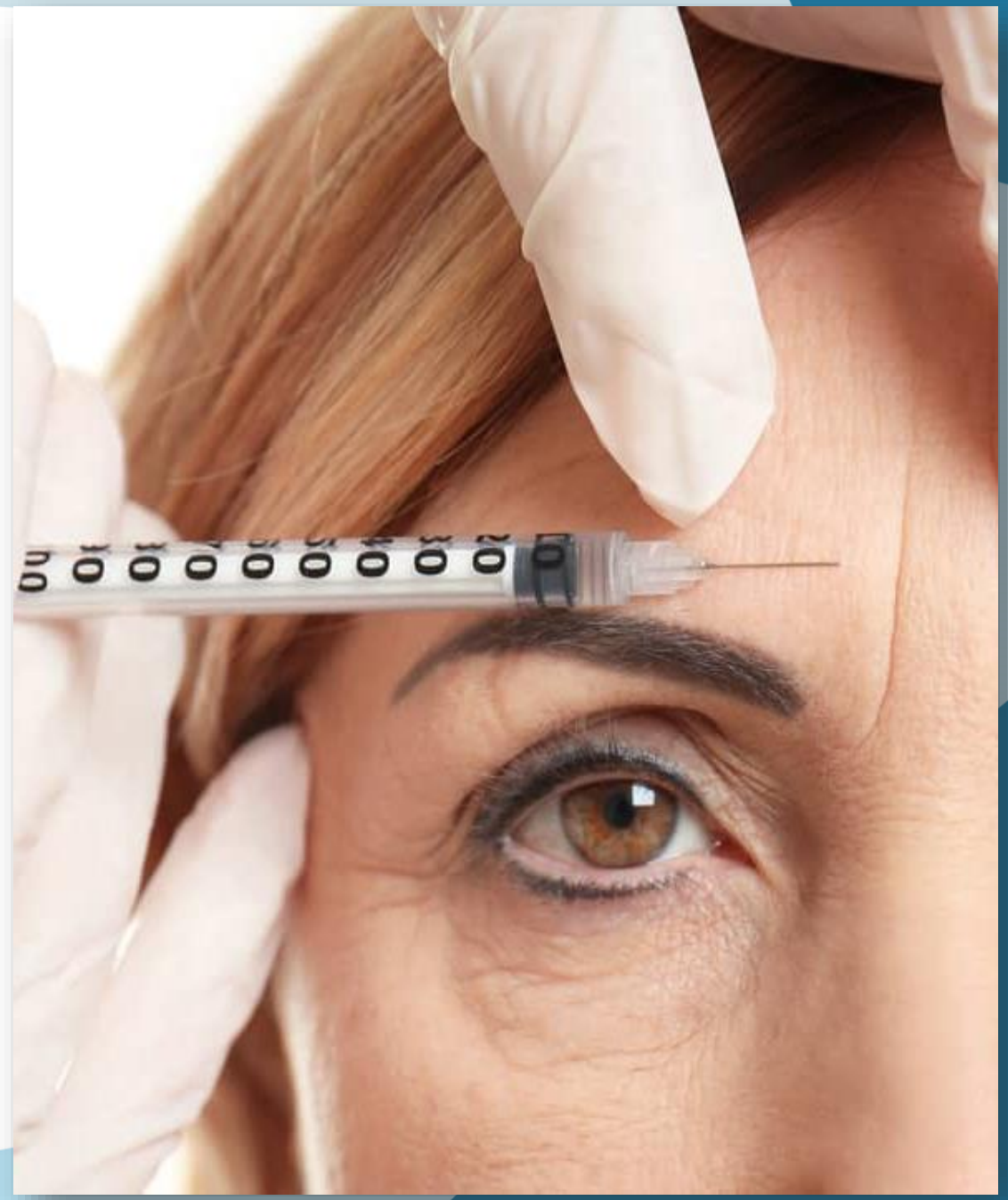
THE ARTISTRY OF INJECTABLES

Comprehensive Training For Your Practice

Basics of Neuromodulators

Karol A Gutowski, MD, FACS
Private Practice
University of Chicago
University of Illinois



Agenda

- Basics of Botulinum Toxin A (BTA)
- What doses the data show
- Patient assessment
- Common injection sites
- Less common uses
- Update on DaxibotulinumtoxinA (Daxxify, Daxi)

What FDA Wants You to Know

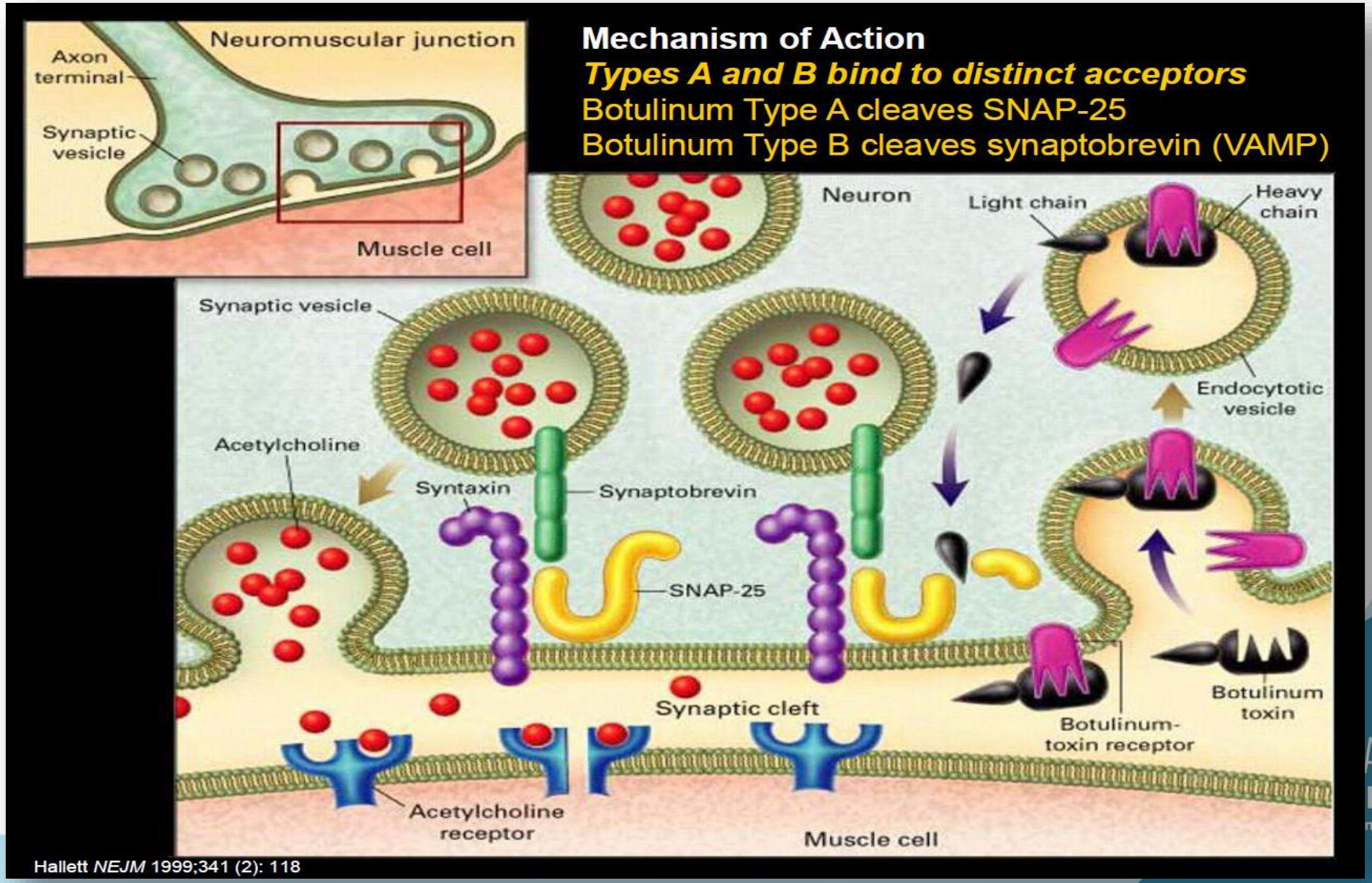
- Black Box Warning
  - Possibility of experiencing potentially life-threatening distant spread of toxin effect from injection site after local injection
  - Not reported in cosmetic uses
- Risk Evaluation and Mitigation Strategy (REMS)
  - *Medication Guide* to help patients understand risks & benefits
- Potency units are specific to each product
  - Doses or units cannot be compared or converted

