

Botulinum Neuromodulators: Clinical Uses

Karol A Gutowski, MD, FACS

plastic
surgery
THE MEETING

Los Angeles

September 23-27, 2016



Disclosures

Angiotech/Surgical Specialties - 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 - **RimabotulinumtoxinB**
- 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
- **DYSPORT** [Galderma]
 - Moderate to severe glabellar lines
- **XEOMIN** [Merz Aesthetics]
 - Moderate to severe glabellar lines
- All for adults ≤ 65 years old

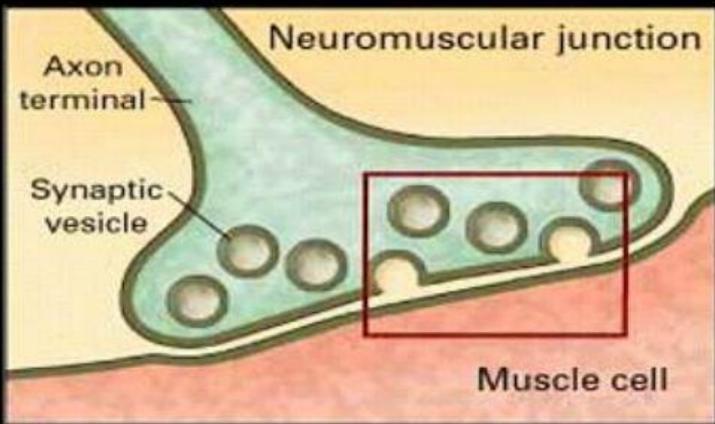
What FDA Wants You to Know

- 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

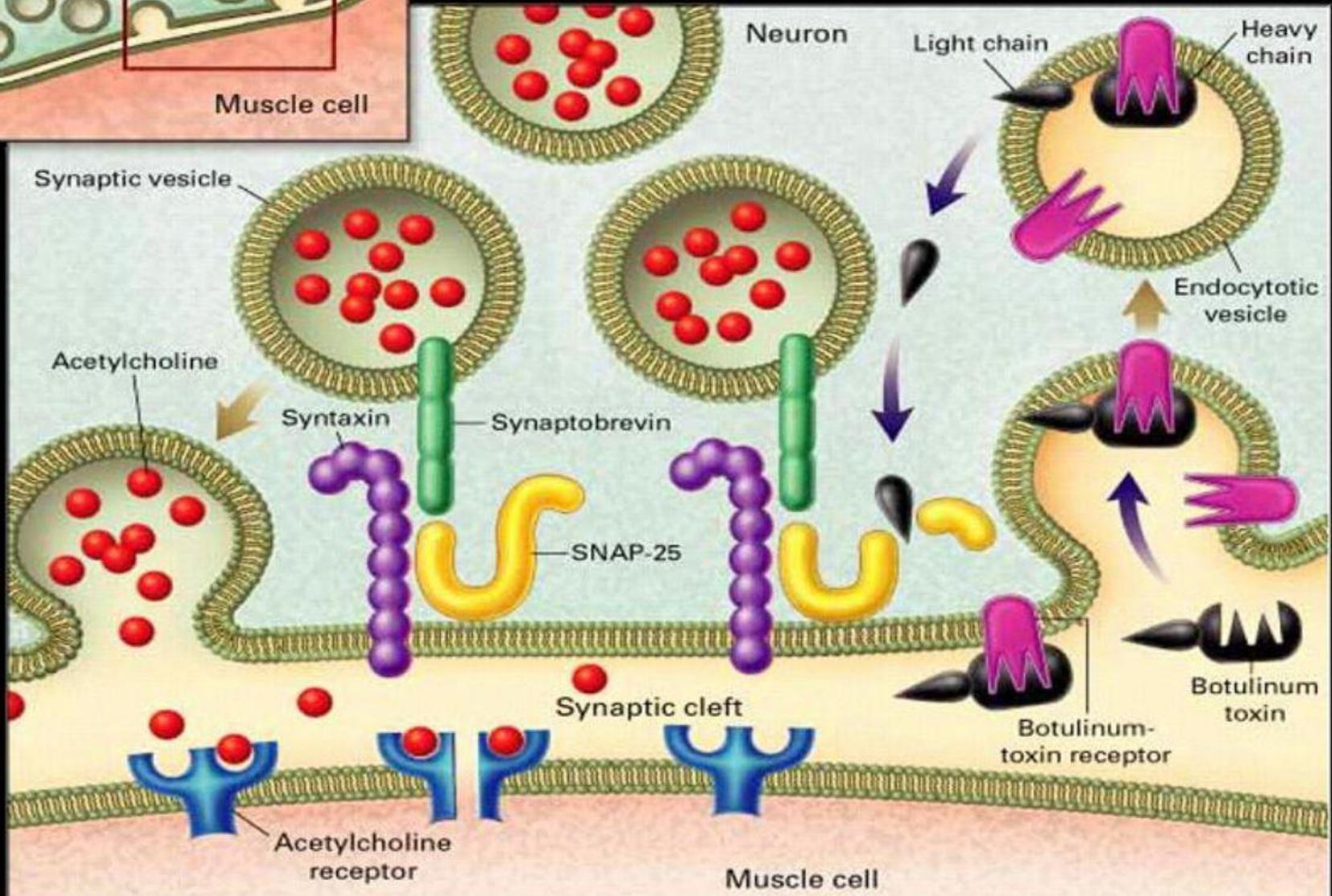


Mechanism of Action

Types A and B bind to distinct acceptors

Botulinum Type A cleaves SNAP-25

Botulinum Type B cleaves synaptobrevin (VAMP)



Product Comparison

	BOTOX[®] Cosmetic¹	DYSPORT^{®2}	XEOMIN^{®3}
Non-Proprietary Name	onabotulinumtoxinA	abobotulinumtoxinA	incobotulinumtoxinA
First Approval	<ul style="list-style-type: none"> • 1989 (US) 	<ul style="list-style-type: none"> • 1991 (UK) 	<ul style="list-style-type: none"> • 2005 (Germany)
Serotype	<ul style="list-style-type: none"> • A 	<ul style="list-style-type: none"> • A 	<ul style="list-style-type: none"> • A
Strain	<ul style="list-style-type: none"> • Hall (Allergan) 	<ul style="list-style-type: none"> • Hall[‡] 	<ul style="list-style-type: none"> • Hall
Receptor/Target	<ul style="list-style-type: none"> • SV2/SNAP-25 	<ul style="list-style-type: none"> • SV2/SNAP-25 	<ul style="list-style-type: none"> • SV2/SNAP-25
Process	<ul style="list-style-type: none"> • Crystallization 	<ul style="list-style-type: none"> • Chromatography 	<ul style="list-style-type: none"> • Chromatography
Complex Size	<ul style="list-style-type: none"> • ~900 kD* 	<ul style="list-style-type: none"> • ≤ 500 kD[^] 	<ul style="list-style-type: none"> • 150 kD
Uniformity	<ul style="list-style-type: none"> • Homogeneous 	<ul style="list-style-type: none"> • Heterogenous 	<ul style="list-style-type: none"> • Homogeneous
Excipients (Inactive ingredients) HAS = Human Serum Albumin	<ul style="list-style-type: none"> • HSA: 500 µg (100U vial) • Sodium chloride 	<ul style="list-style-type: none"> • HSA:125 µg (300, 500U vial) • Lactose 	<ul style="list-style-type: none"> • HSA: 1 mg (50, 100U vial) • Sucrose
Stabilization	<ul style="list-style-type: none"> • Vacuum drying 	<ul style="list-style-type: none"> • Lyophilization 	<ul style="list-style-type: none"> • Lyophilization
Solubilization	<ul style="list-style-type: none"> • Normal saline 	<ul style="list-style-type: none"> • Normal saline 	<ul style="list-style-type: none"> • Normal Saline
Unitage (U/Vial)	<ul style="list-style-type: none"> • 100, 200 	<ul style="list-style-type: none"> • 300, 500 	<ul style="list-style-type: none"> • 50, 100
Protein (ng/Vial)	<ul style="list-style-type: none"> • 5 (100U vial) 	<ul style="list-style-type: none"> • 4.35[‡] (500U vial) 	<ul style="list-style-type: none"> • 0.6 (100U vial)

Product Composition

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Strain	• Hall (Allergan)	• Hall*	• Hall
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Process	• Crystallization	• Chromatography	• Chromatography
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Product Composition

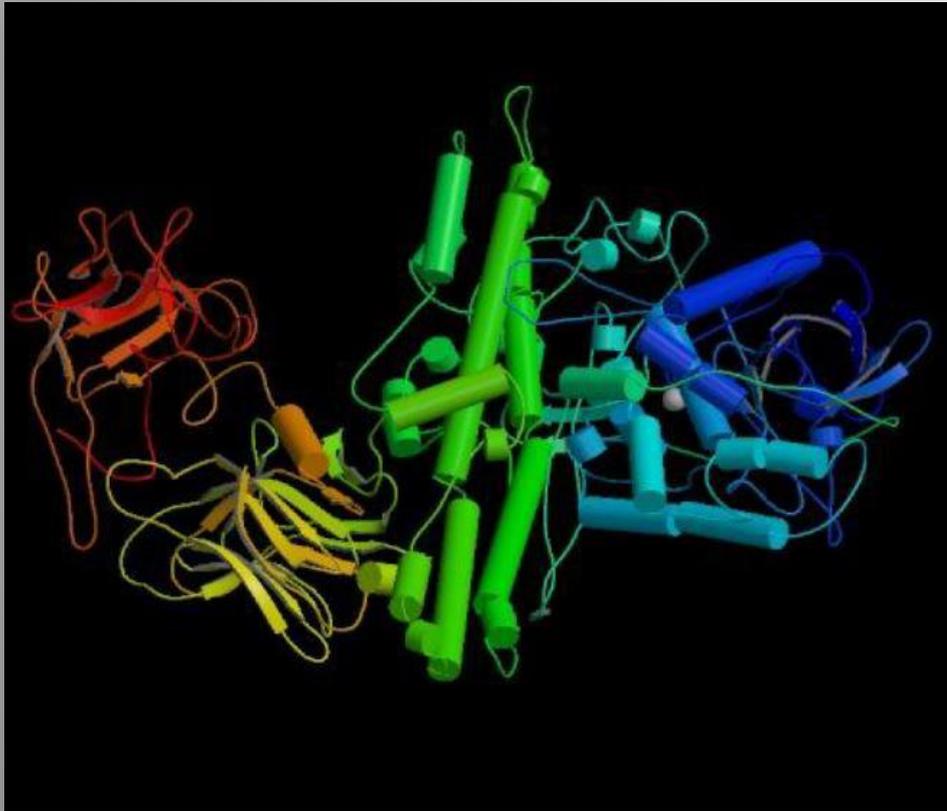
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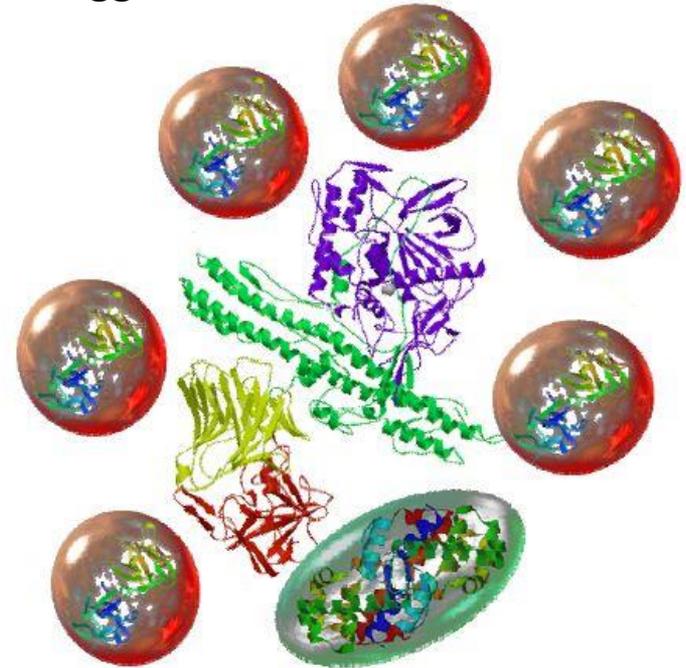
BoTN-A Molecule

