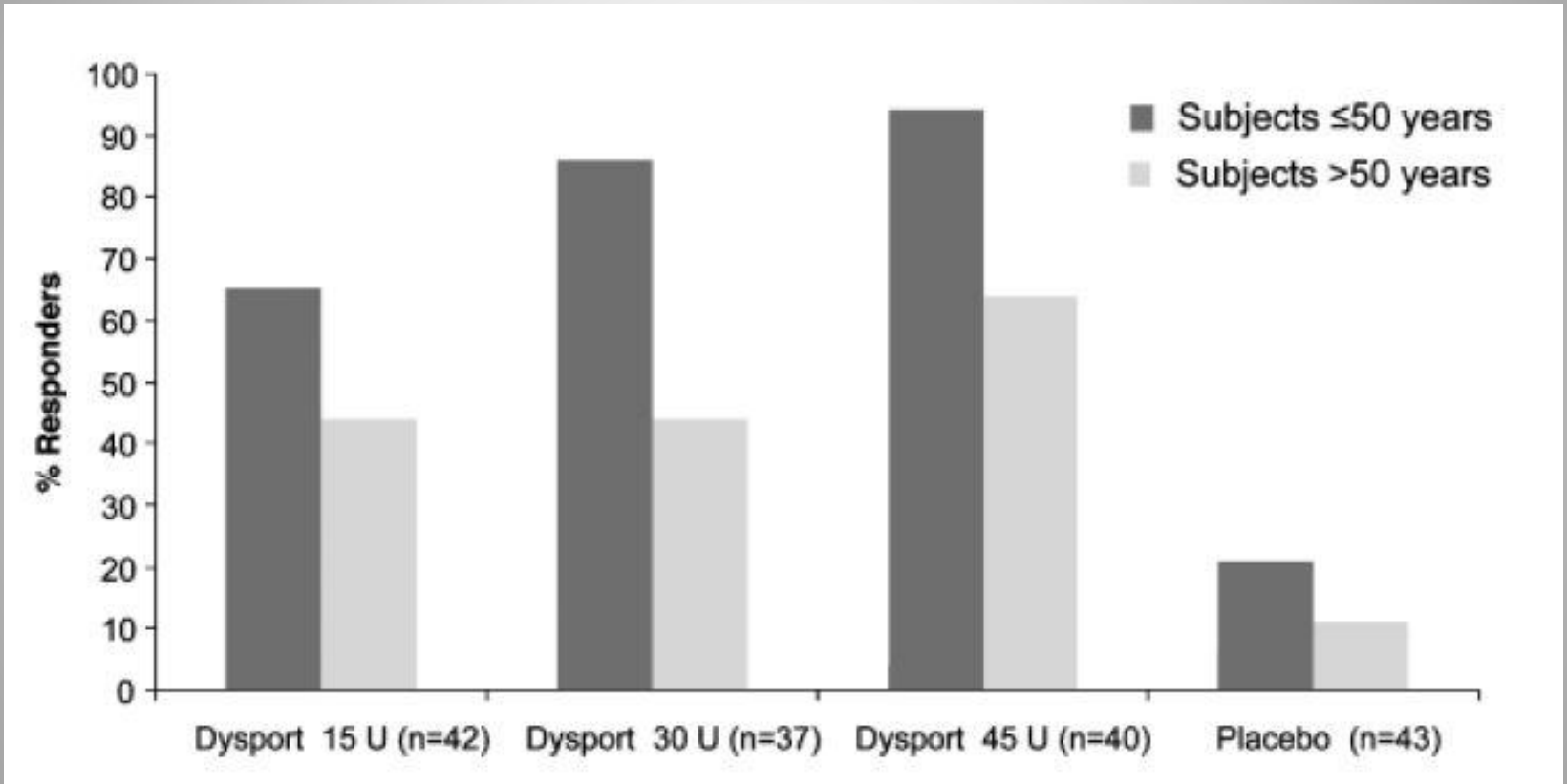
30U & 45U better than 15U

Dysport Dose Response



Patient satisfaction similar at all doses

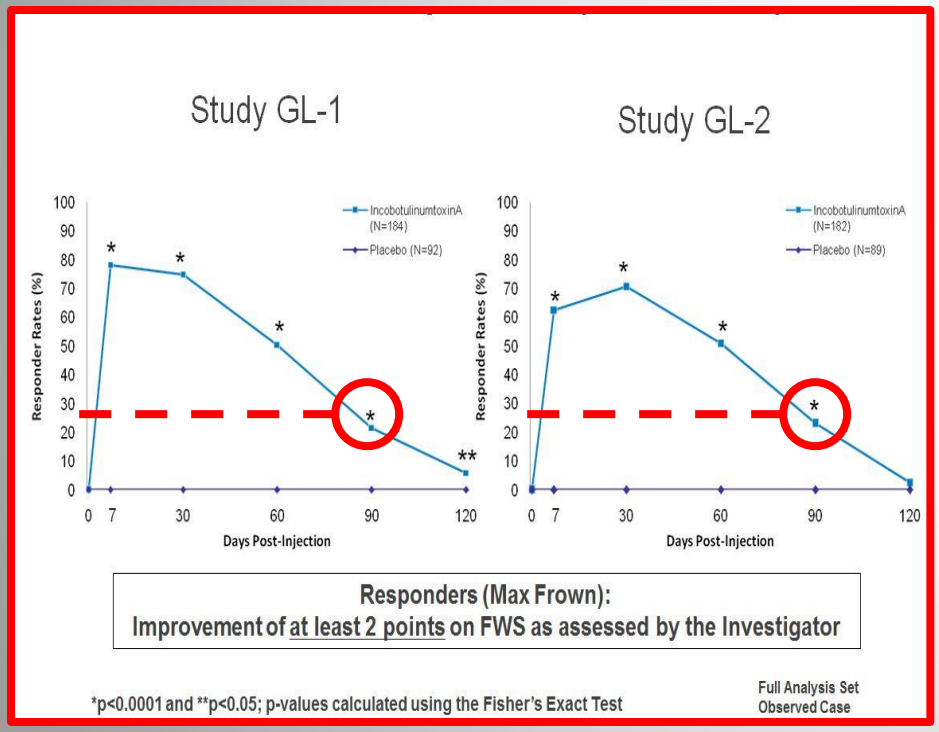
Dysport Dose Response

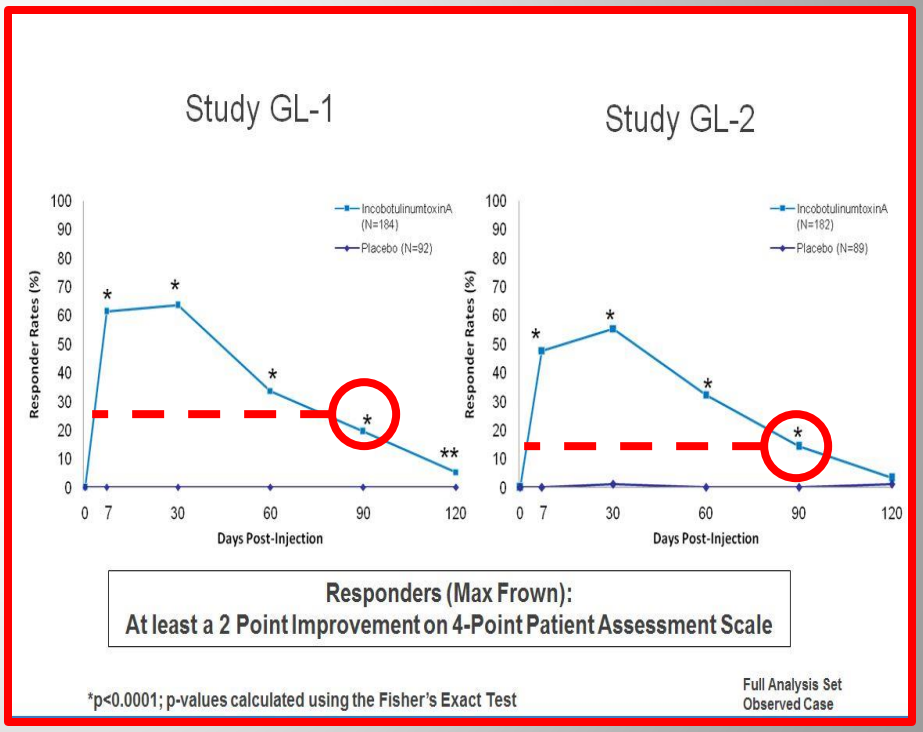