Botulinum Toxin A (BTA) 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

BTA Mechanism of Action



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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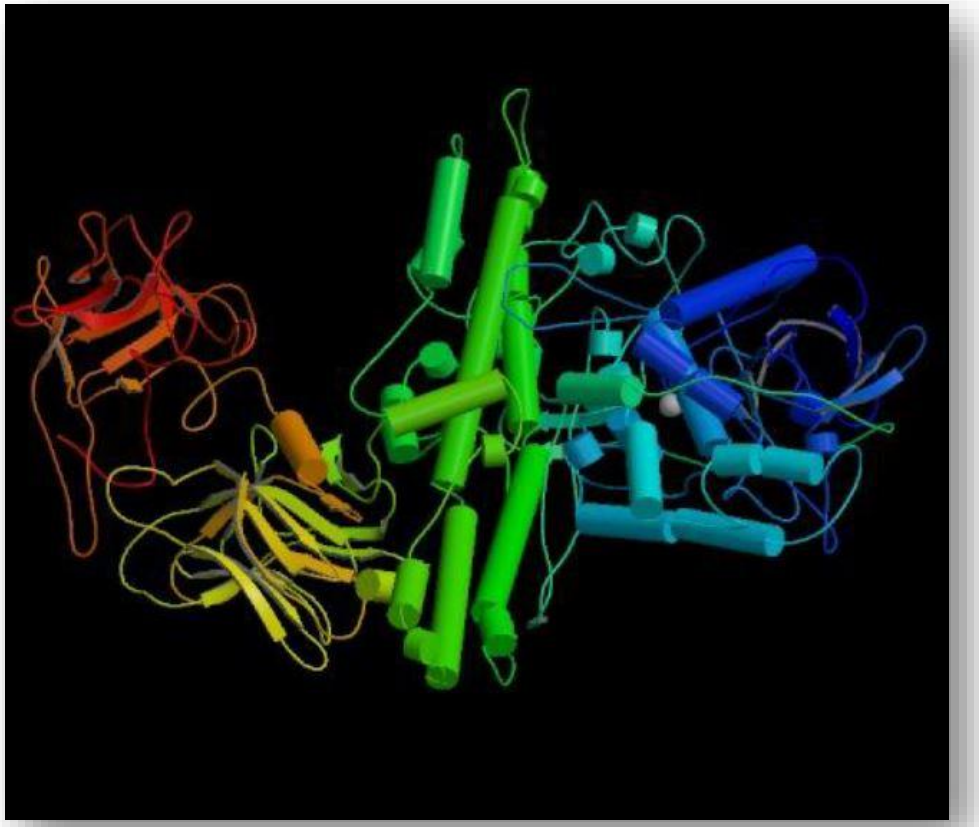
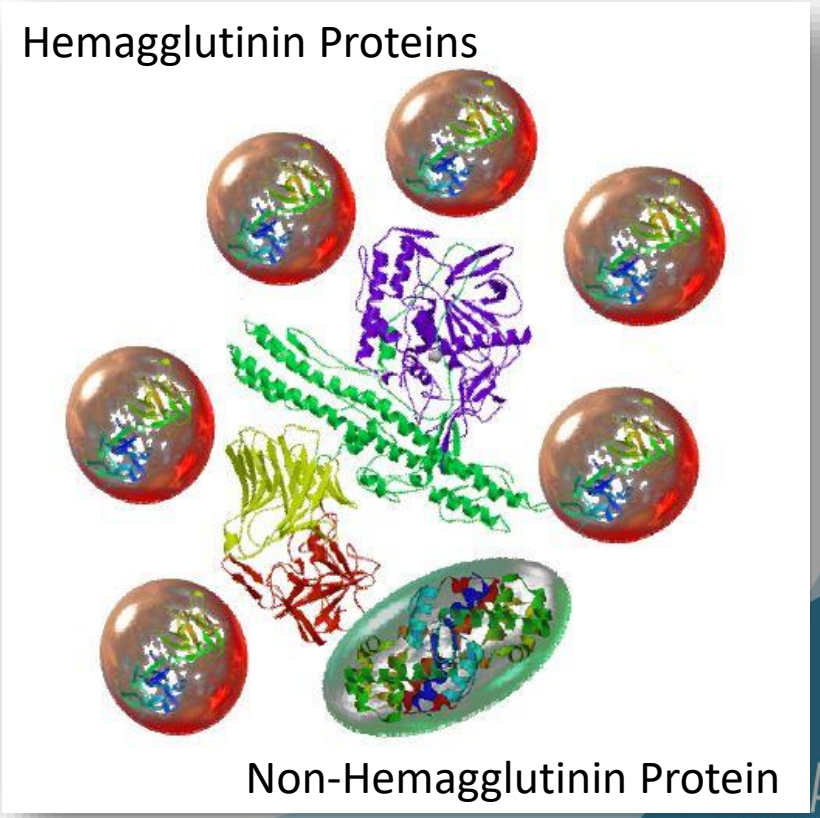
BTA Molecule