BoTN-A



BoTN-A + Accessory Proteins

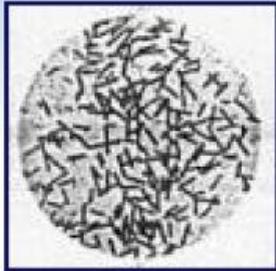
Hemagglutinin Proteins



Non-Hemagglutinin Protein

BoTN-A Protein Comparison

BOTOX



Ethanol Precipitation and Crystallization¹

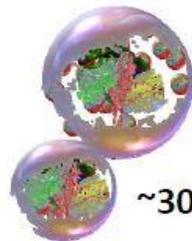


~900 kD

DYSPORT



Ion Exchange²



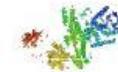
~500 kD

~300 kD

XEOMIN



Ion Exchange and pH Change^{3,4}



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

Pivotal Study Doses

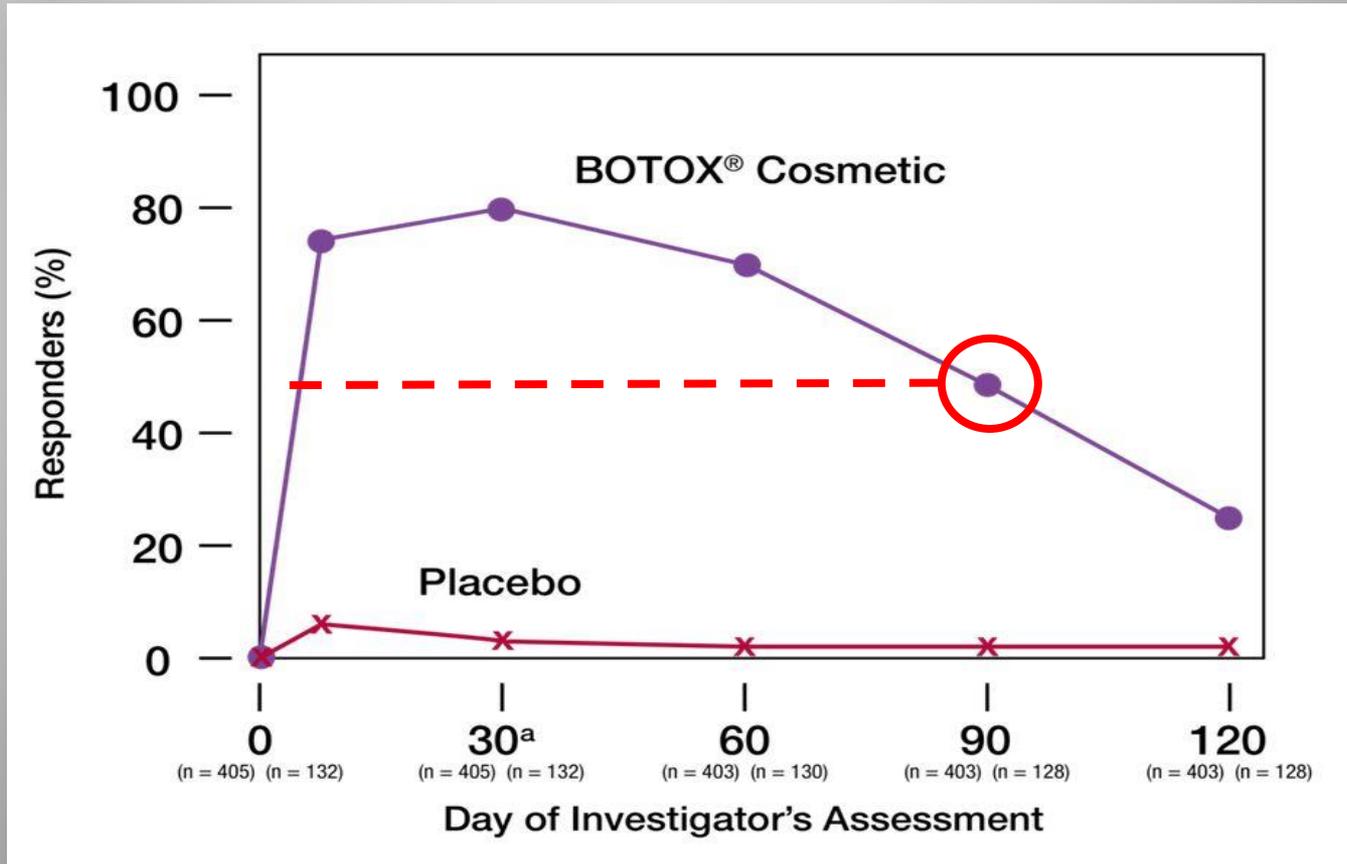
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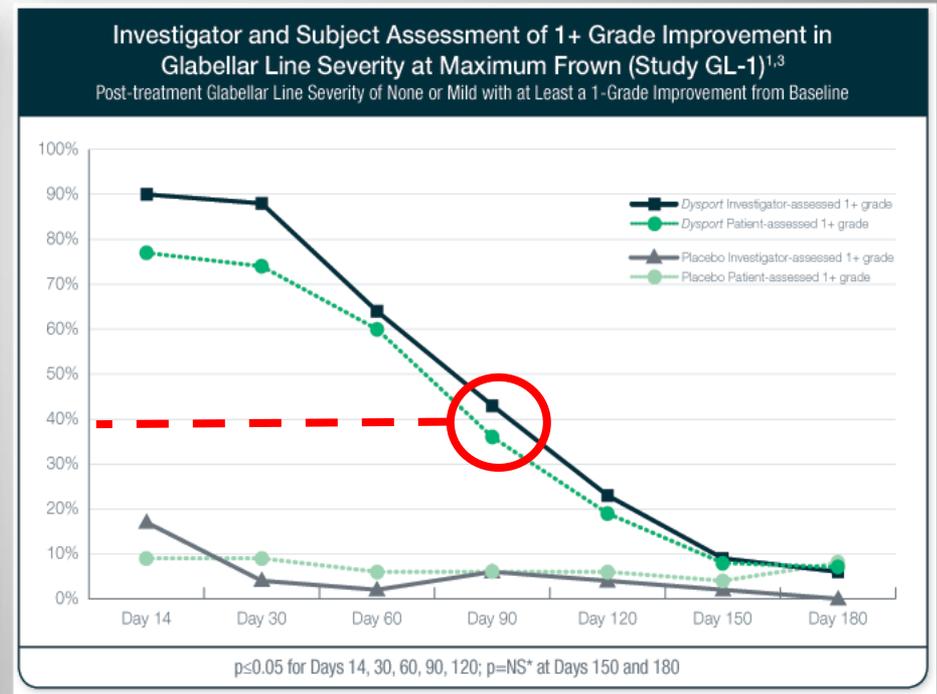
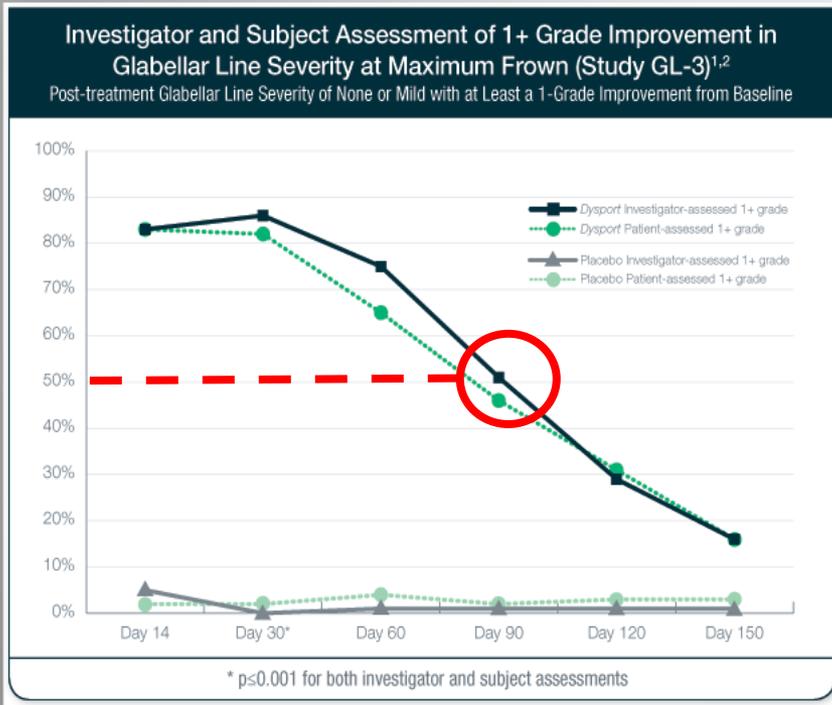
BOTOX Pivotal Studies

50% of patients maintain improvement at 3 months



DYSPORT Pivotal Studies

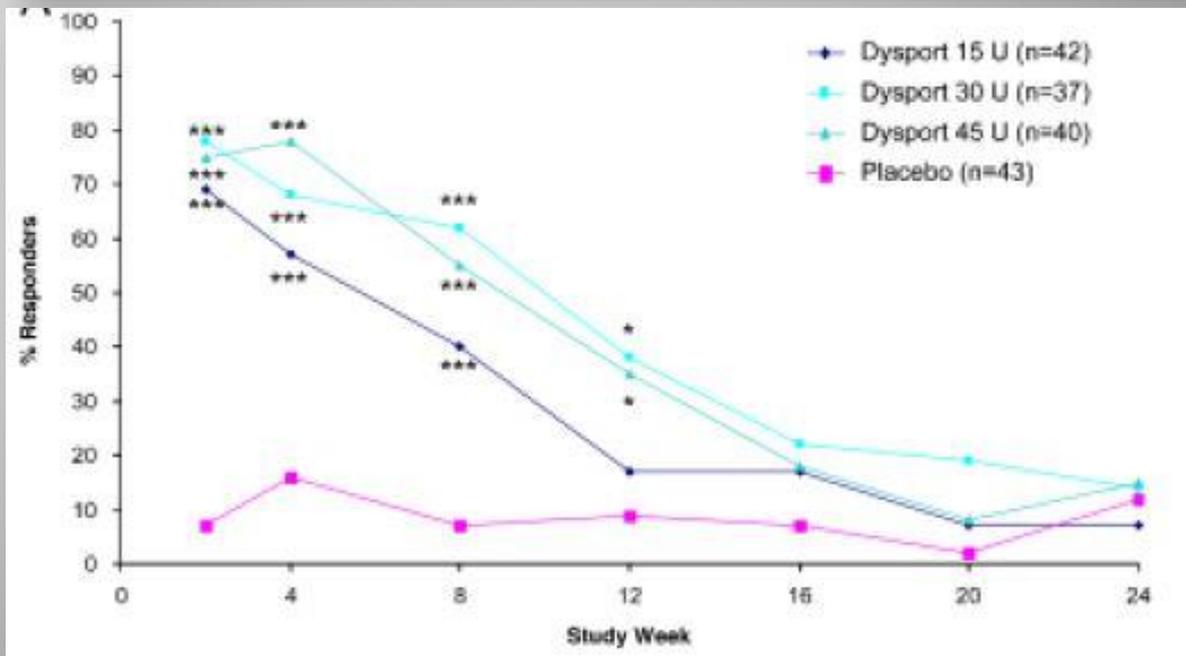
40% - 50% of patients maintain 1-Grade improvement at 3 months



DYSPORT Dose Response

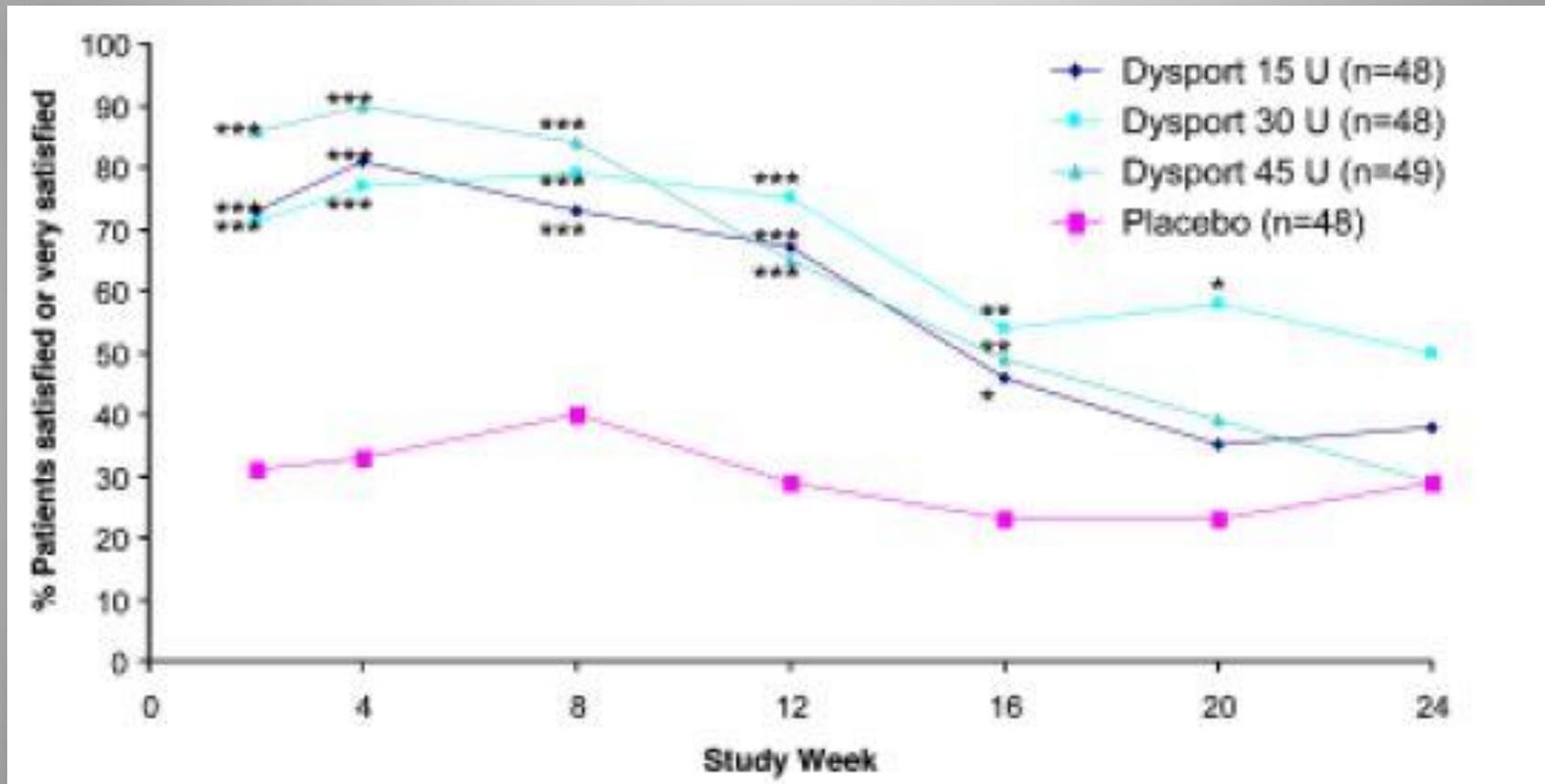
Efficacy and Safety of Botulinum Toxin Type A in the Treatment of Lateral Crow's Feet: Double-Blind, Placebo-Controlled, Dose-Ranging Study

BENJAMIN ASCHER, MD,* BERTHOLD J. RZANY, MD, ScM,[†] AND
RAJIV GROVER, BSc, MB, BS, MD, FRCS (PLAST)[‡]



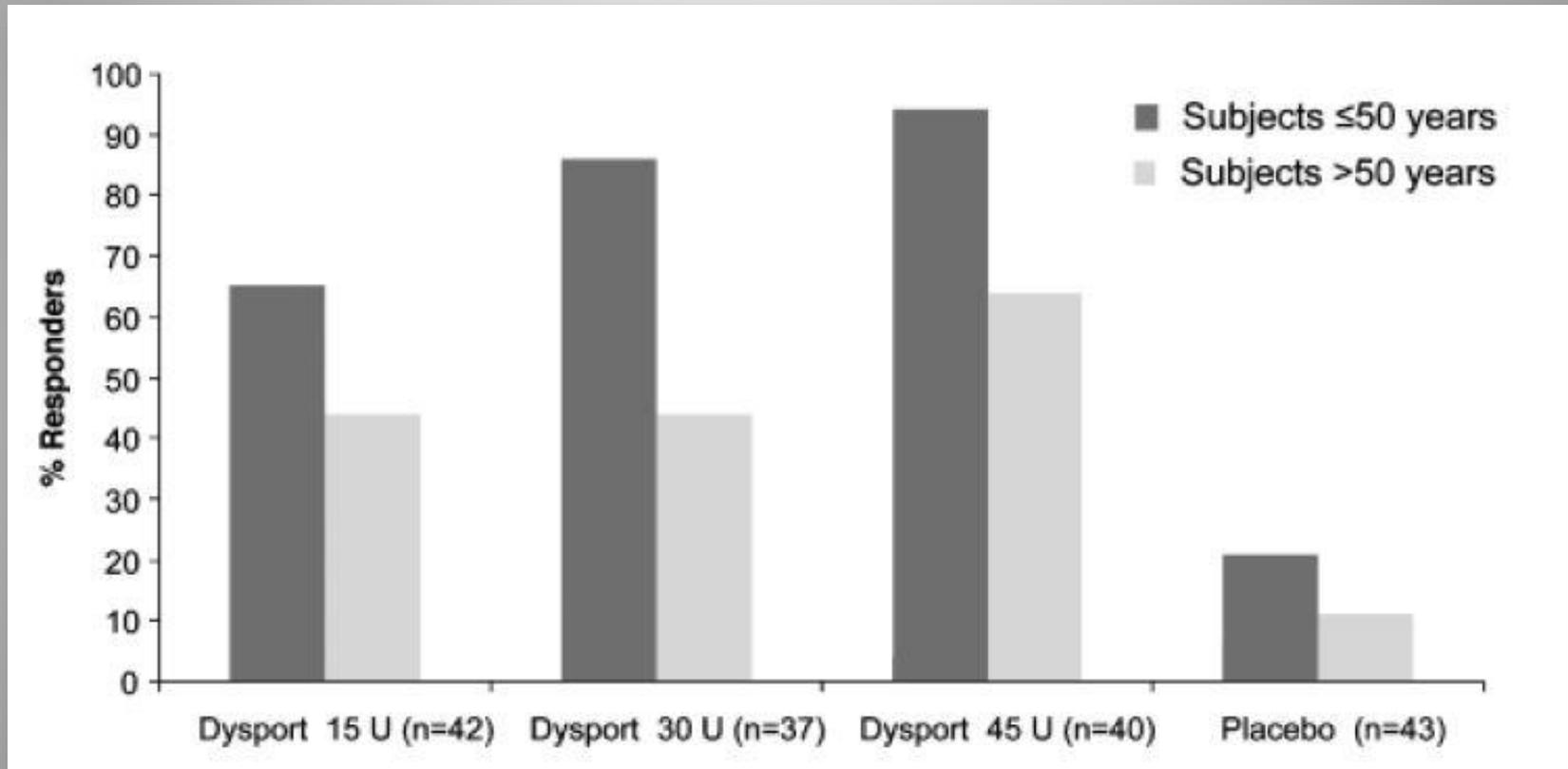
30U & 45U better than 15U

DYSPORT Dose Response



Patient satisfaction similar at all doses

DYSPORT Dose Response

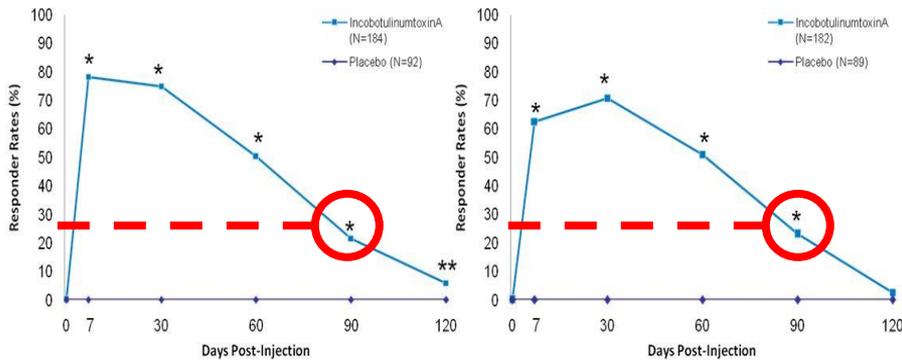


Older patients less likely to respond

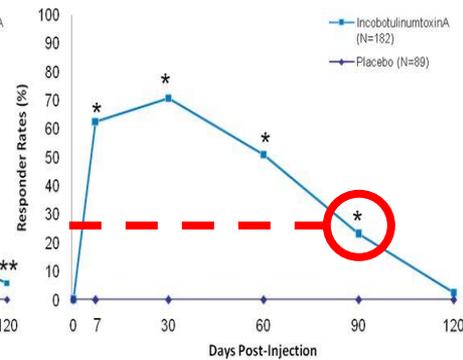
XEOMIN Pivotal Studies

15% - 25% of patients maintain 2-Grade improvement at 3 months

Study GL-1



Study GL-2

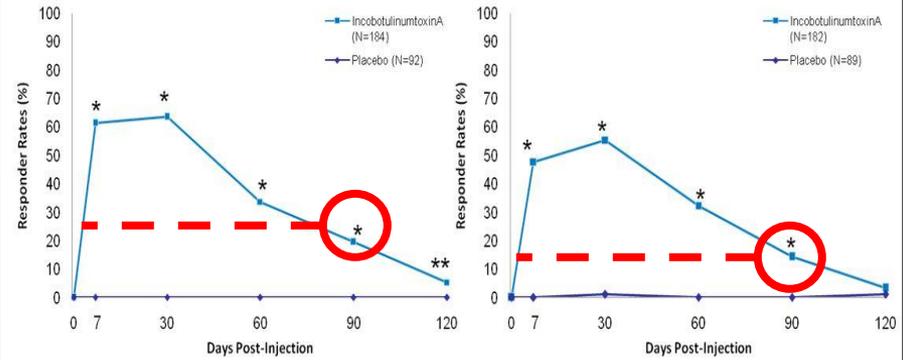


Responders (Max Frown):
Improvement of at least 2 points on FWS as assessed by the Investigator