Older patients less likely to respond

XEOMIN Pivotal Studies

15% - 25% of patients maintain <u>2-Grade</u> improvement at 3 months



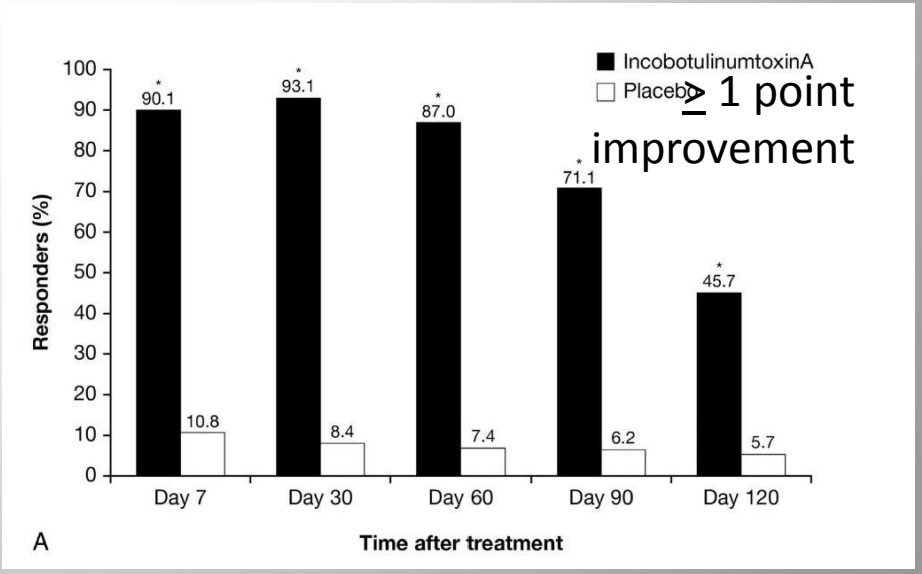


Xeomin Phase 3 Post Hoc Analysis