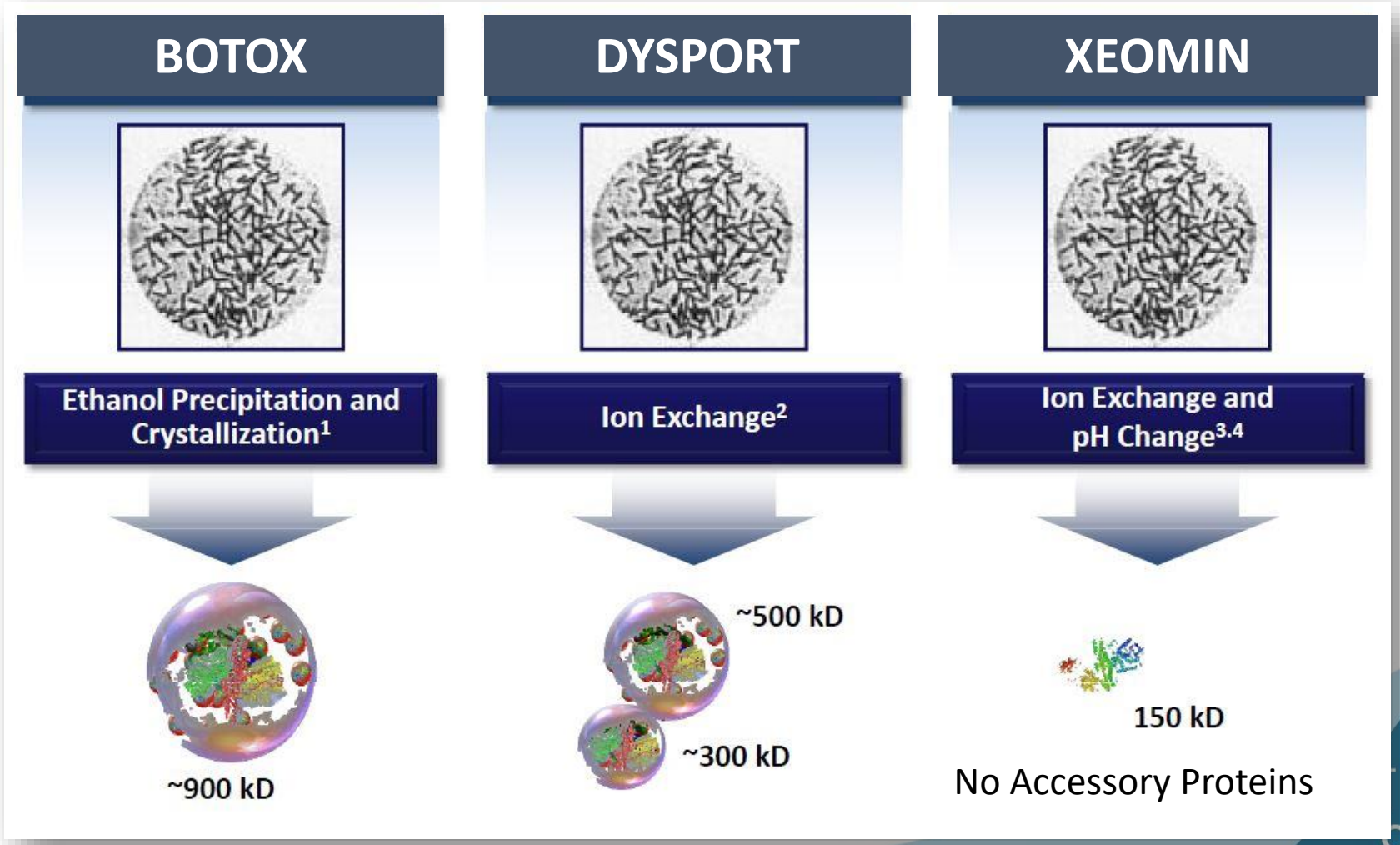
BoTN-A



BoTN-A + Accessory Proteins



BTA Protein Comparison



Pivotal Study Doses

BTA	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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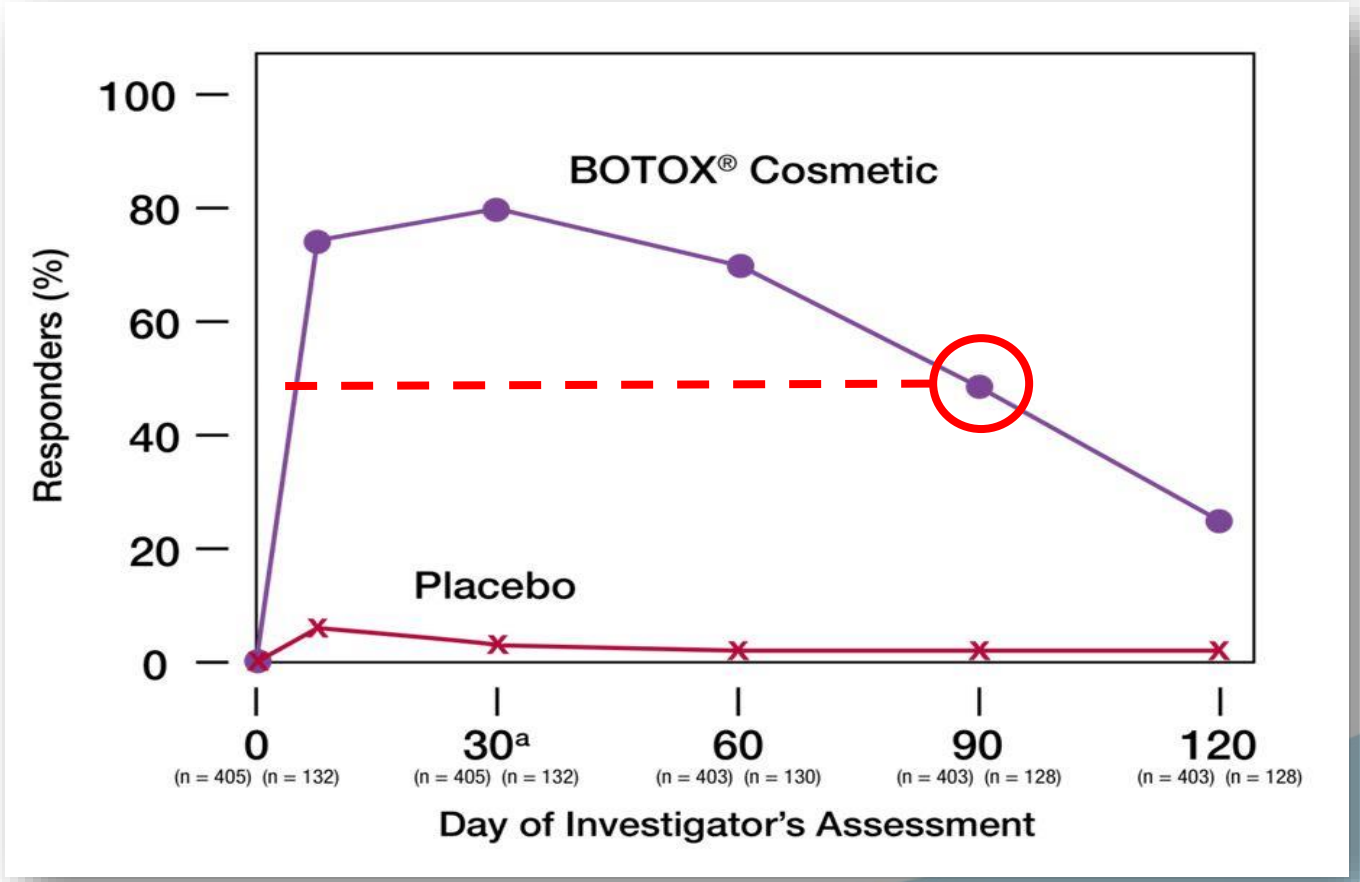
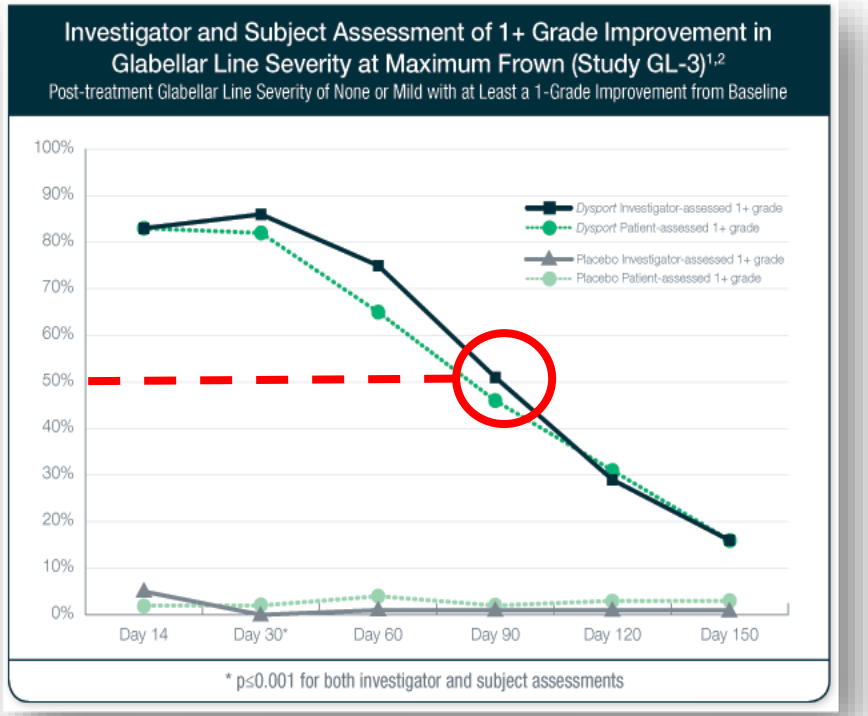
BOTOX Pivotal Studies

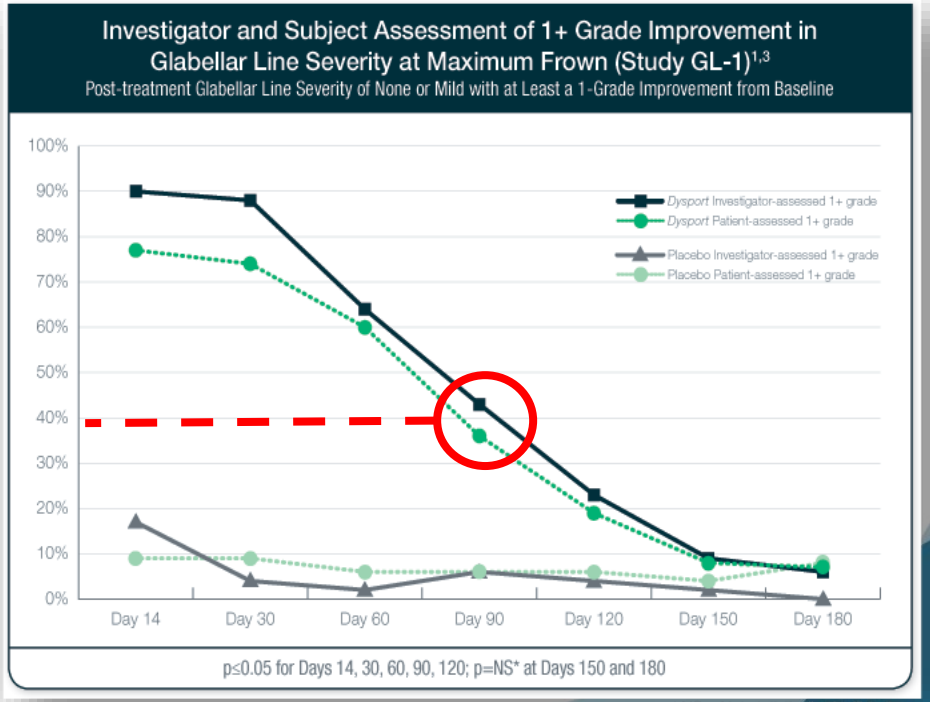
50% of patients maintain improvement at 3 months