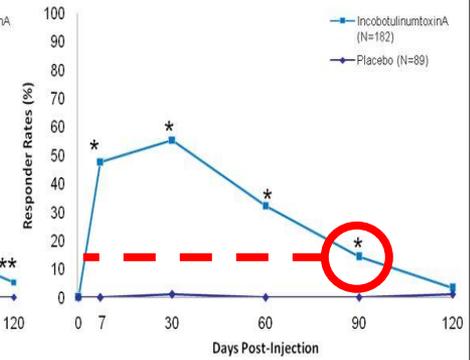
*p<0.0001 and **p<0.05; p-values calculated using the Fisher's Exact Test

Full Analysis Set
Observed Case

Study GL-1



Study GL-2



Responders (Max Frown):
At least a 2 Point Improvement on 4-Point Patient Assessment Scale

*p<0.0001; p-values calculated using the Fisher's Exact Test

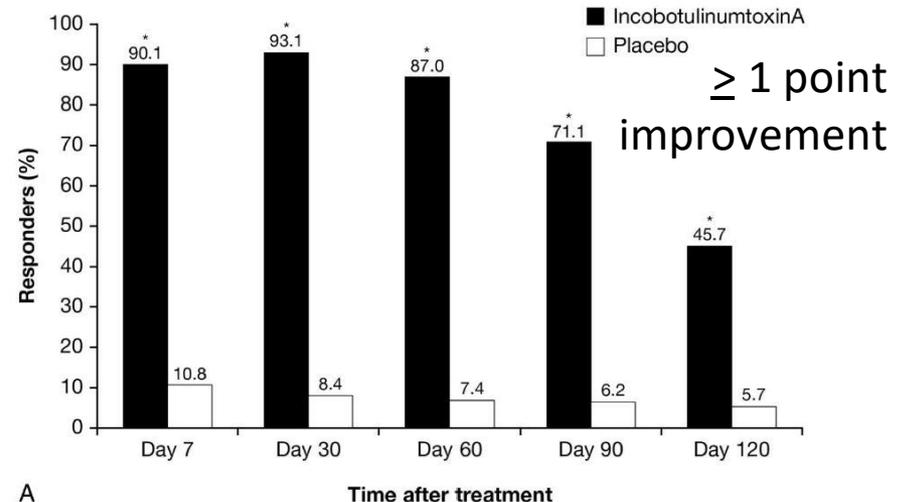
Full Analysis Set
Observed Case

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

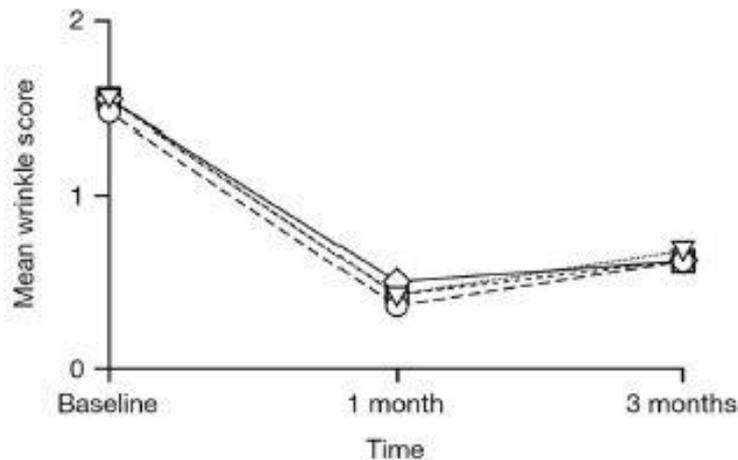


BOTOX vs XEOMIN

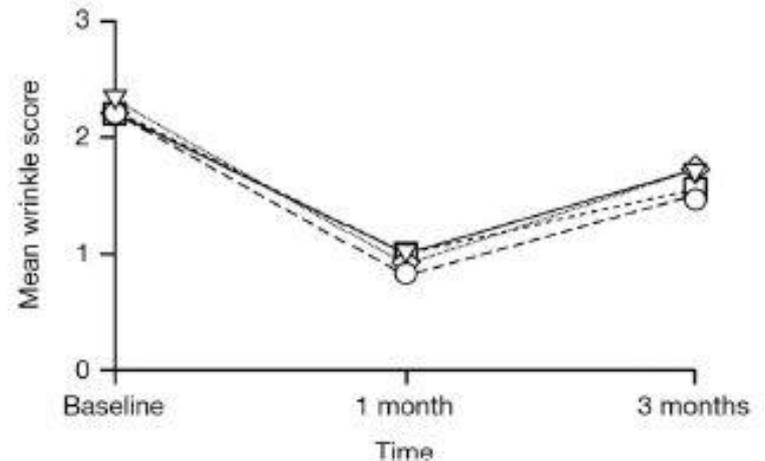
A Prospective Rater- and Subject-Blinded Study Comparing the Efficacy of IncobotulinumtoxinA and OnabotulinumtoxinA to Treat Crow's Feet: A Clinical Crossover Evaluation

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

--○-- IncobotulinumtoxinA left ◇ IncobotulinumtoxinA right
--▽-- OnabotulinumtoxinA right --□-- OnabotulinumtoxinA left



--○-- IncobotulinumtoxinA left ◇ IncobotulinumtoxinA right
--▽-- OnabotulinumtoxinA right --□-- OnabotulinumtoxinA left



BOTOX vs XEOMIN Dose

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

JUNE 2012

731

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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.

BOTOX vs XEOMIN

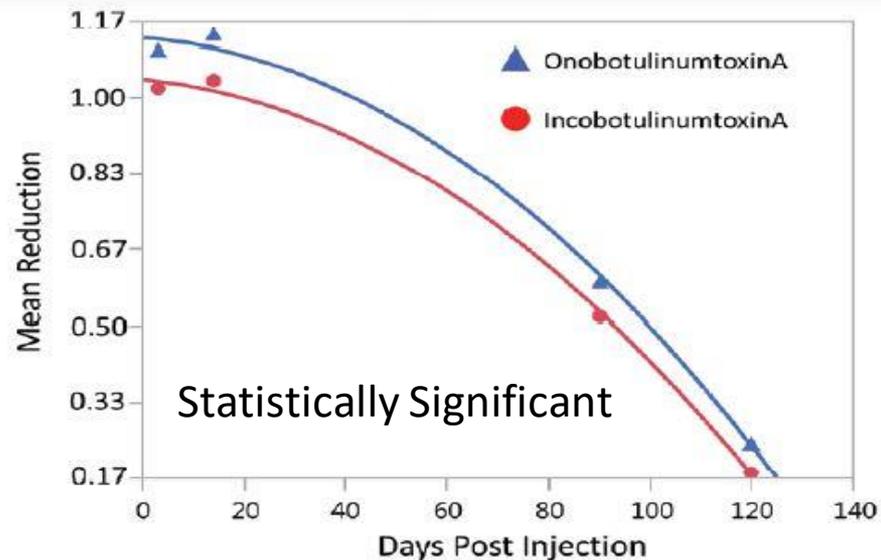
COSMETIC

2015

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.

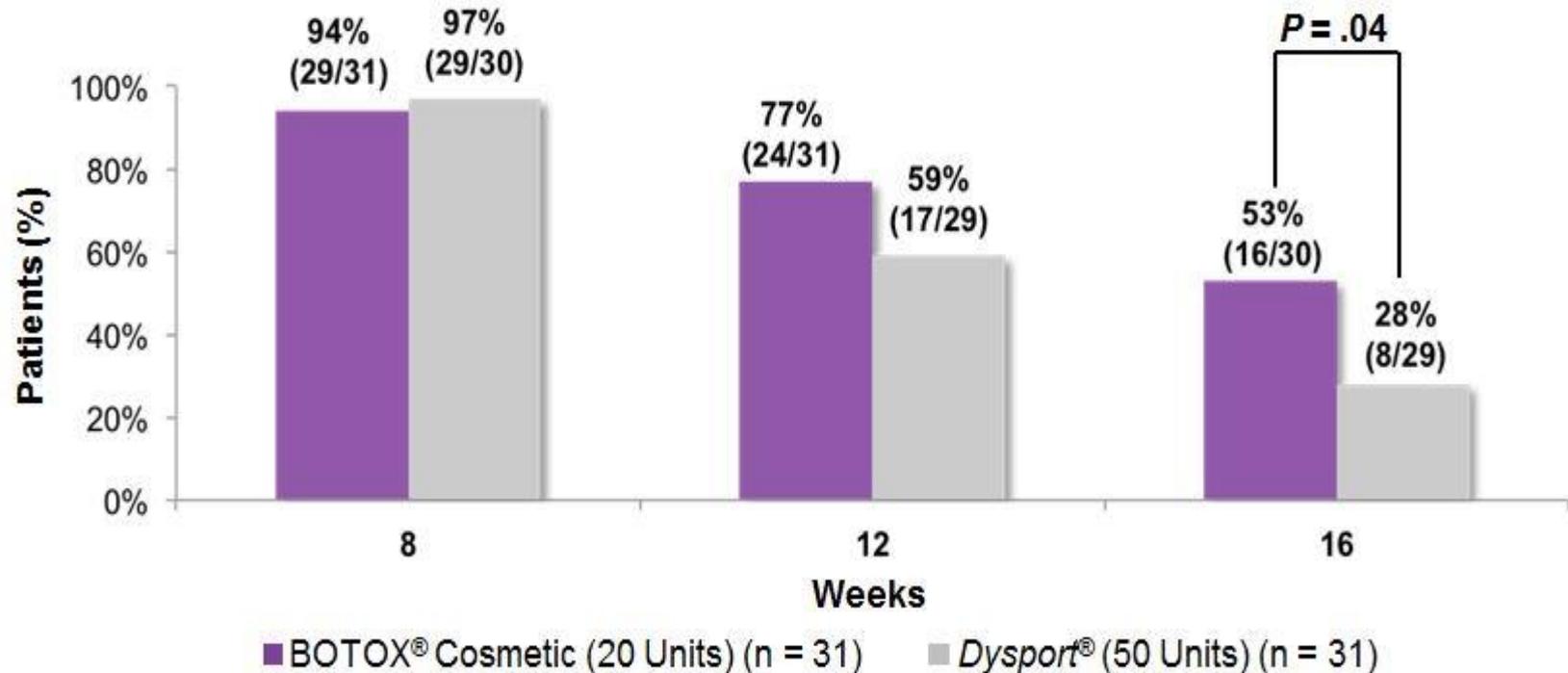
Background: The authors sought to compare the newest U.S. Food and Drug Administration–approved botulinum toxin type A product, incobotulinumtoxinA, to onabotulinumtoxinA for upper face wrinkles. This is the first prospec-



BOTOX vs DYSPORT Duration

Duration From a Double-Blind, Randomized, Parallel-Group Study¹

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



BTX, XEO, DYS Strain Study

COSMETIC

Rectangular Strain

2016

A Quantitative Analysis of OnabotulinumtoxinA, AbobotulinumtoxinA, and IncobotulinumtoxinA: A Randomized, Double-Blind, Prospective Clinical Trial of Comparative Dynamic Strain Reduction

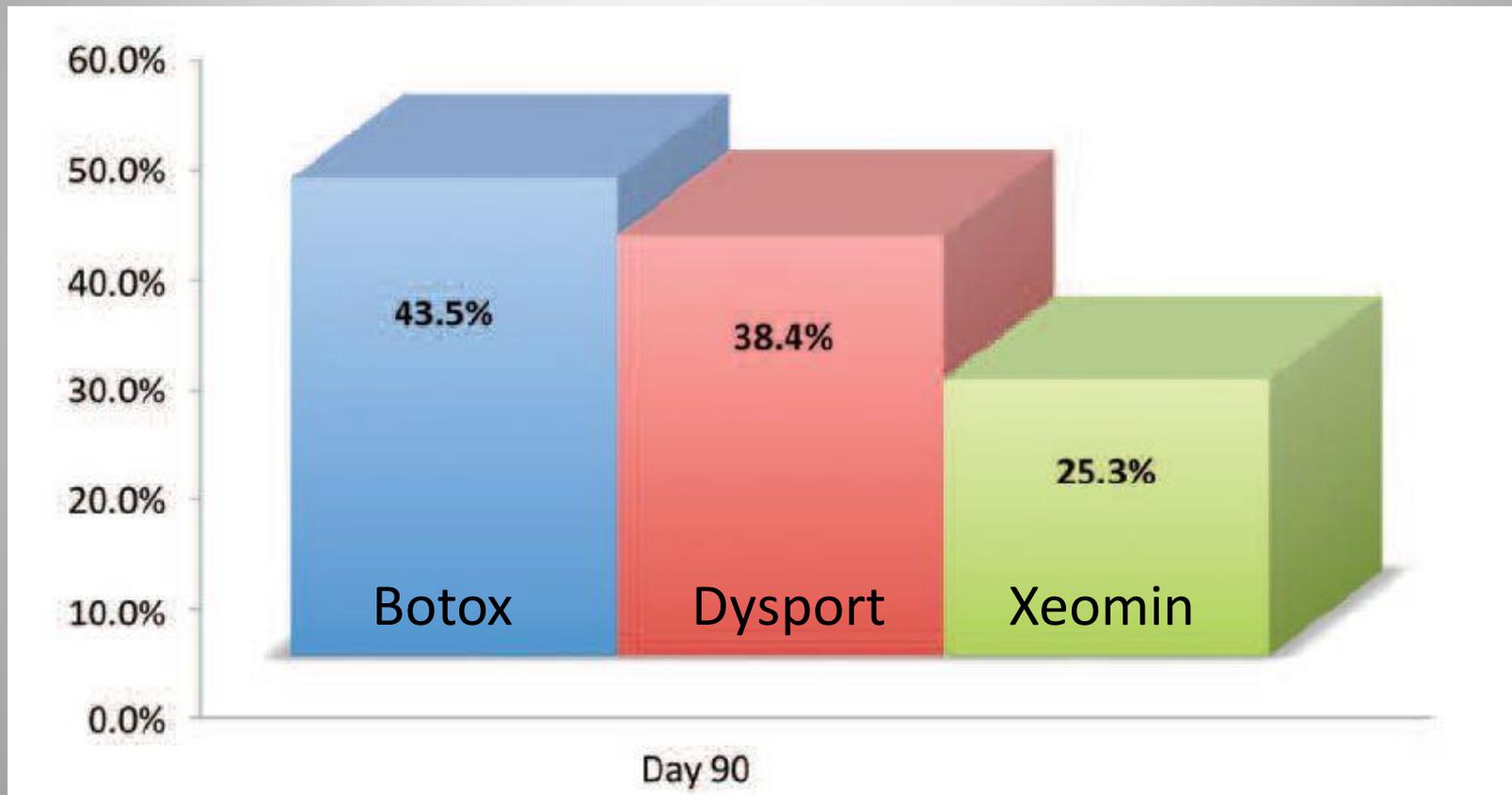
Anthony J. Wilson, M.D.
Brian Chang, B.S.
Anthony J. Taglienti, M.D.
Bianca C. Chin, M.D.
Catherine S. Chang, M.D.
Nancy Folsom, R.N.
Ivona Percec, M.D., Ph.D.