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#

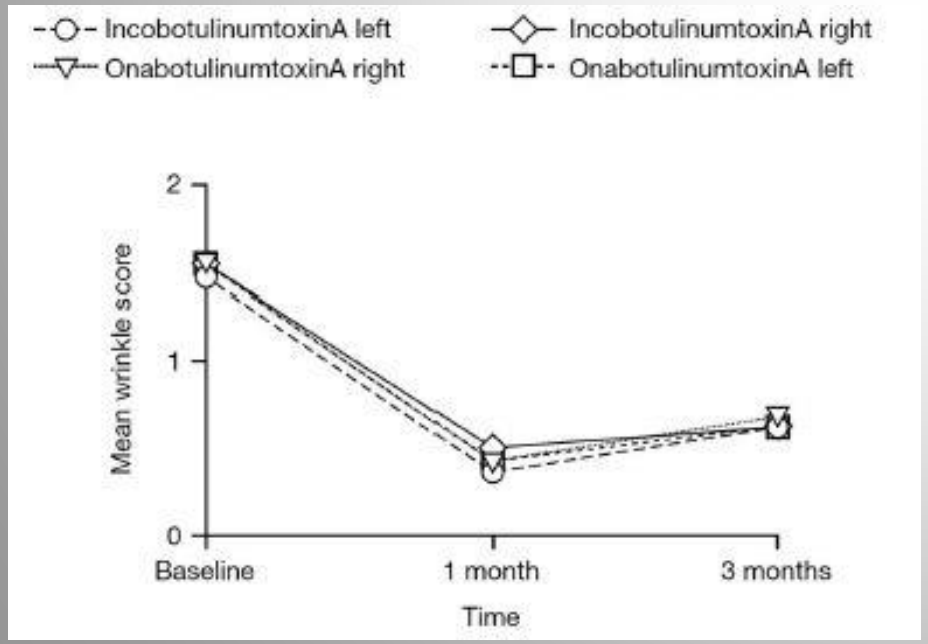
- Issue of 1 vs 2 point clinical response
- 20u divided in 5 glabella sites
- Response no worse (or better) than Botox