DYSPORT Pivotal Studies

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

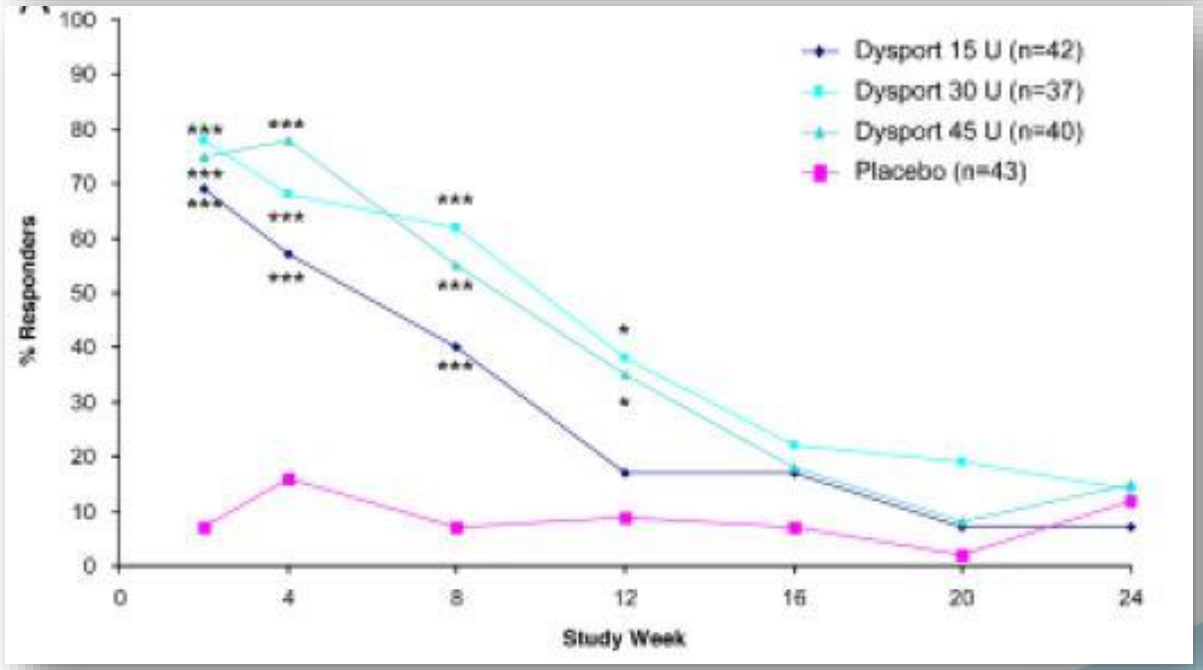




DYSPORT Dose Response

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

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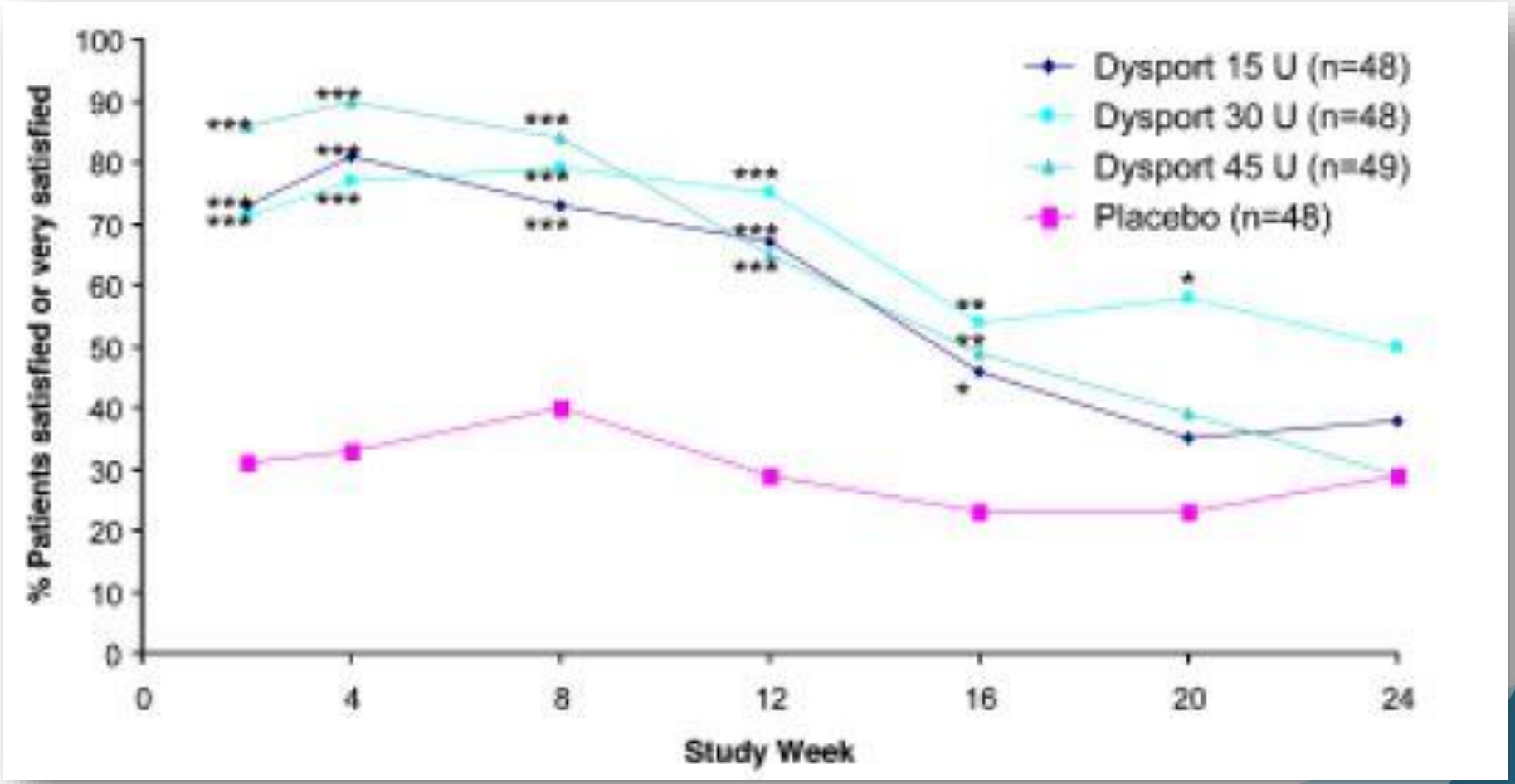
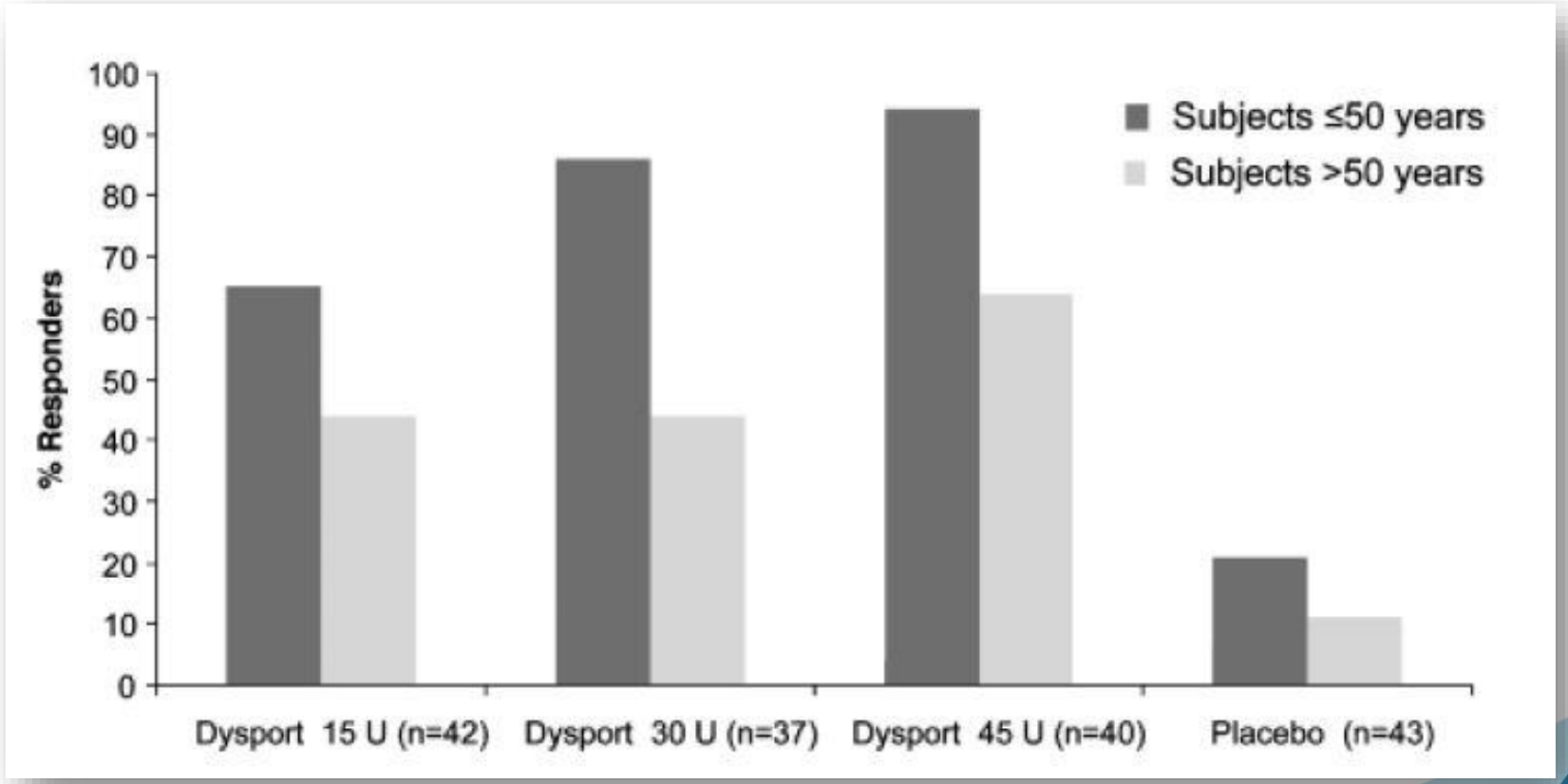
DYSPORT Dose Response