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-naïve female patients aged were random-



Muscle Strain Reduction



BTX, XEO, DYS Systematic Review

2016

Rectangular Ship

COSMETIC

A Comparative Assessment of Three Formulations of Botulinum Toxin Type A for Facial Rhytides: A Systematic Review with Meta-Analyses

James P. Bonaparte, M.D.,
M.Sc.

David Ellis, M.D.

Jason G. Quinn, B.Sc., M.D.

Jessica Rabski, B.Sc.

Brian Hutton, M.Sc., Ph.D.

Ottawa and Toronto, Ontario, Canada

Background: Three formulations of botulinum toxin are available for facial rhytides. It is unclear which formulation offers the greatest balance of benefits and harms. The objective of this study was to conduct a systematic review with meta-analyses to compare formulations of botulinum toxin for reduction of facial rhytides at the glabella.

Methods: The authors' protocol was registered with the International Prospective Register of Systematic Reviews (CRD4201200377). A systematic literature

“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*†



- DYSPORE greater anhidrotic effect than XEOMIN
- Similar muscular effects by EMG

Unique Characteristics

DYSPO

- 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 \neq no response
 - Absence of antibody \neq 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, PhD¹⁻⁴

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

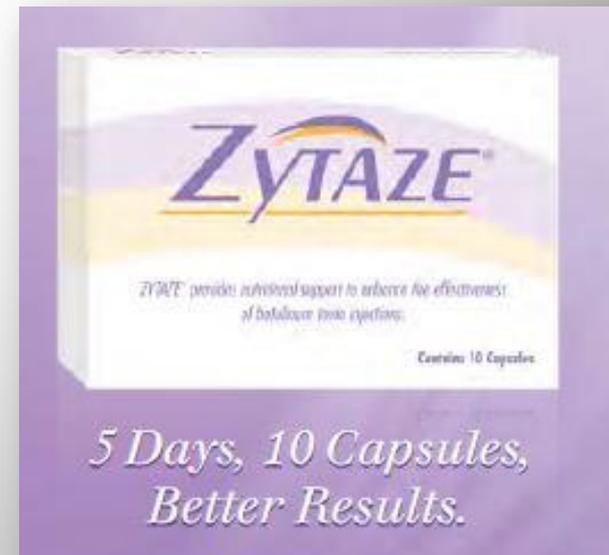
- BoTN-A is zinc dependent
- Phytates block zinc absorption

Zinc Supplementation to Increase Duration

Effect of Dietary Zinc and Phytase Supplementation on Botulinum Toxin Treatments

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, PhD¹⁻⁴

- 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

MURAD ALAM, MD,^{*†‡} DIANA BOLOTIN, MD, PhD,[§] JEAN CARRUTHERS, MD,^{||}
DORIS HEXSEL, MD,^{¶#} NAOMI LAWRENCE, MD,^{**} KIRA MINKIS, MD, PhD,^{*†‡}
AND EDWARD VICTOR ROSS, MD^{†‡}

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

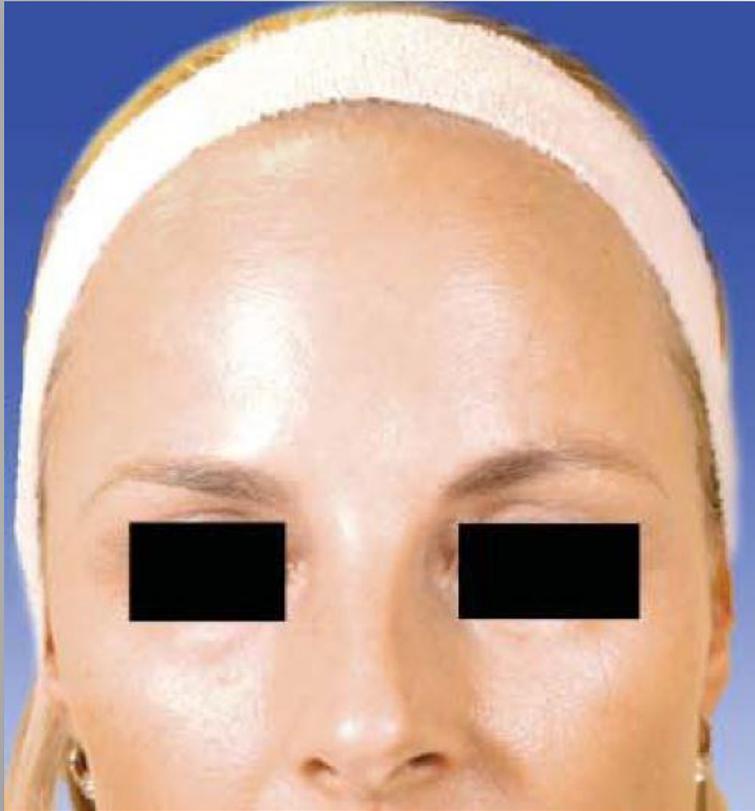
Does Injection Depth Matter?

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

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 DYSPOORT (1-3 days)

Personal Experience

- Fastest time to onset DYSPOORT (1-3 days)
- Duration Equal

Personal Experience

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

* Depends on dose & rebates

Personal Experience

- Fastest time to onset DYSPOORT (1-3 days)
- Duration Equal
- **Cost*** **BOTOX \geq DYSPOORT > 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 \geq 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

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



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 nondesirable 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

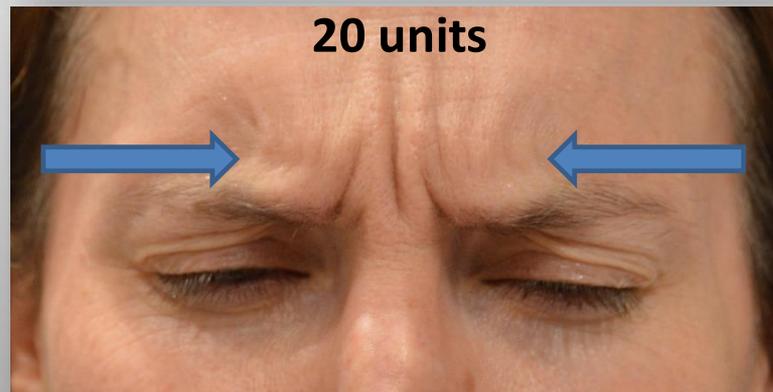
NEUROTOXINS

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

Gary Monheit, MD
Birmingham, Ala.

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.)

Clinical Muscle Assessment



Clinical Muscle Assessment



Size of Treatment Area

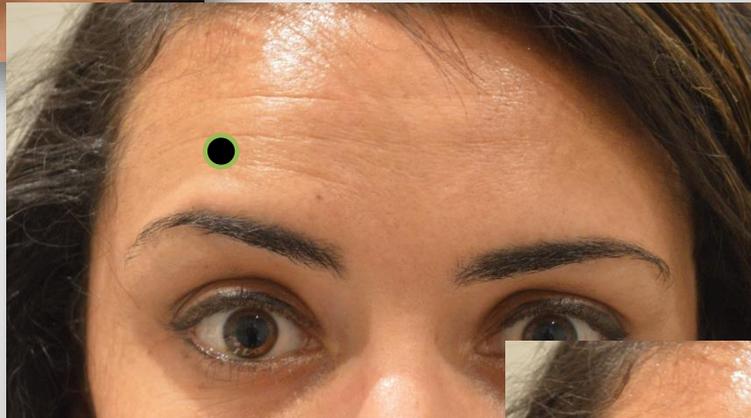


Watch for Asymmetry



6 units per side

+ Right 2 units



Consider 2 units
Left lateral brow



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

- $1.0\text{cc} = 10\text{u}/0.1\text{ cc}$

Low injection volume limits diffusion (Glabella)
More product waste

- $2.0\text{ cc} = 5\text{u}/0.1\text{ cc}$

- $2.5\text{ cc} = 4\text{u}/0.1\text{ cc}$

- $4.0\text{ cc} = 2.5\text{u}/0.1\text{cc}$

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 _____ **Date** _____ **Injector:** Karol A Gutowski, MD

Allergy & Medical Update: _____

Results after Last Injection: _____

Neuromodulator

BOTOX Dilution A ___ 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

Filler or Stimulator

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

For first time injections

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

Injection

G Needle
 G Microcannula

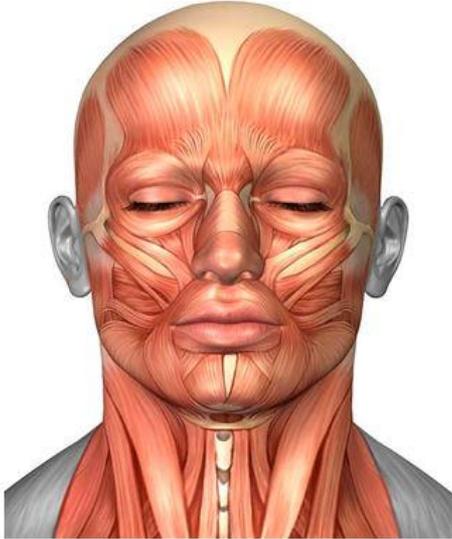
Anesthetic

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

Treatment outcomes: _____

Complications: _____

Place Product Stickers Here



Additional Notes

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

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

Injection

32 G Needle
27 G Microcannula

Anesthetic

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

Treatment outcomes:

Complications: None

Place Product Stickers Here

C 32 1578

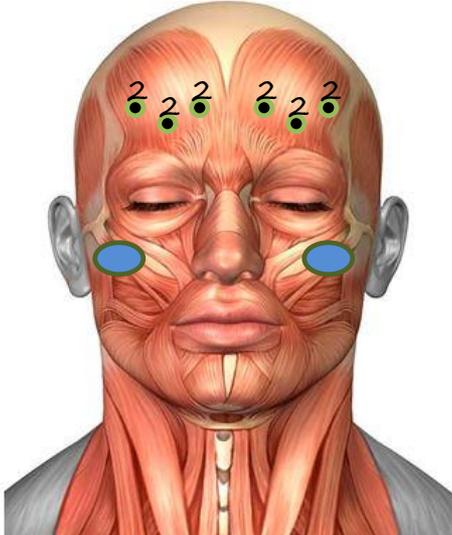
Voluma 13-578

Additional Notes

F = 2u x 6 = 12u

Malar = 0.5cc per side

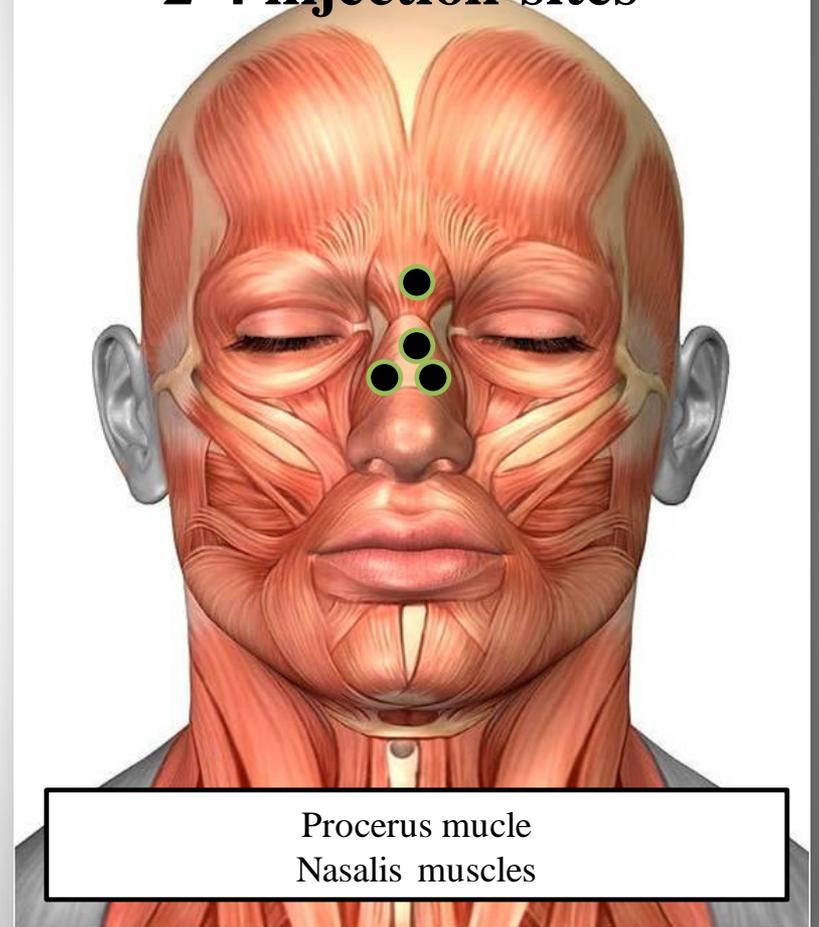
May need more in 2 weeks



Bunny Lines

2 Units per Injection Site

2-4 injection sites

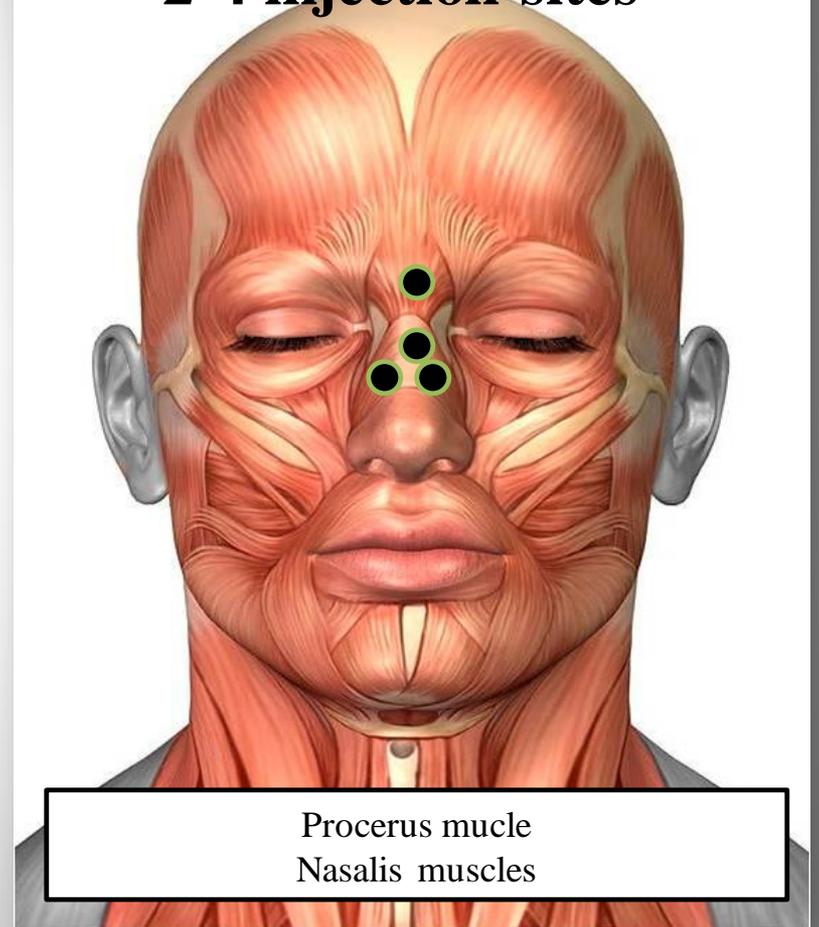


Bunny Lines

2 Units per Injection Site



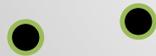
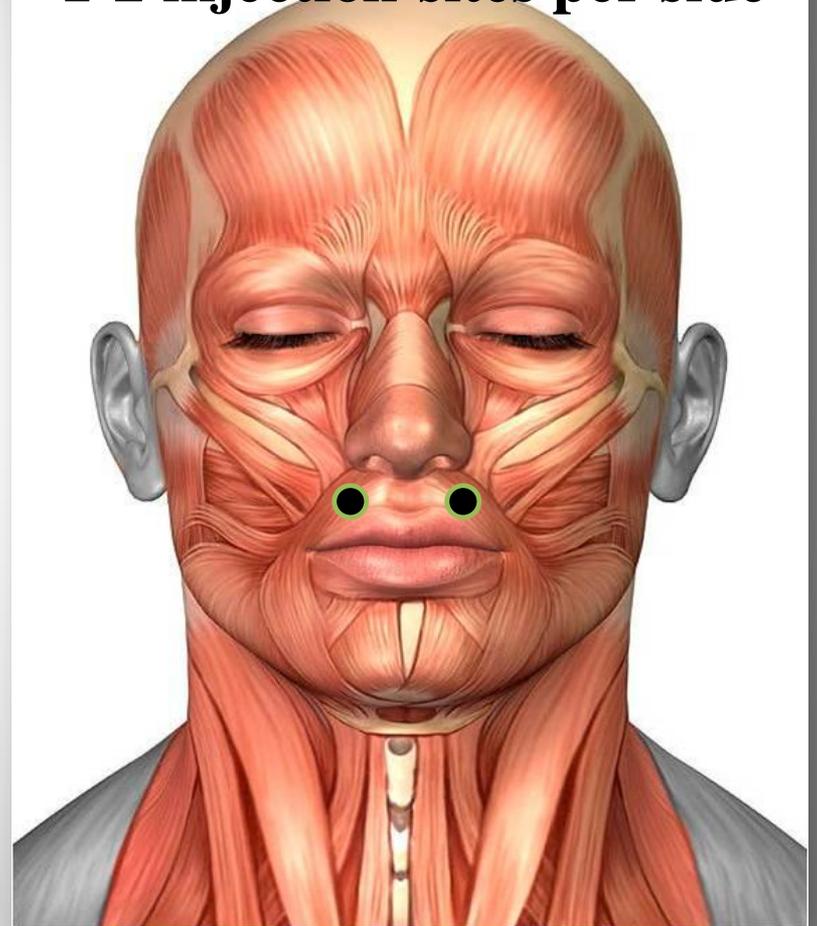
2-4 injection sites