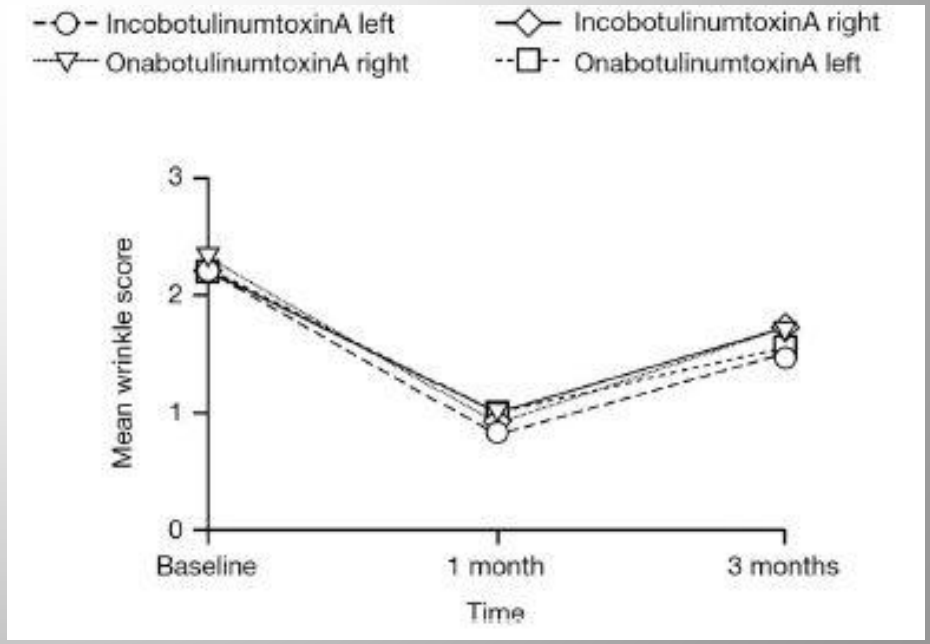


Xeomin vs Botox

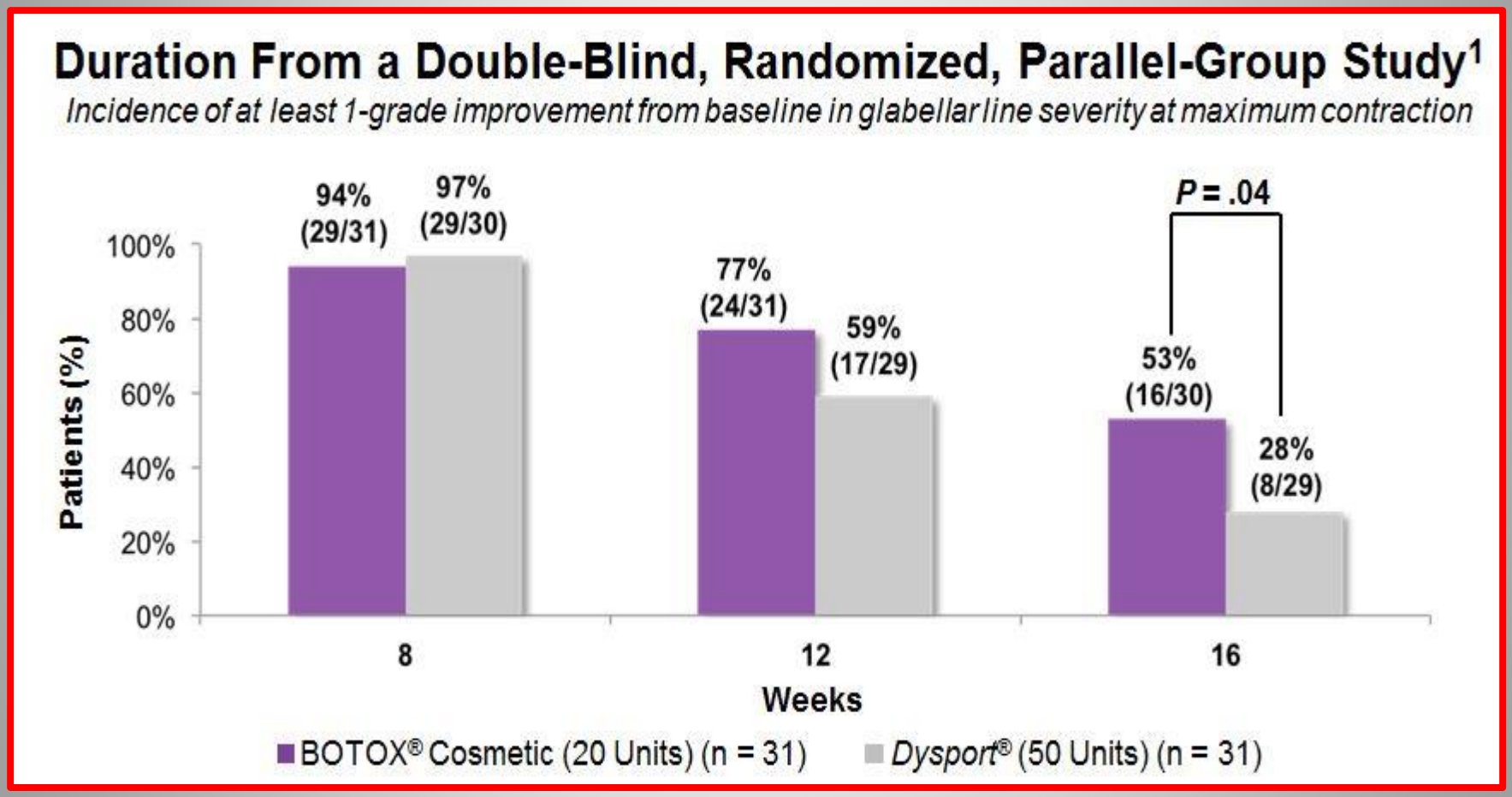
A Prospective Rater- and Subject-Blinded Study Comparing the Efficacy of IncobotulinumtoxinA and OnabotulinumtoxinA to Treat Crow's Feet: A Clinical Crossover Evaluation

GABRIELE MUTI, MD,* AND LAURA HARRINGTON, PHD†





BOTOX vs DYSPORT Duration



Lowe, J Am Acad Dermatol 2006

BOTOX vs XEOMIN Dose

Meta-analysis established 1:1 dose <u>effectiveness</u> but <u>not duration</u>

JUNE 2012 731 VOLUME 11 • ISSUE 6

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

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.

J Drugs Dermatol. 2012;11(6):731-736.

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

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

Personal Experience

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

* 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**	**1BOTOX = 1XEOMIN = 3DYSPORT**

* Depends on dose & rebates

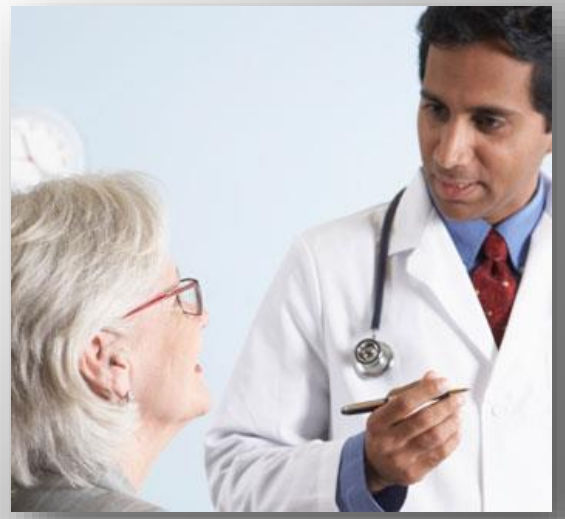
Personal Experience

• 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?