Patient satisfaction similar at all doses

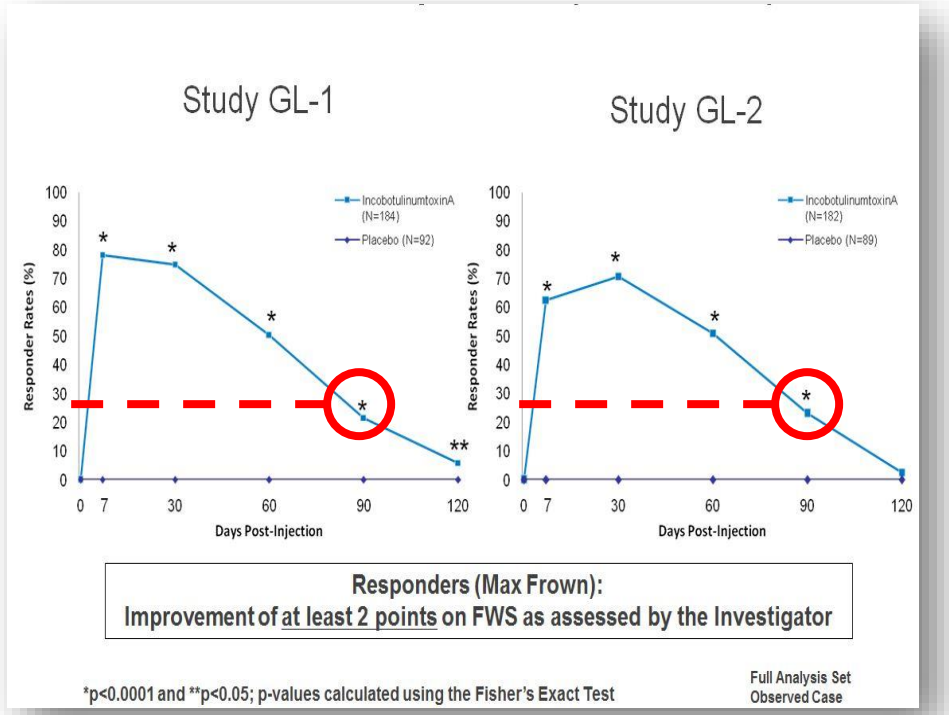
DYSPORT Dose Response

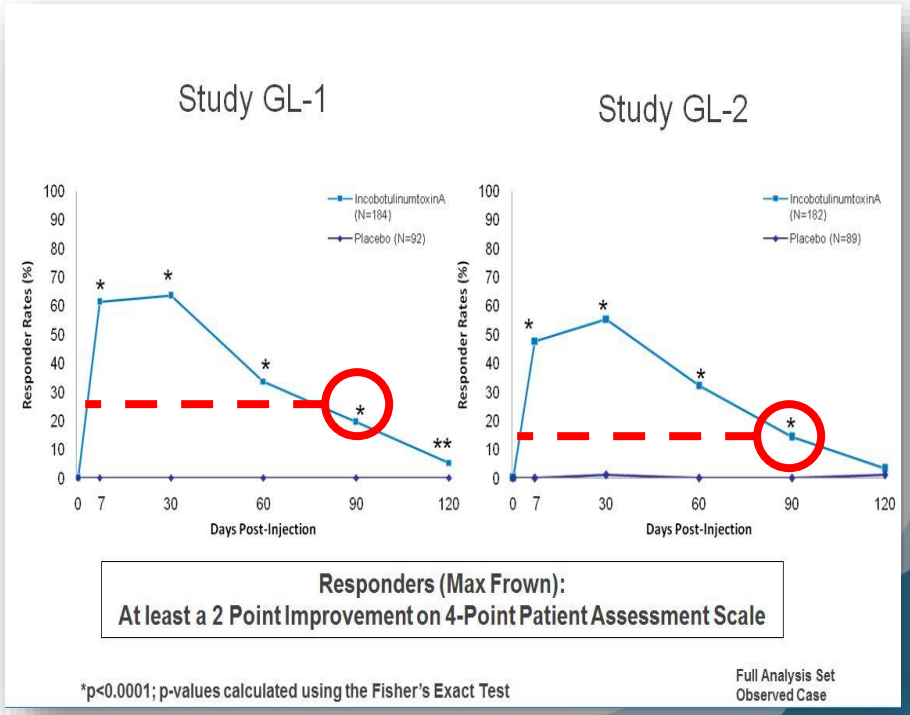


Older patients less likely to respond

XEOMIN Pivotal Studies

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





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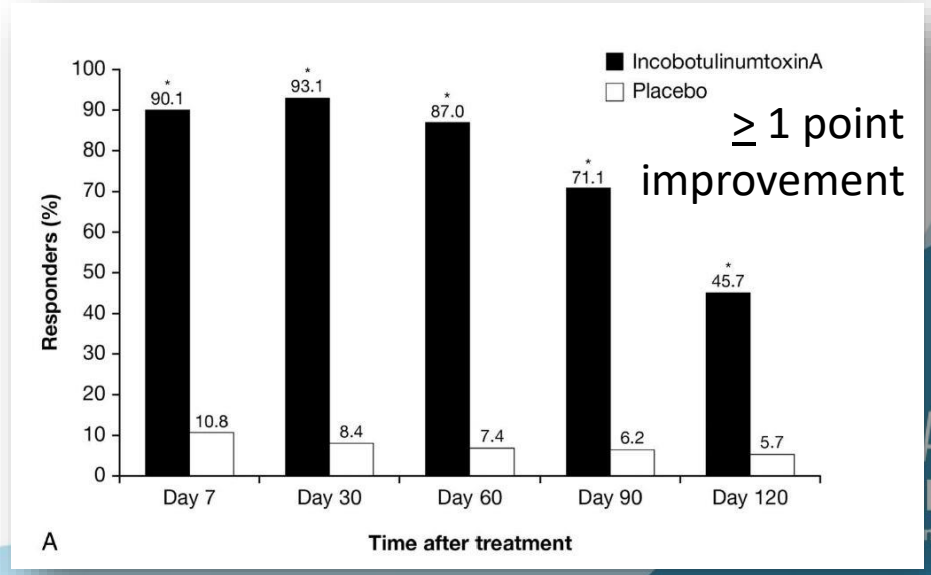
XEOMIN Phase 3 Post Hoc Analysis

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



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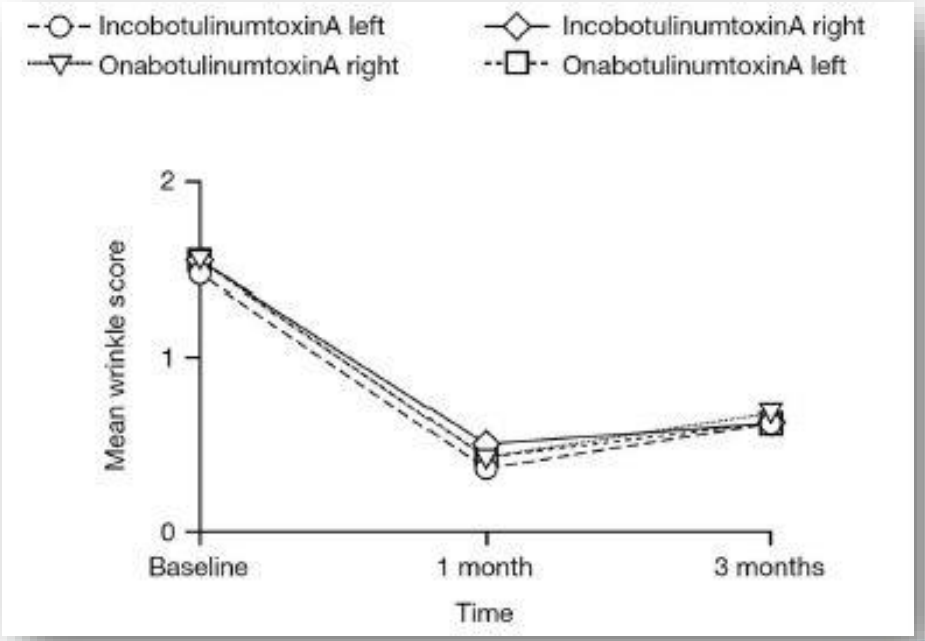
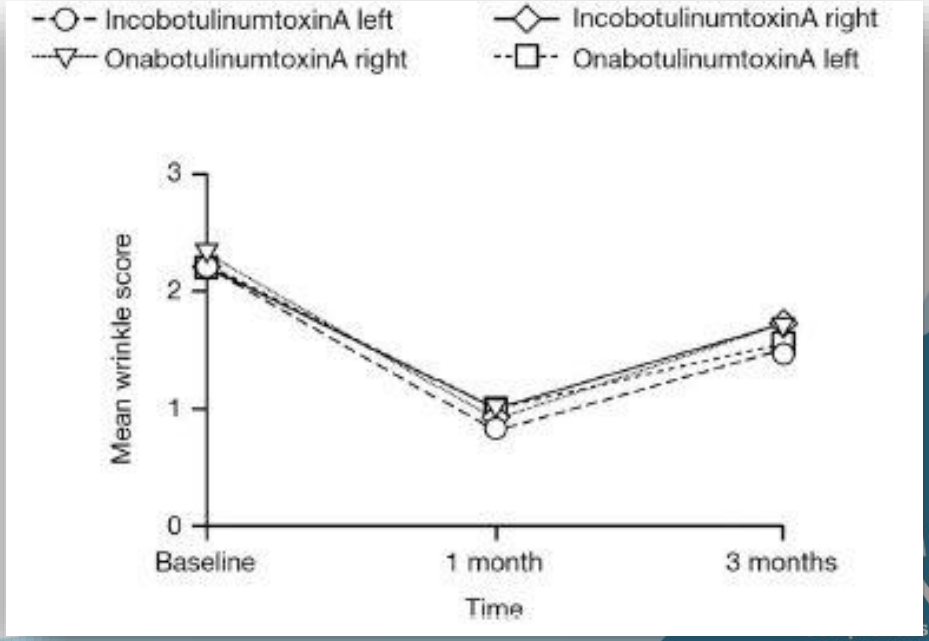
BOTOX vs XEOMIN