Upper Lip Lines

2 Units per Injection Site

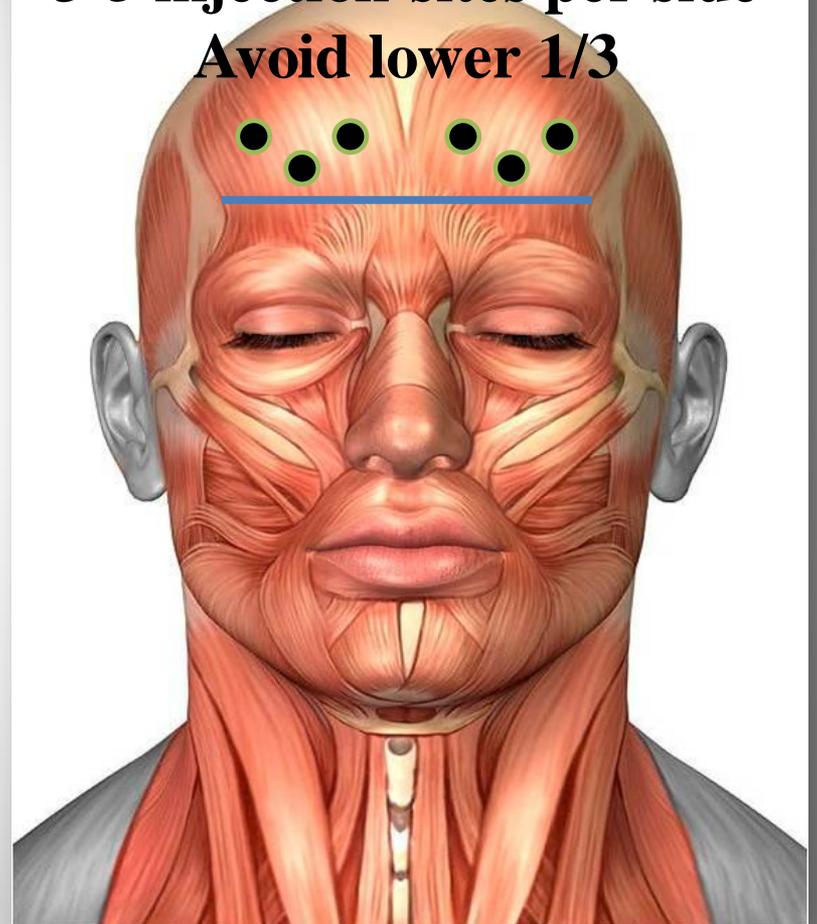
1-2 injection sites per side



Forehead

2 Units per Injection Site

3-5 injection sites per side
Avoid lower 1/3

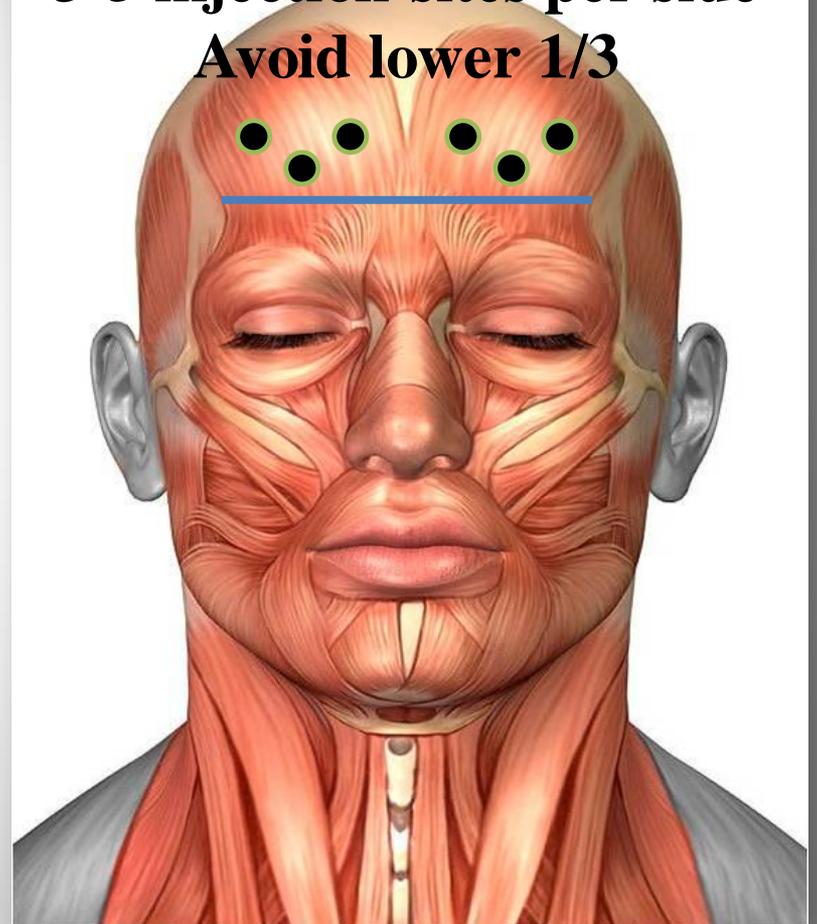


Forehead

2 Units per Injection Site



3-5 injection sites per side
Avoid lower 1/3



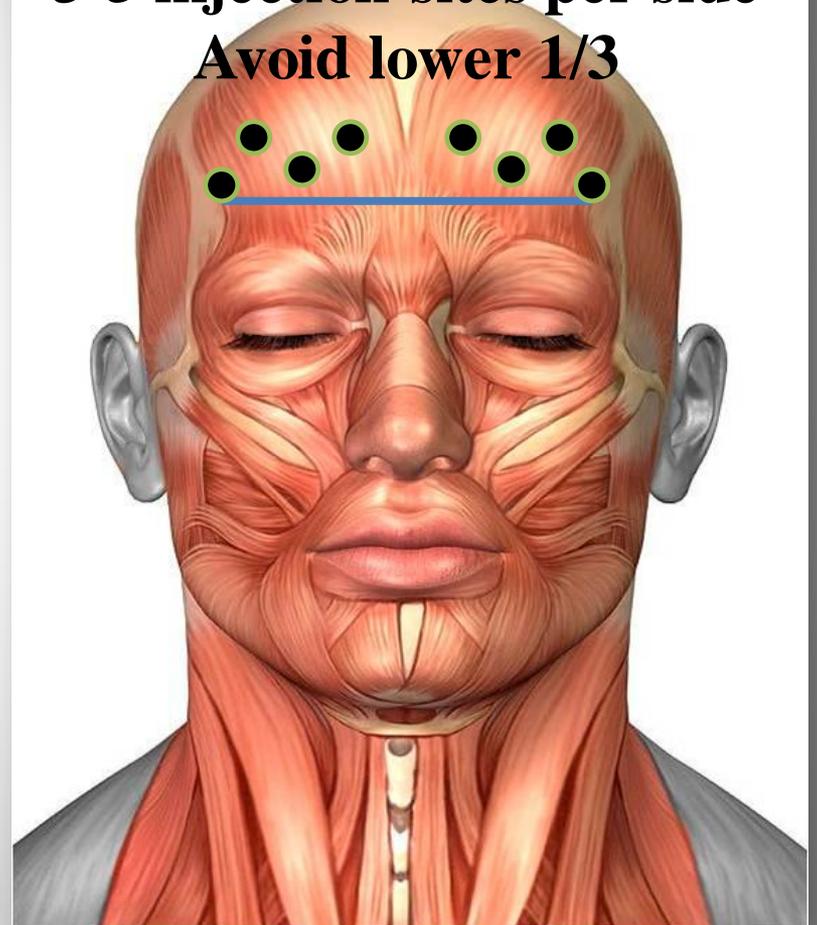
Forehead

2 Units per Injection Site

16 to 20 units



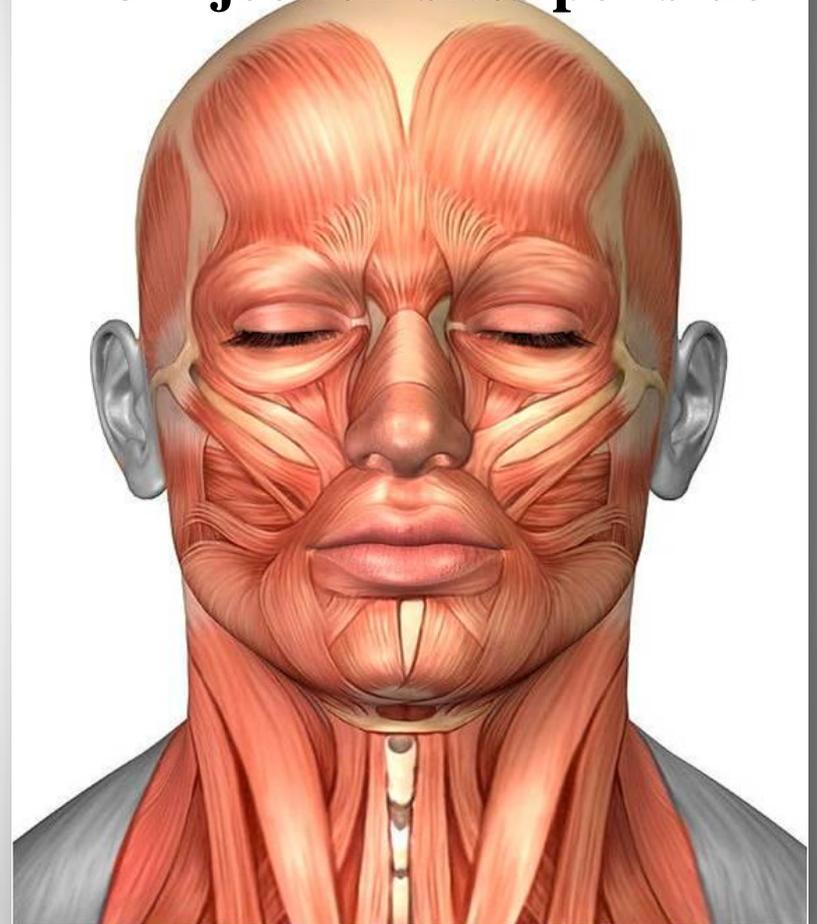
3-5 injection sites per side
Avoid lower 1/3