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

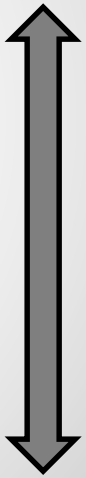
- Explain what it can & what it can't improve
- Introduce the "4 R's"
  - Relax, Resurface, Refill, then Relift

Product Dilutions

Assume vial with 100 units of BOTOX

- 1.0cc = 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



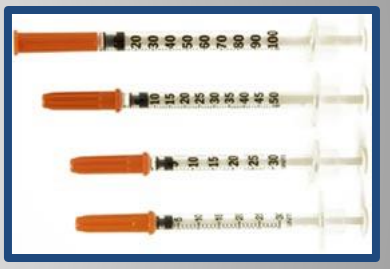
High injection volume increases diffusion (Forehead)
Less product waste

Injection

Assume vial with 100 units of BOTOX

- 1.0cc = 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)

Document the Treatment

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

X BOTOX Dilution A X U/0.1 mL Dilution B ___ U/0.1 mL
__ DYSPORT Dilution A ___ U/0.1 mL Dilution B ___ U/0.1 mL
__ XEOMIN Dilution A ___ U/0.1 mL Dilution B ___ U/0.1 mL
100 U in 1 mL = 10 U/0.1 mL then, dilute 1:1.5 = 4 U/0.1 mL
100 U in 1 mL = 10 U/0.1 mL then, dilute 1:1 = 5 U/0.1 mL
100 U in 1 mL = 10 U/0.1 mL then, dilute 1:3 = 2.5 U/0.1 mL

For first time injections

___ Limitations discussed
___ Duration of results explained
___ Risk & complications discussed
___ Pictures taken
___ Aftercare instructions given
___ Artefill skin test negative

Filler or Stimulator

__ Artefill [A]
__ Belotero [B]
__ Juvederm Ultra [J]
__ Juvederm Ultra Plus [J+]
__ Sculptra [S] ____ cc/vial
__ Restylane [Rs]
__ Perlane [P]
__ Radiesse [Rd]
__ Voluma [V]

Injection

32 G Needle
27 G Microcannula

Anesthetic

B None
__ 1% Lido + Epi at injection sites
___ Nerve block
___ Topical
___ Ice

Treatment outcomes: ____

Complications: None

Place Product Stickers Here

C 32 1578

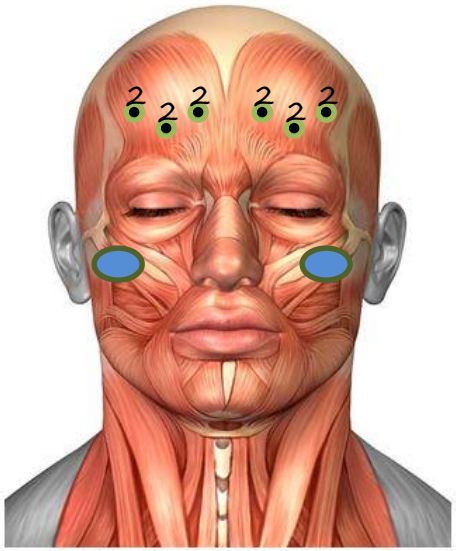
Voluma 13-578

Additional Notes

F= 2u x6 = 12u

Malar = 0.5cc per side

May need more in 2 weeks



BoTN-A Non-responders

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 non-responders 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

Effect of Dietary Zinc and Phytase Supplementation on Botulinum Toxin Treatments

John C. Koshy, MD,[1] Safa E. Sharabi, MD,[1] Evan M. Feldman, MD,[1] Larry H. Hollier Jr, MD,[1] James R. Patrinely, MD,[1-4] Charles N. S. Soparkar, MD, PhD[1-4]