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

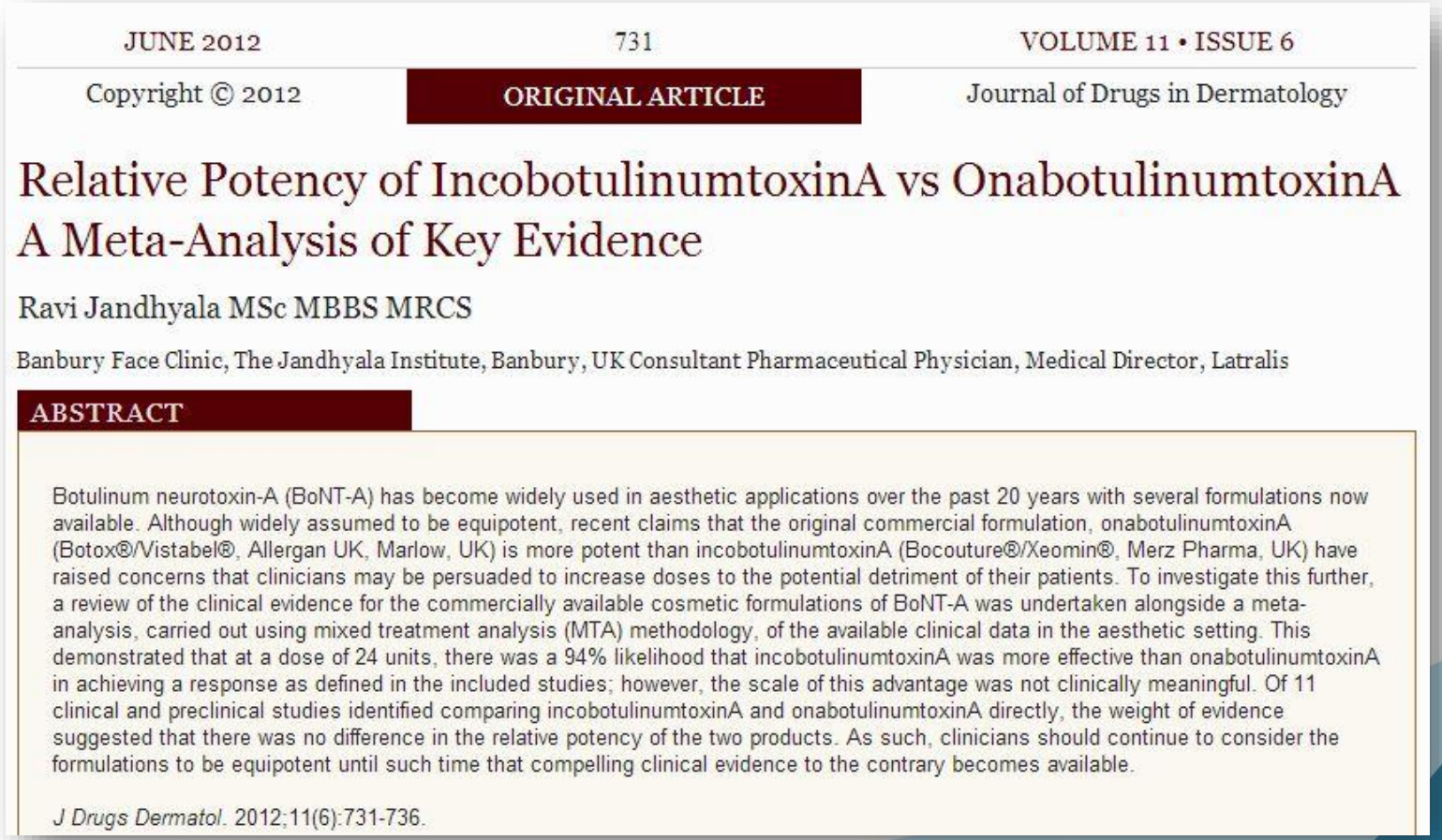
GABRIELE MUTI, MD,* AND LAURA HARRINGTON, PHD†





BOTOX vs XEOMIN Dose

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



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.