Crow's Feet & Laugh Lines

2 Units per Injection Site

2-3 injection sites per side

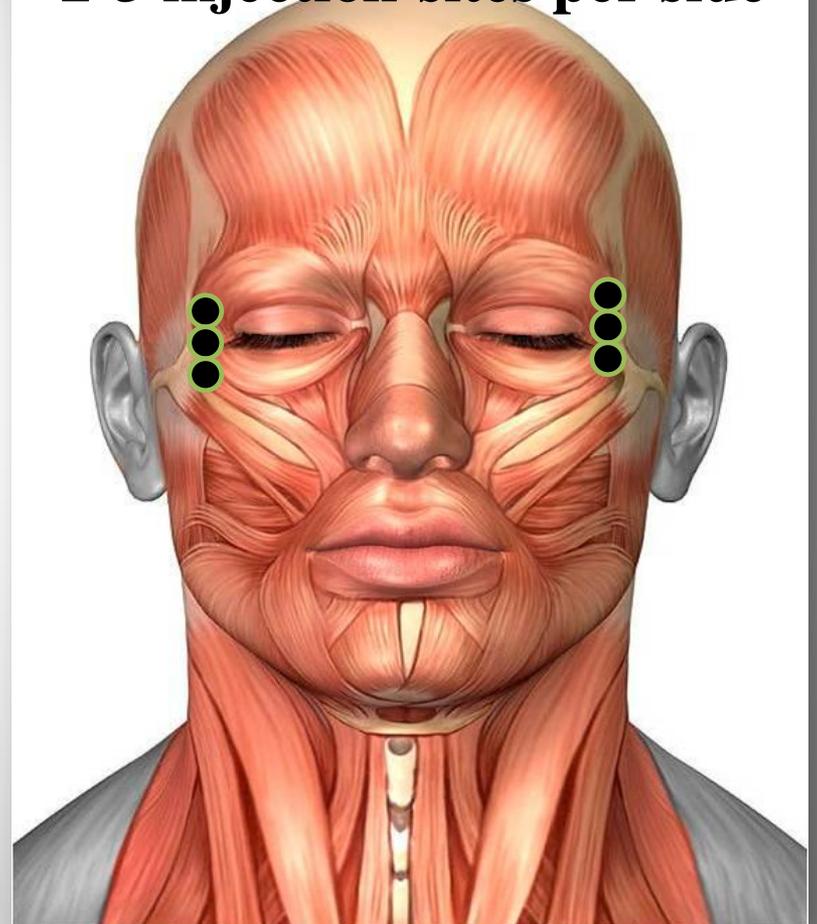


Crow's Feet & Laugh Lines

2 Units per Injection Site



2-3 injection sites per side

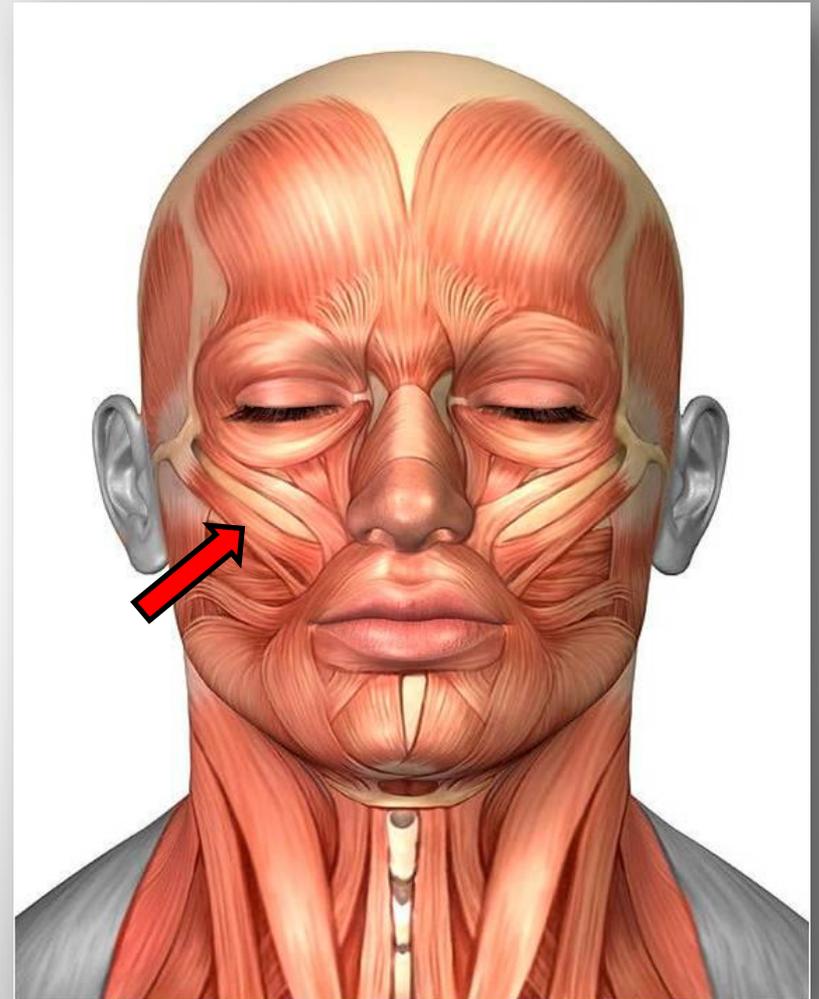


Crow's Feet & Laugh Lines

Limitations due to Contributing Muscle Groups



Recognize contribution of
zygomaticus muscles

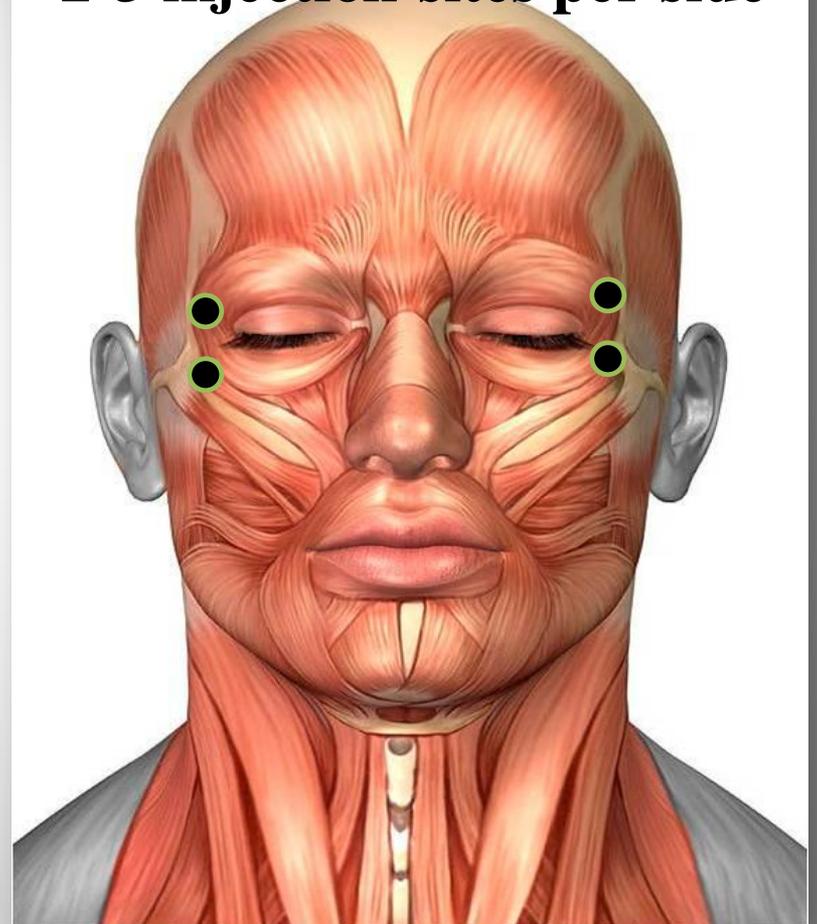


Crow's Feet & Laugh Lines

2 Units per Injection Site



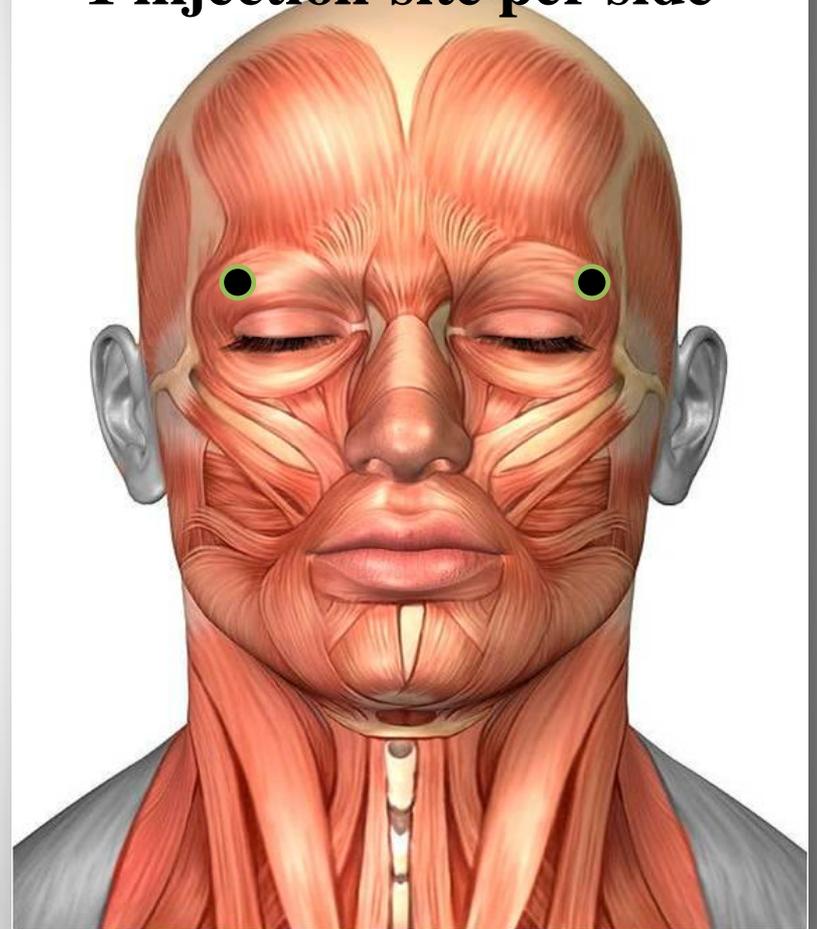
2-3 injection sites per side



Lateral Brow Lift

2 Units per Injection Site

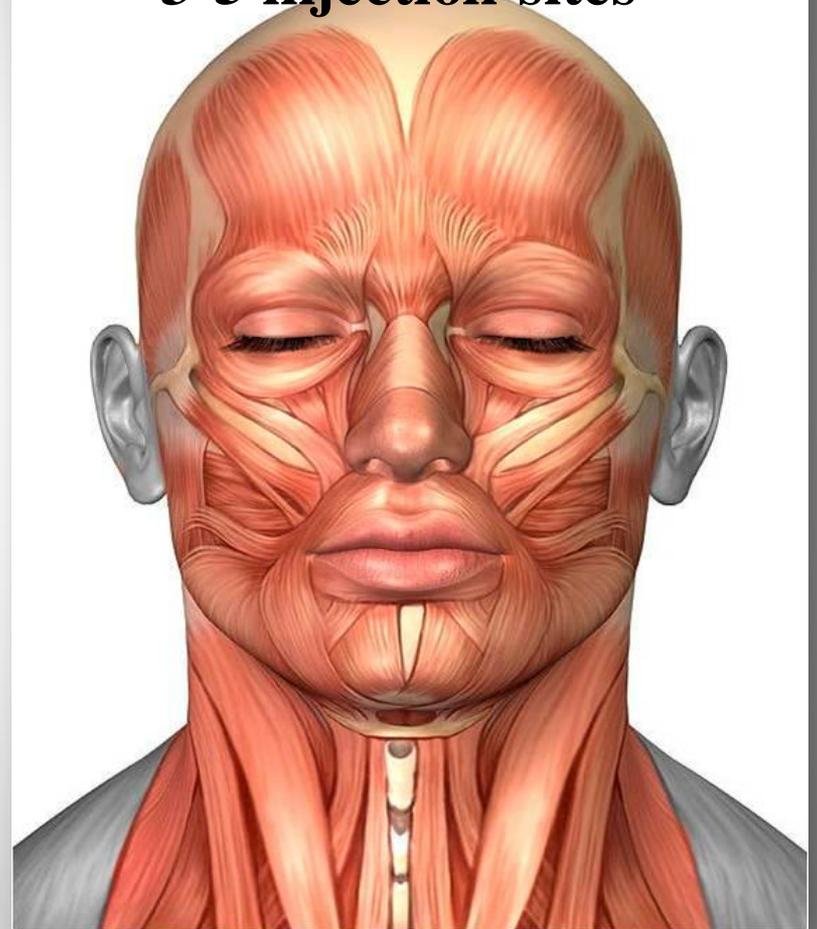
1 injection site per side



Glabella

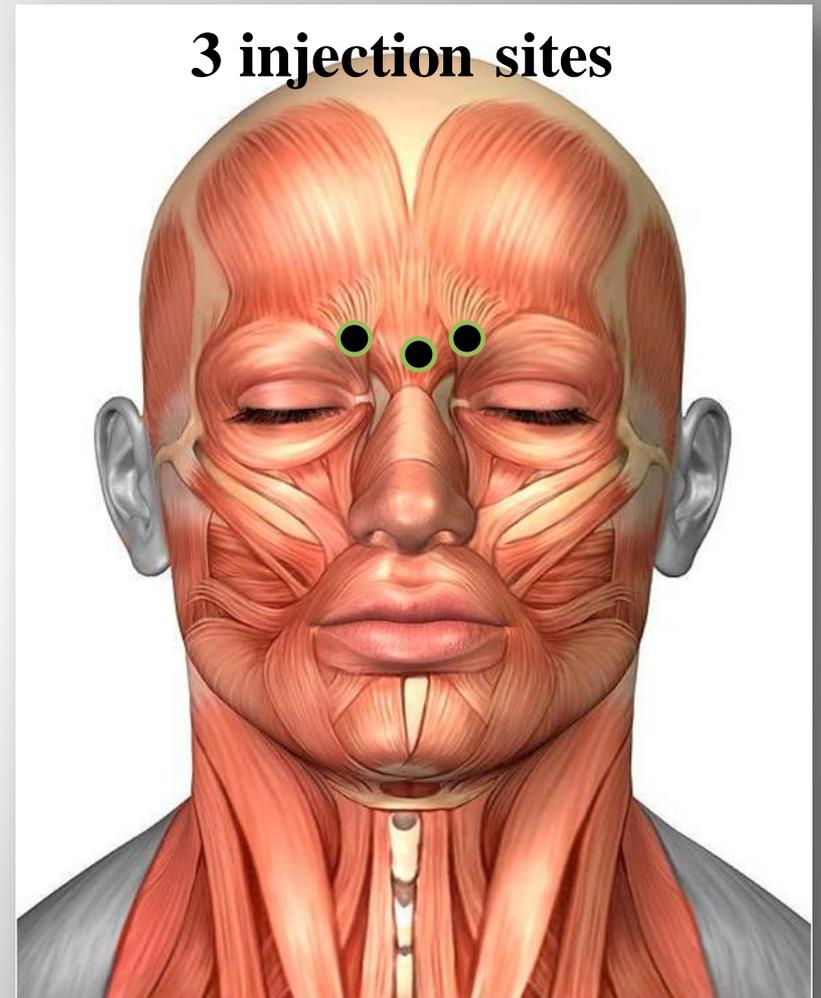
4-5 Units per Injection Site

3-5 injection sites



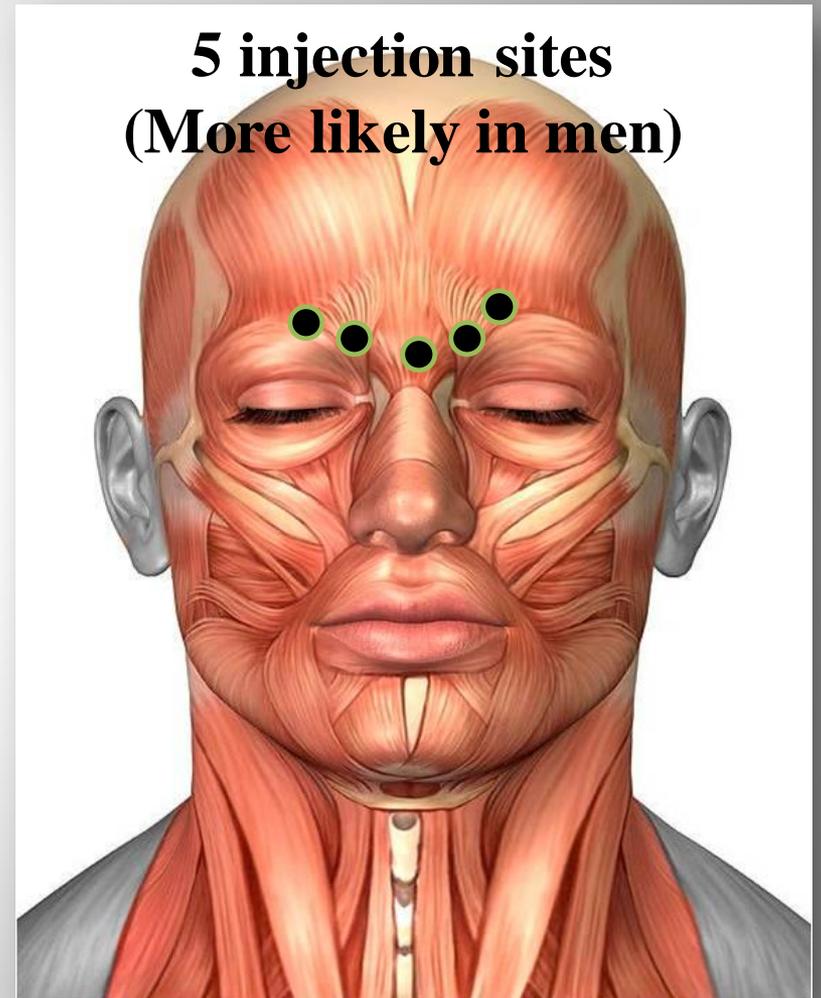
Glabella

4-5 Units per Injection Site



Glabella

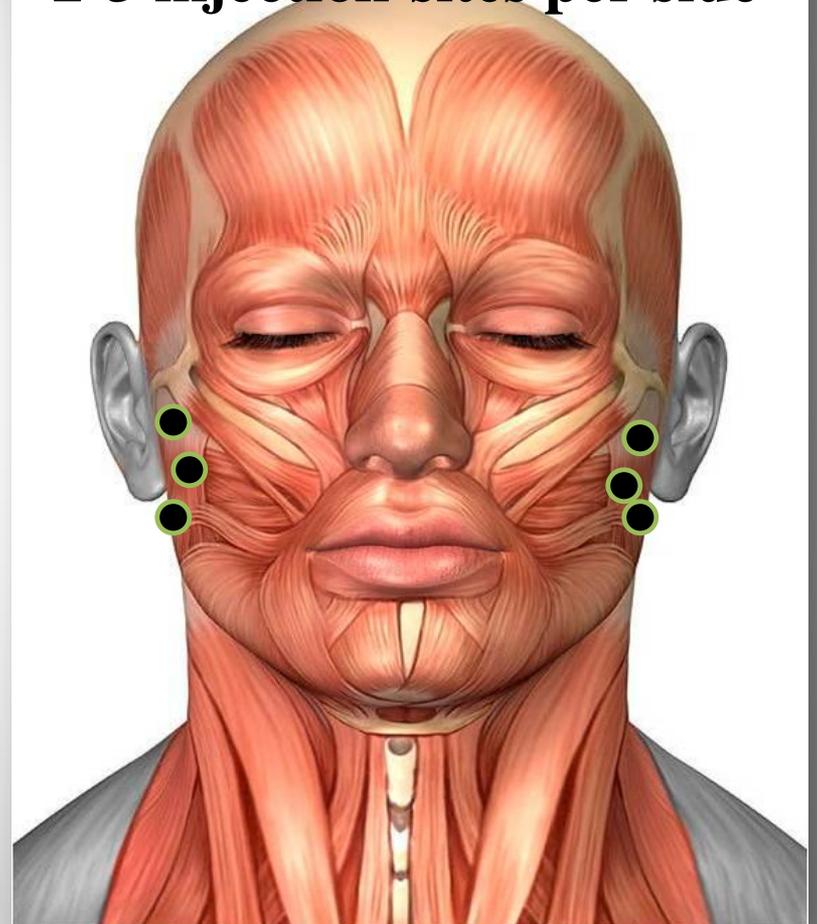
4-5 Units per Injection Site



Masseter Hypertrophy

5-10 Units per Injection Site

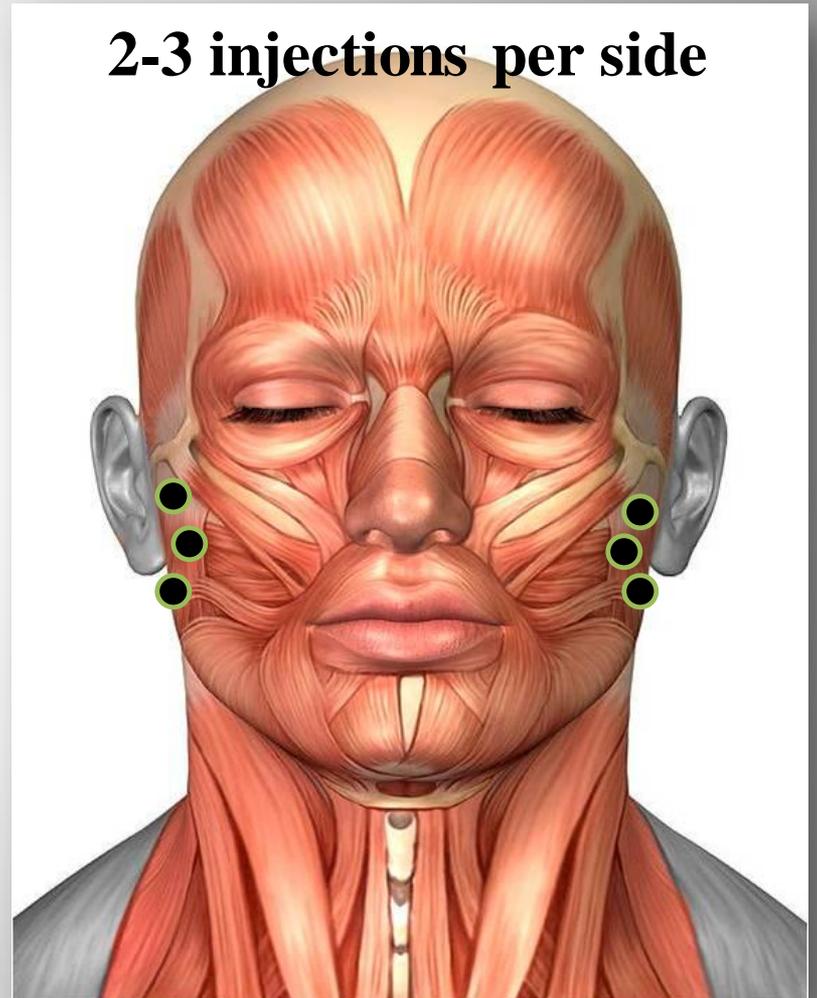
2-3 injection sites per side



Masseter Hypertrophy

5-10 Units per Injection Site

2-3 injections per side

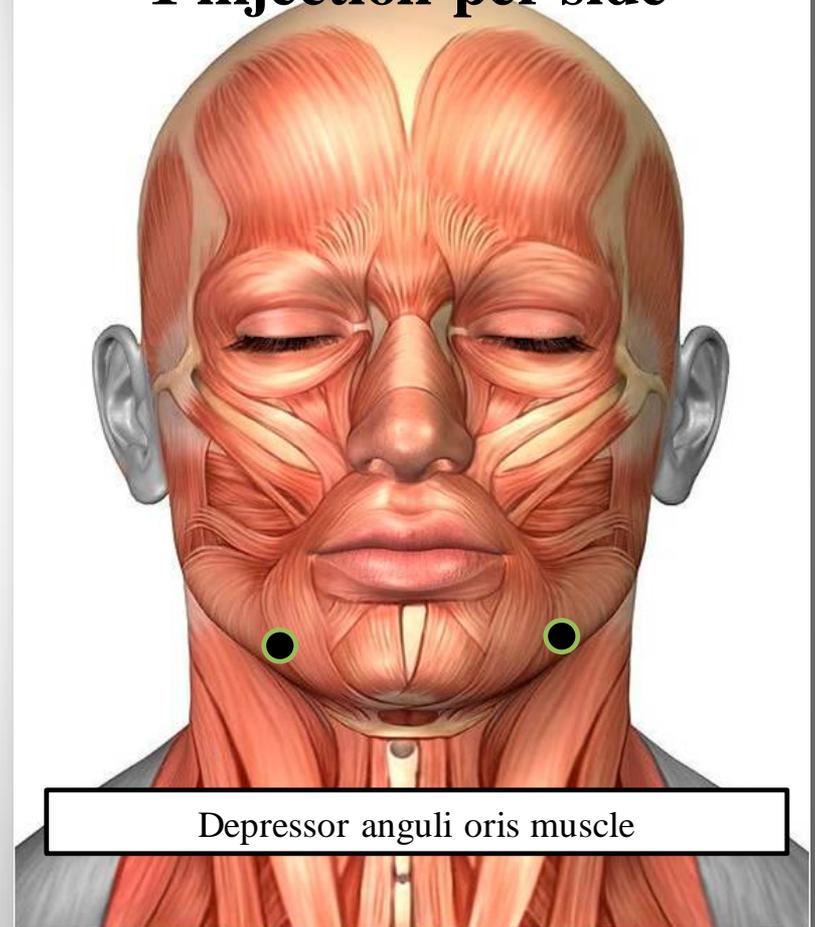


Avoid medial injection to risorius muscle

Lip Corner Elevation