- 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

Effect of Dietary Zinc and Phytase Supplementation on Botulinum Toxin Treatments

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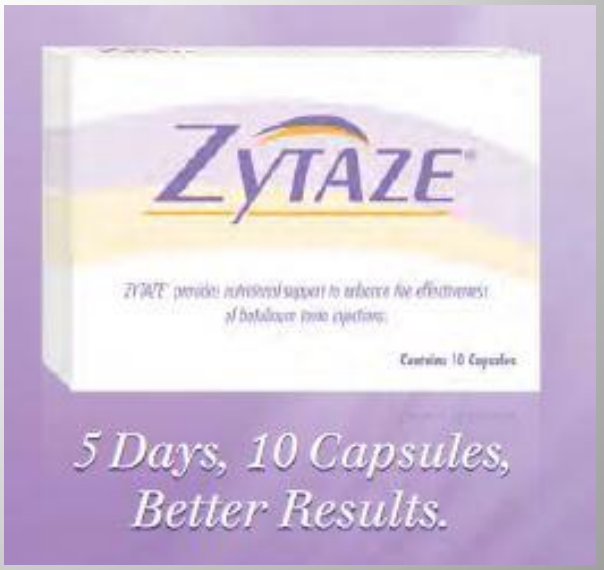
- 92% of patients reported 30% increase in duration
- Older patients
  - Greater improvement
  - No increase in duration
- Zytase $40 per treatment



Can I Really Store BoTN-A for 4 Weeks?

Consensus Statement Regarding Storage and Reuse of Previously Reconstituted Neuromodulators

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- Literature review & 2 round Delphi process
- Can be refrigerated or refrozen for 4 weeks
- Can use on multiple patients (proper handling)

Does Injection Depth Matter?

Injecting Botulinum Toxin at Different Depths Is Not Effective for the Correction of Eyebrow Asymmetry

Jason Sneath, MD,* Shannon Humphrey, MD,* Alastair Carruthers, MD, FRCPC, FAAD,* and Jean Carruthers, MD, FRCSC†

Selective eyebrow depressors cannot be targeted due to BoTN diffusion radius

Clinical Examples

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NEUROTOXINS

Aesthetic Uses of Neuromodulators: Current Uses and Future Directions

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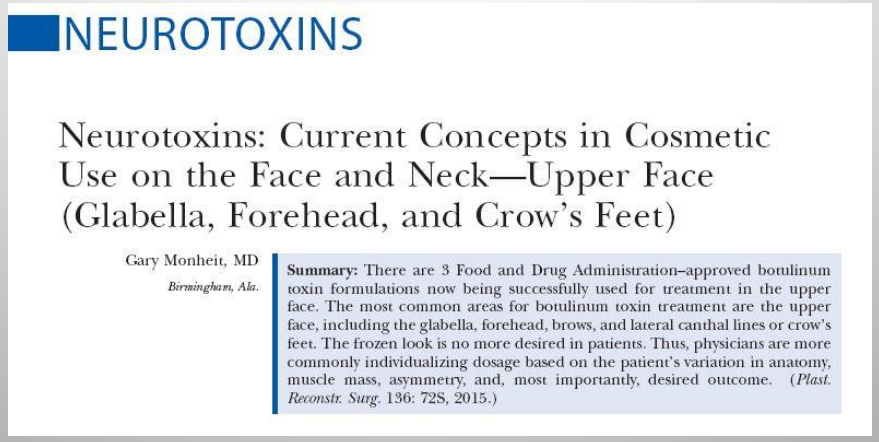
Background: The introduction of neuromodulators for aesthetic facial improvements greatly expanded the limits of nonsurgical facial rejuvenation. Although many current uses are considered "off-label," the widespread acceptance and favorable safety profile of properly used botulinum toxins have made them one of the most common aesthetic treatments available.

Individual Patient Assessment for Natural Result

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/incobotulinum toxin or 50–60 units of abobotulinum toxin can be reduced to allow movement and expression.[4] 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



NEUROTOXINS

Neurotoxins: Current Concepts in Cosmetic Use on the Face and Neck—Upper Face (Glabella, Forehead, and Crow's Feet)

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Summary: There are 3 Food and Drug Administration–approved botulinum toxin formulations now being successfully used for treatment in the upper face. The most common areas for botulinum toxin treatment are the upper face, including the glabella, forehead, brows, and lateral canthal lines or crow's feet. The frozen look is no more desired in patients. Thus, physicians are more commonly individualizing dosage based on the patient's variation in anatomy, muscle mass, asymmetry, and, most importantly, desired outcome. (*Plast. Reconstr. Surg.* 136: 72S, 2015.)

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

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

Nonsurgical Facial Rejuvenation: Botulinum Neuromodulators