BOTOX vs XEOMIN

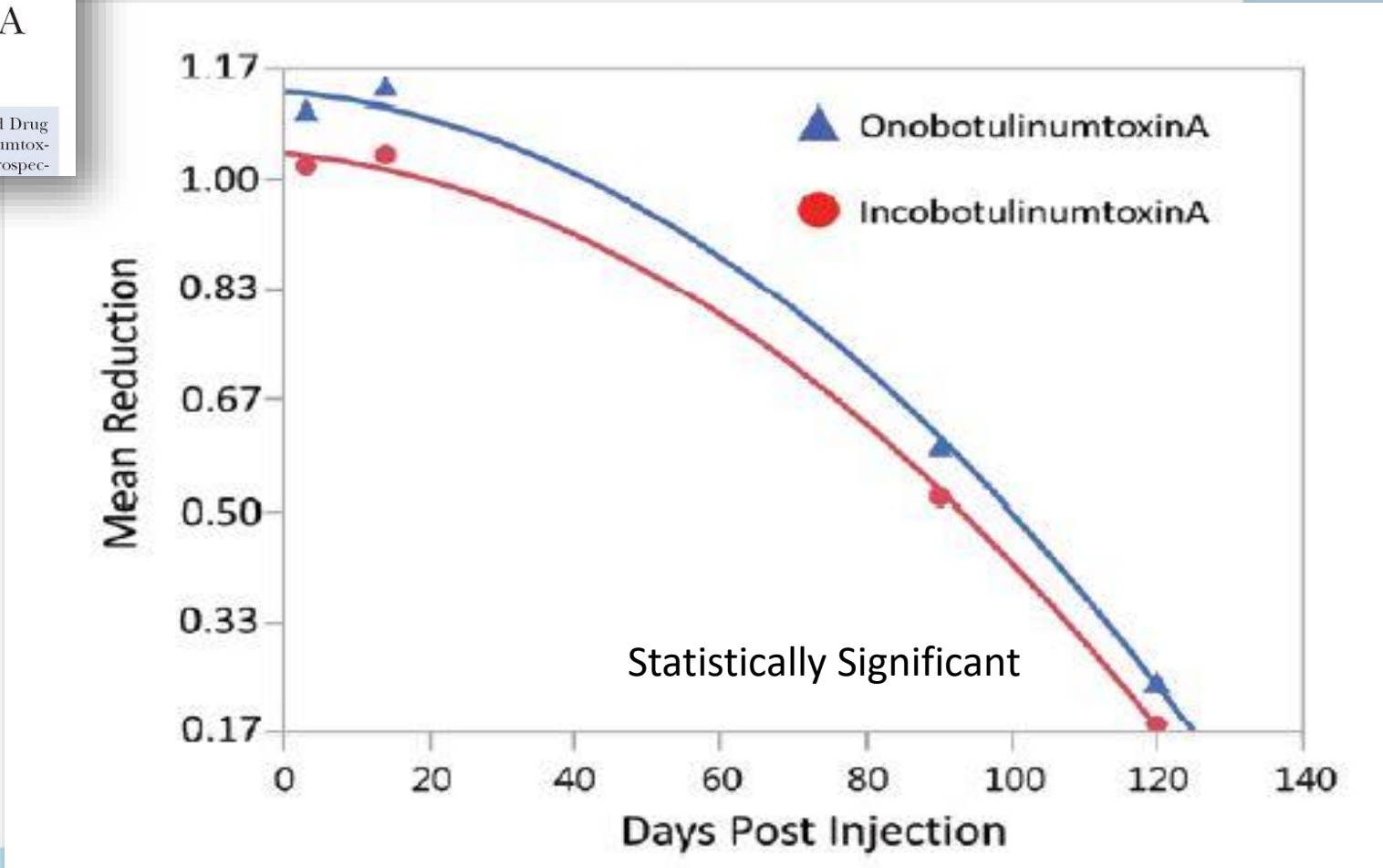
COSMETIC

2015

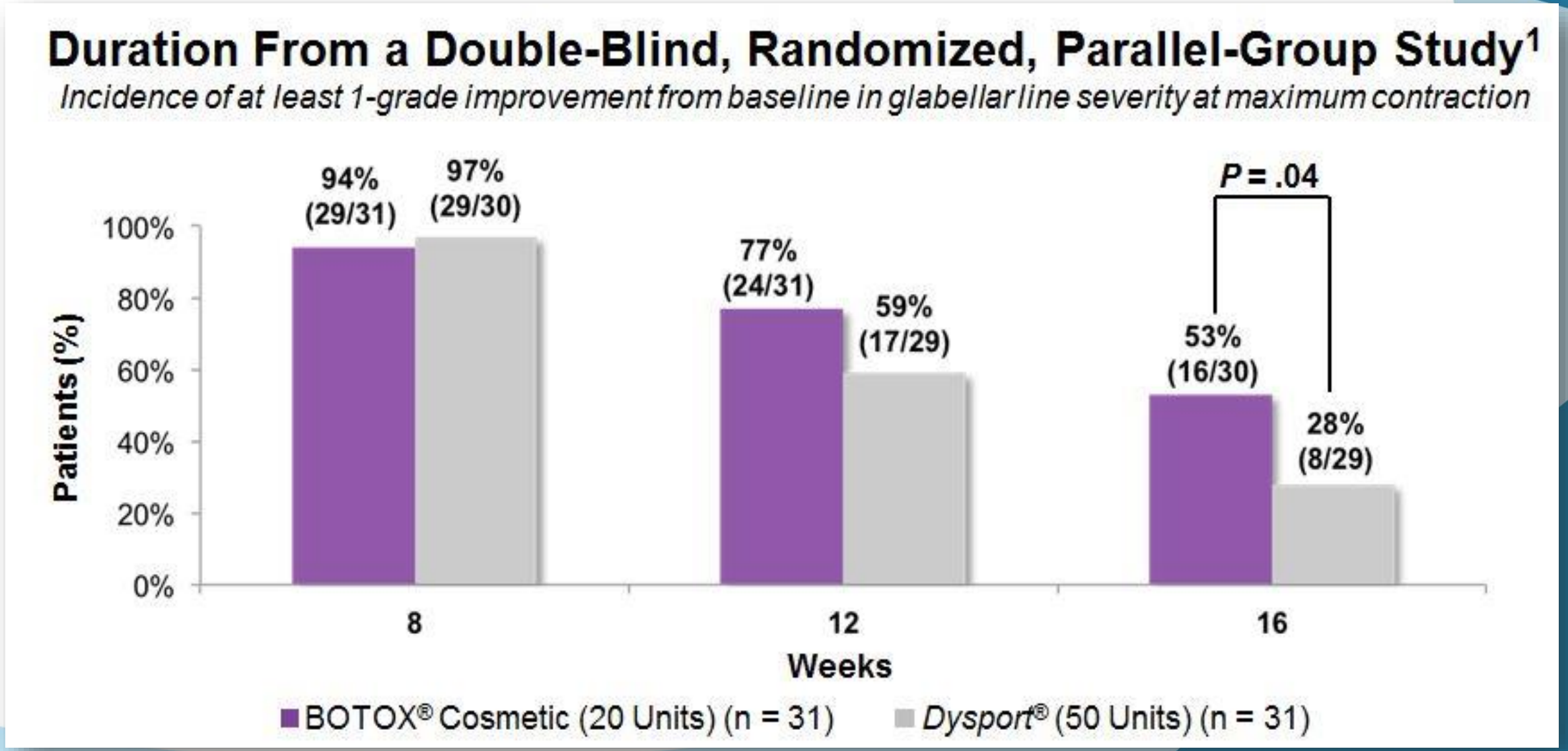
A Prospective, Split-Face, Randomized, Double-Blind Study Comparing OnabotulinumtoxinA to IncobotulinumtoxinA for Upper Face Wrinkles