3 to 5 Units per Injection Site

1 injection per side

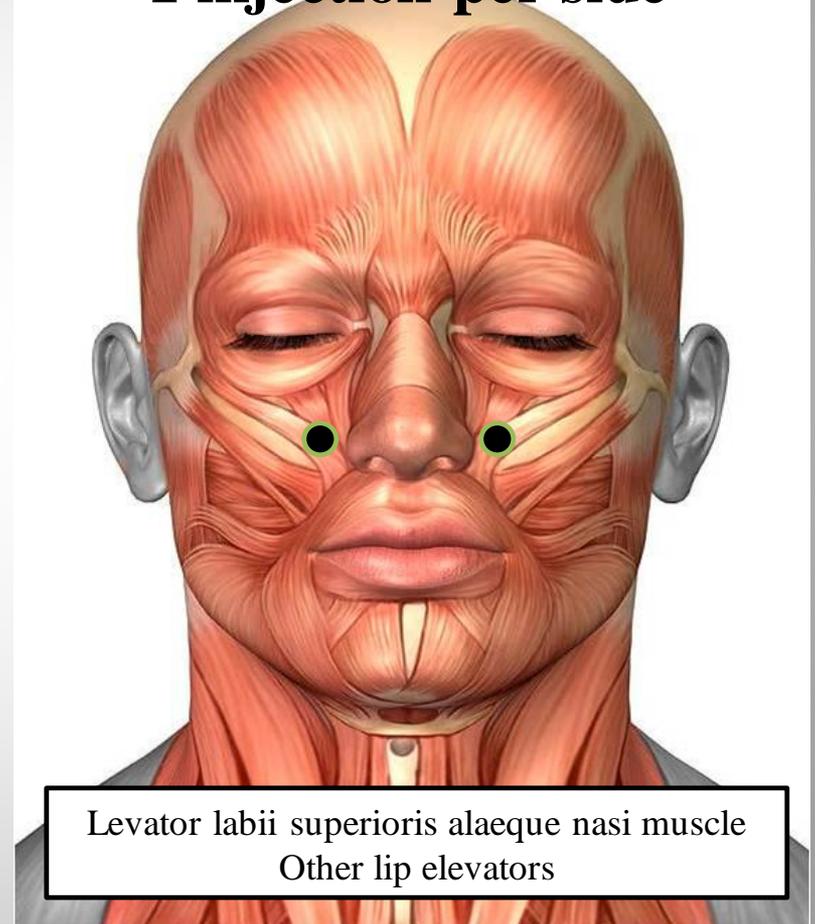


Inject lateral to commissure to
avoid central lip depression

Gummy Smile

4-5 Units per Injection Site

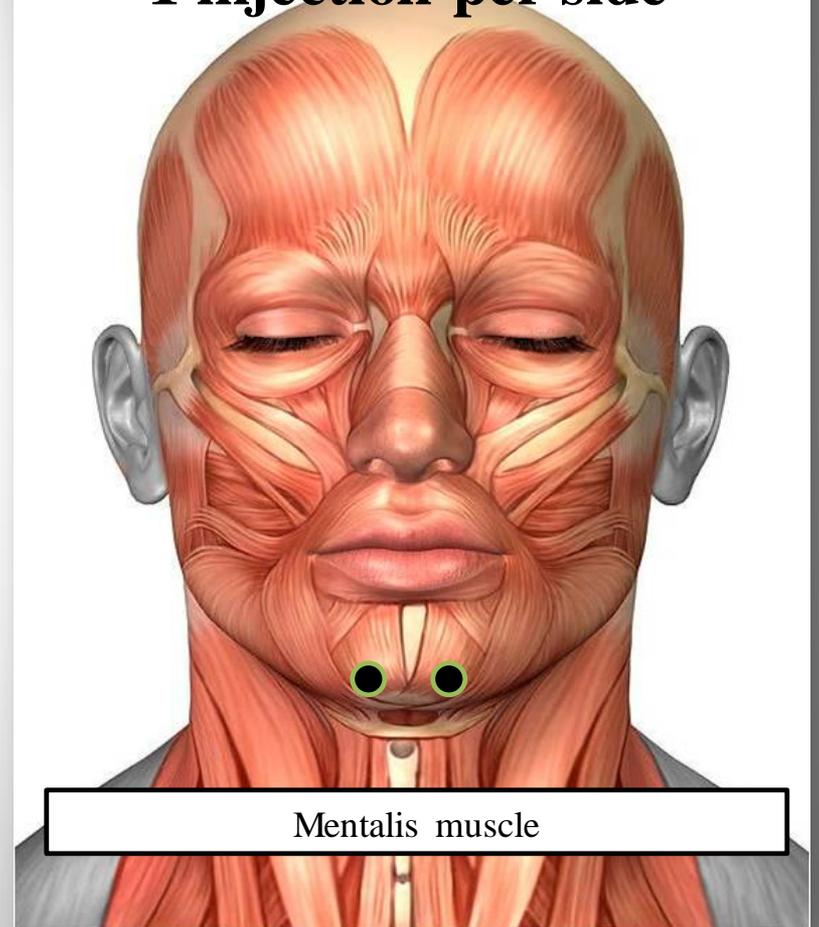
1 injection per side



Chin Dimples

4-5 Units per Injection Site

1 injection per side

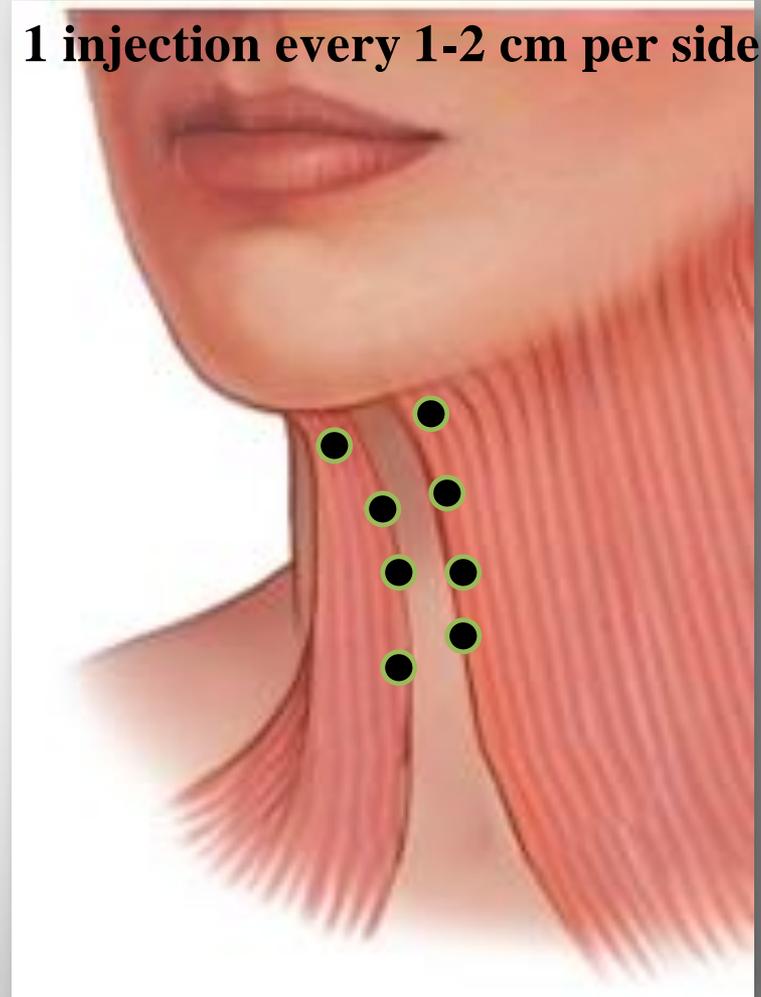


Mentalis muscle

Platysmal Bands

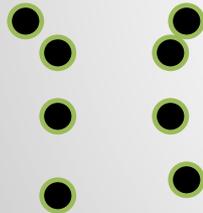
4 Units per Injection Site

1 injection every 1-2 cm per side

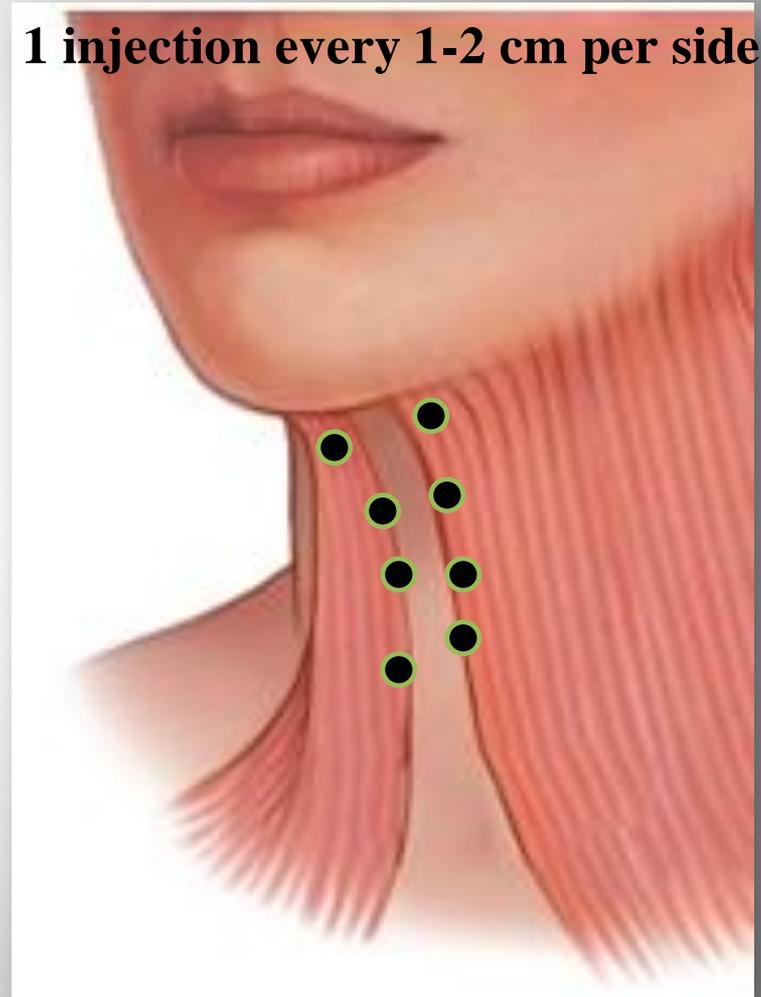


Platysmal Bands

4 Units per Injection Site



1 injection every 1-2 cm per side



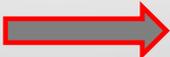
BoTN-A for Rosacea

- Erythematotelangiectatic Subtype
- DYSPORT: 15U to 45U intradermal injections



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

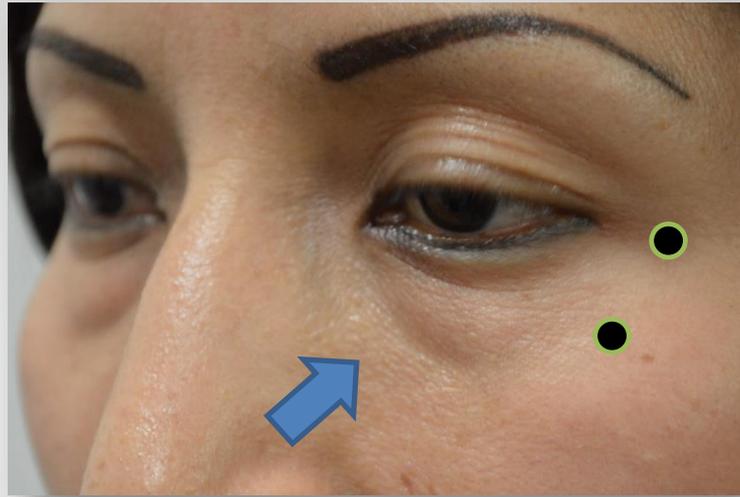
BoTN-A & the Four R's

- **Relax** the muscle: BoTN-A
- **Refill** the face (volume): Fillers
- **Resurface** the skin: Lasers
 - Fractional CO₂
- **Relift** the tissue: Energy-based
 - Ultherapy
 - Neck laser-assisted liposuction

BoTN-A + Fractional CO₂ Laser



BoTN-A + Filler



Learn More in PRS Supplement

NEUROTOXINS

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.

Botulinum Neuromodulators: What's New?

Karol A Gutowski, MD, FACS

plastic
surgery
THE MEETING

Los Angeles

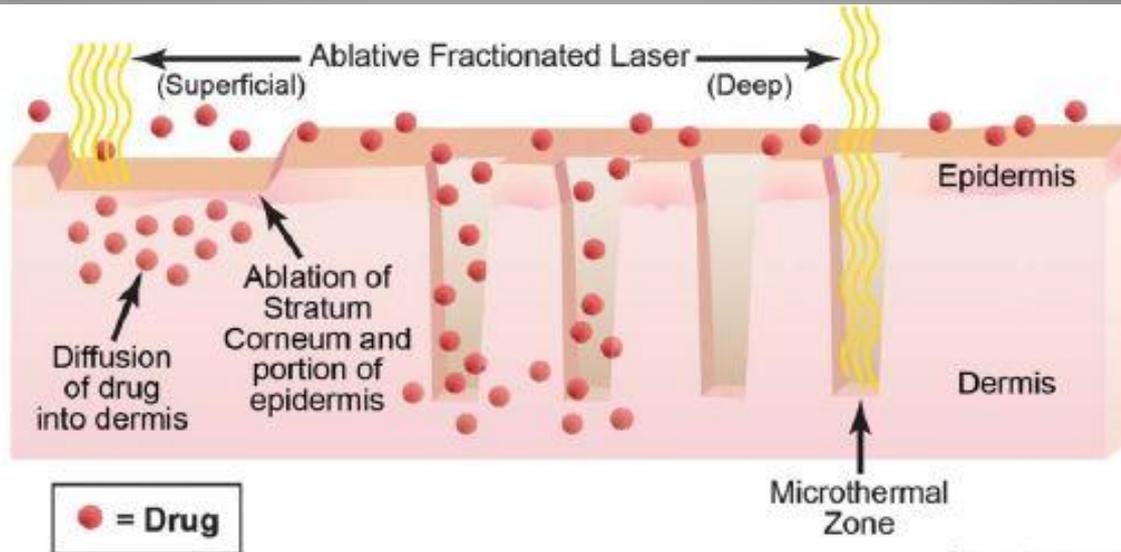
September 23-27, 2016



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

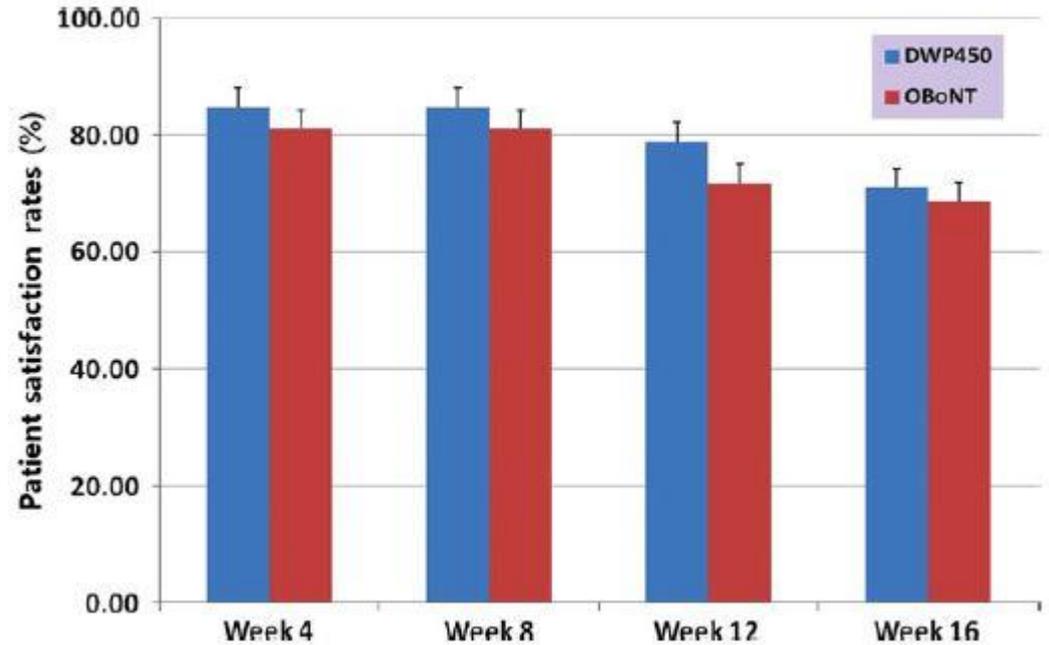
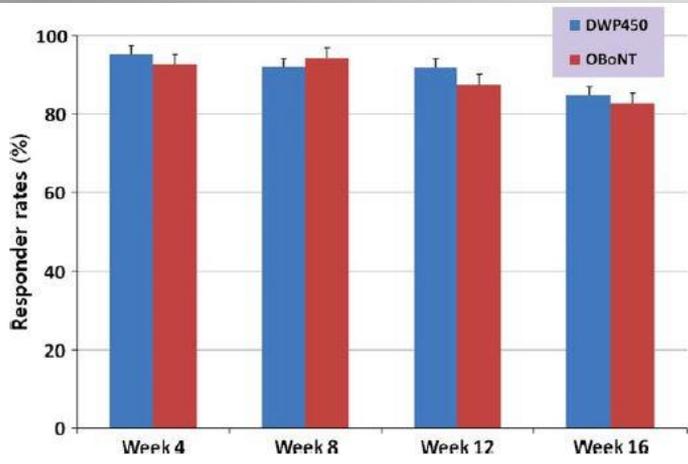
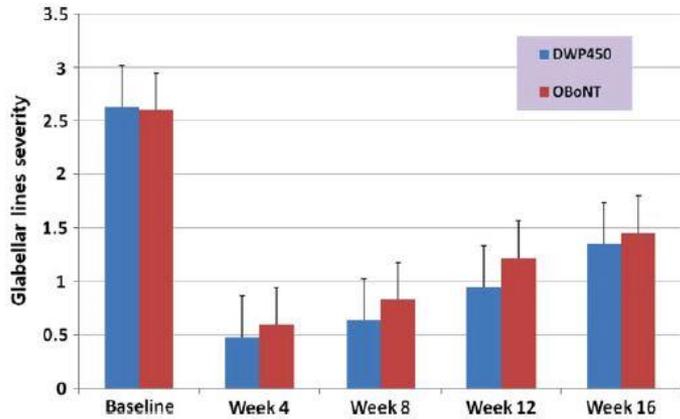
Chong Hyun Won¹, MD, PhD, Hyun Kyu Kim², MD, Beom Joon Kim², MD, PhD, Hoon Kang³, MD, PhD, Joon Pio Hong⁴, MD, PhD, Su-Young Lee⁵, BS, and Chung-Sei Kim⁵, PhD

Daewoong, Korea

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

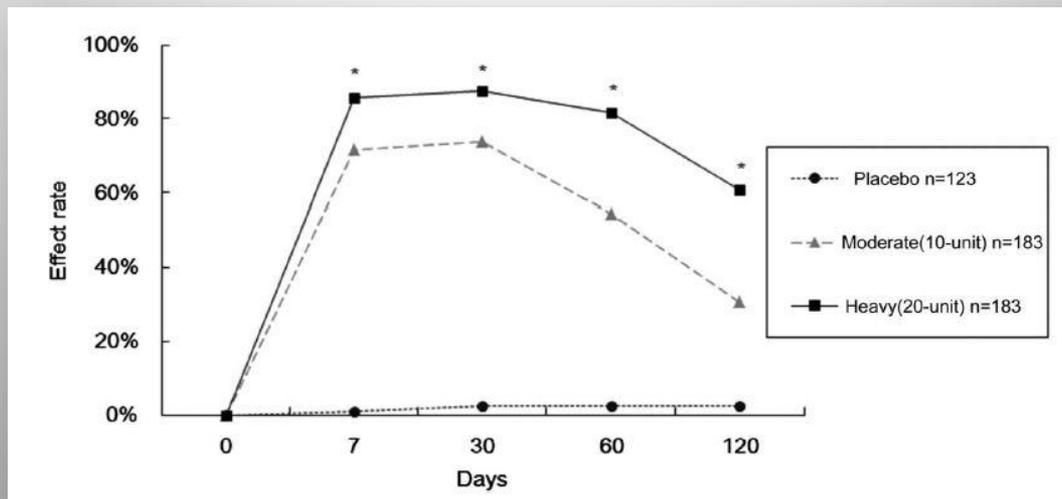


Nabota (DWP450)



Chinese BoTN-A

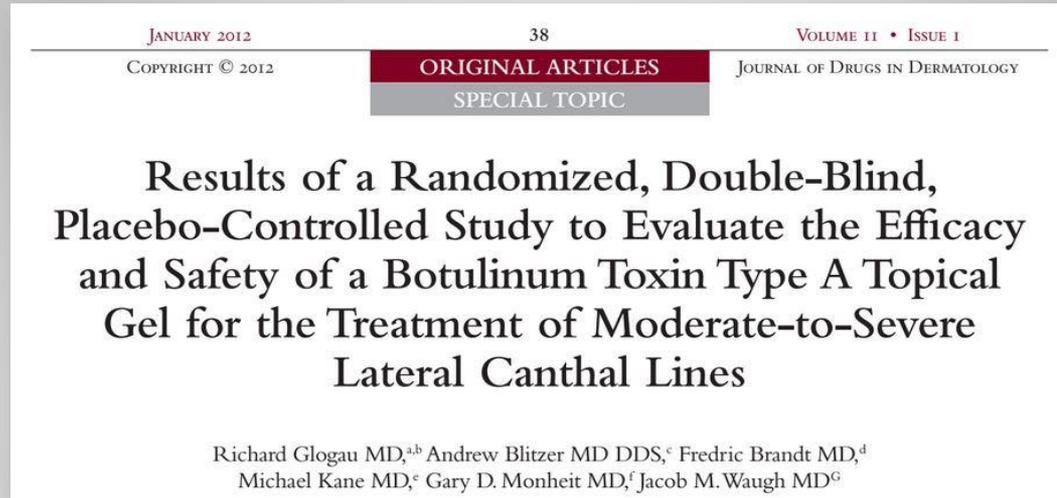
- CBoTN-A (aka Hengli BoTN-A, HBoTN-A)
- Greater diffusion area than BOTOX
 - Based on forehead anhidrosis test
- Possible longer duration than BOTOX
- Glabella: 20U > duration than 10U



RT001: Topical BoTN-A

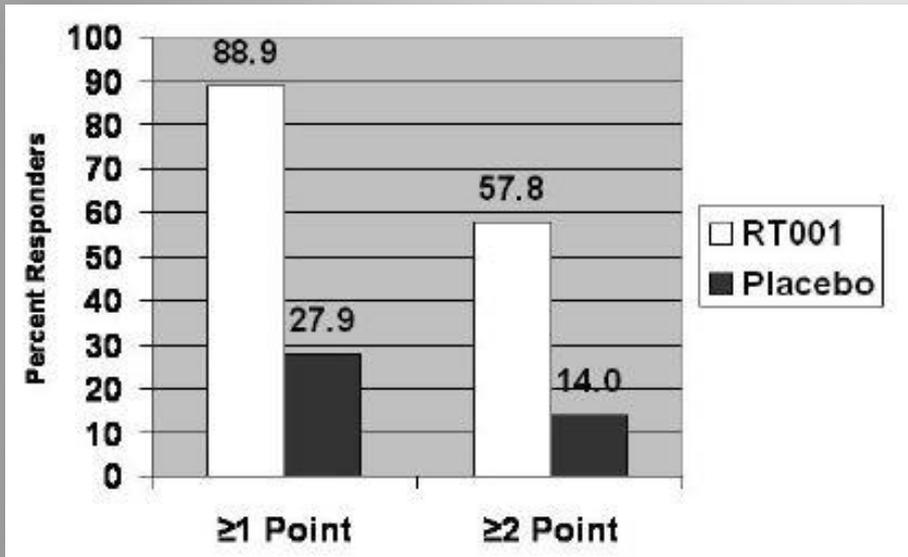
- Revance developed mechanism to allow transepidermal transfer of large molecules
- Supplied as lyophilized 150kD BoTN-A + proprietary peptide
- Reconstituted with poloxamer diluent
- Gels on contact with skin
- Removed after 30 min

RT001 Lateral Canthal Lines

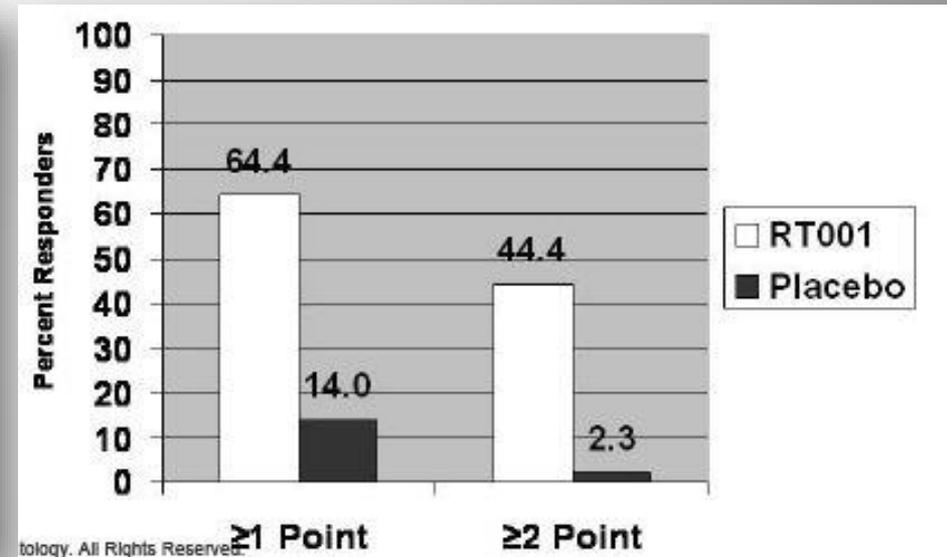


- 45 patients in each arm
- ≥ 2 point improvement
- At 4 weeks
 - 44% ≥ 2 point improvement
 - 89% clinically relevant improvement

RT001: 4 Week Response



Investigator



Patient

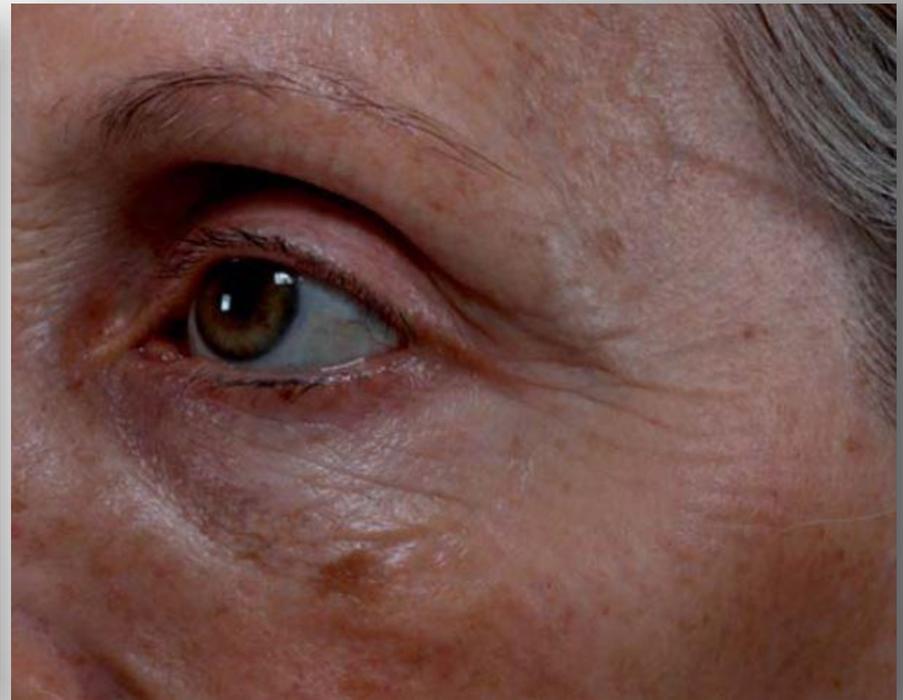
RT001: Topical BoTN-A

- 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 1/2 of face

RT001: Topical BoTN-A



RT002

Safety and Efficacy of RT002, an Injectable Botulinum Toxin Type A, for Treating 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. HORNFELODT, PHD[‡]

- Less BoTN-A spread
- Allows greater injection
 - Possible longer duration?

RT002

- 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*

plastic
surgery

THE MEETING

Los Angeles

September 23-27, 2016