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



Lowe, J Am Acad Dermatol 2006

BTX, XEO, DYS Strain Study

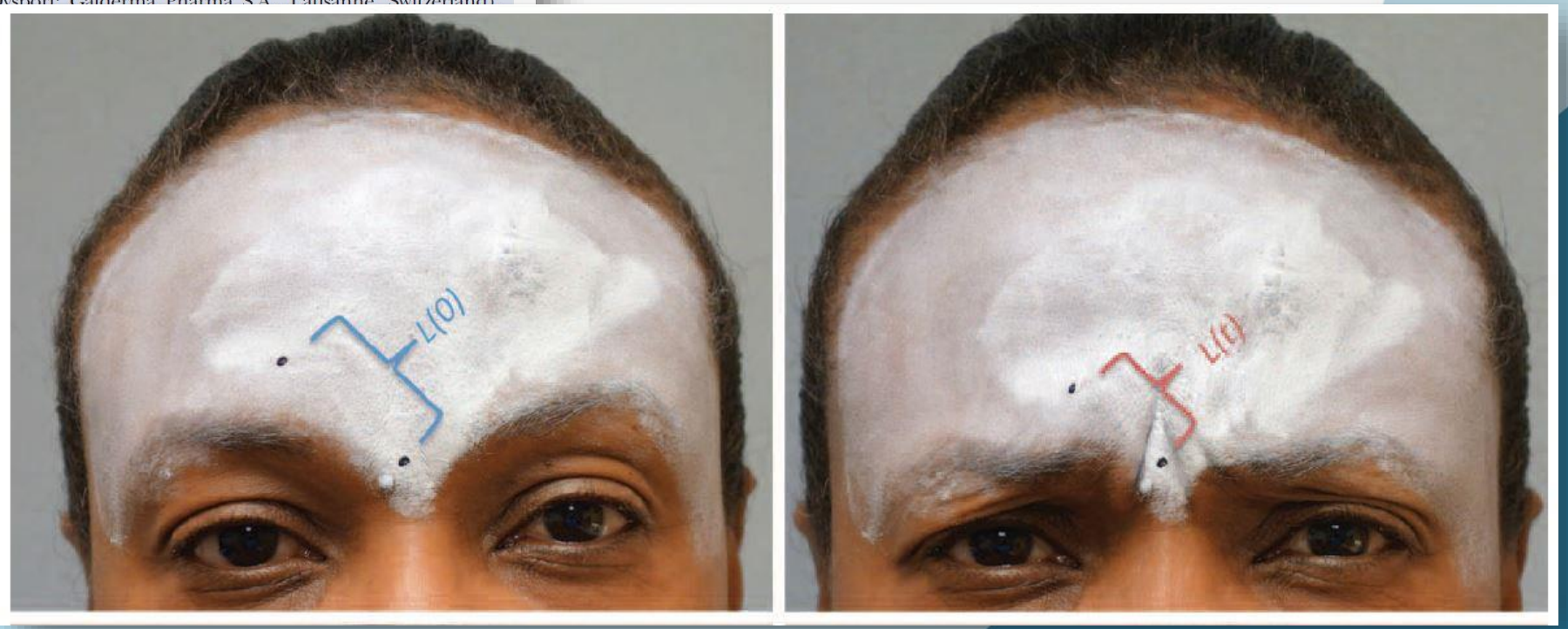
COSMETIC

2016

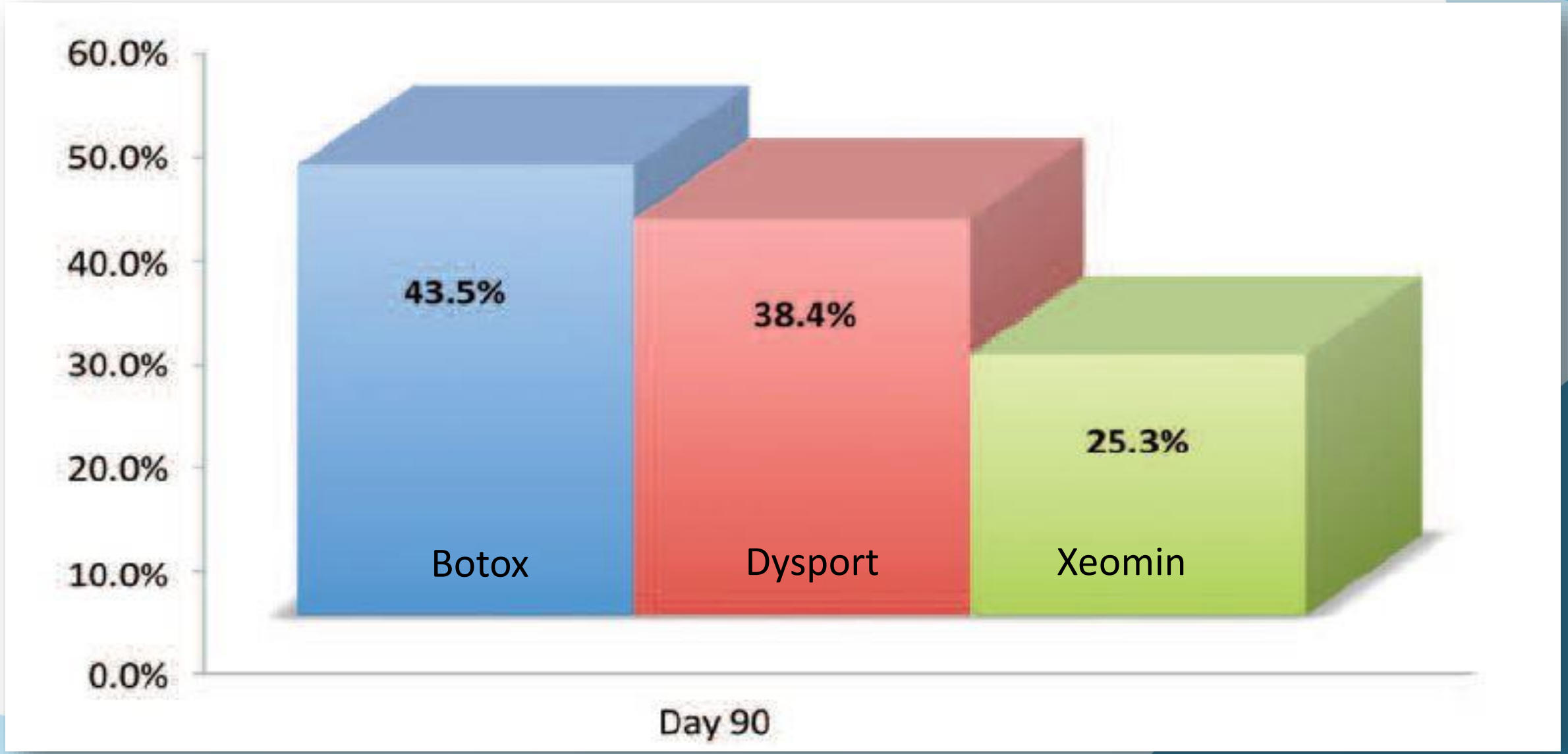
A Quantitative Analysis of OnabotulinumtoxinA, AbobotulinumtoxinA, and IncobotulinumtoxinA: A Randomized, Double-Blind, Prospective Clinical Trial of Comparative Dynamic Strain Reduction

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 incobotulinumtoxin
Main, Germany). This s
strain reduction betwee
Methods: Seventy-thre

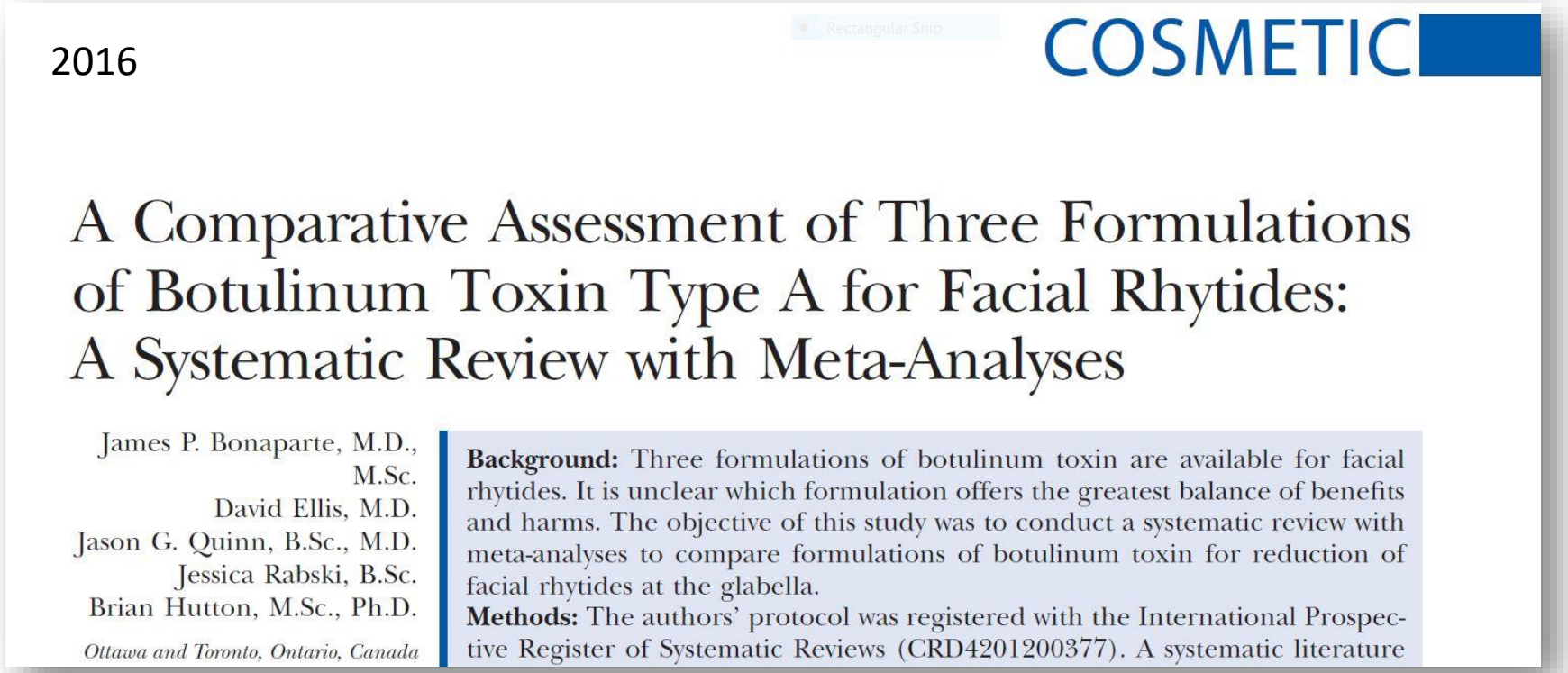


Muscle Strain Reduction



BTX, XEO, DYS Systematic Review

2016



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*‡

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

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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 & DAXI

- Un-reconstituted can store at room temperature

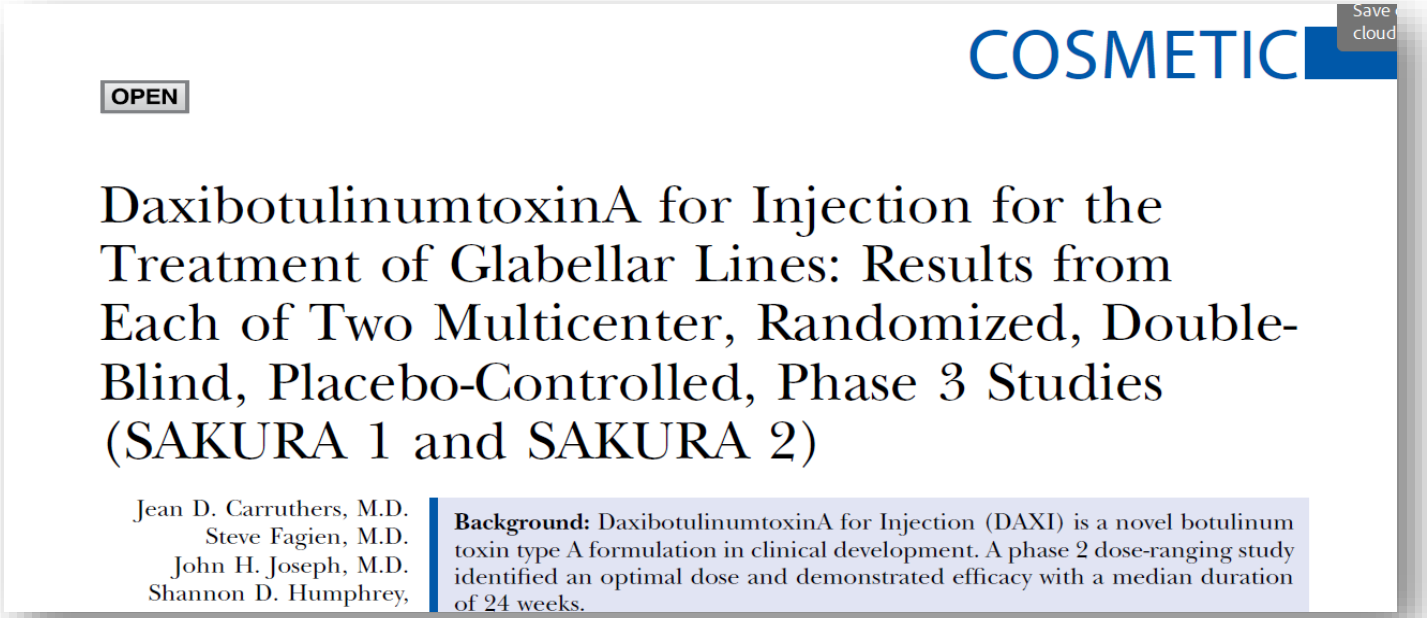
DaxibotulinumtoxinA (Daxxify, Daxi)

- Latest BTA approved in USA
- 5 to 6 month mean duration
- 1 unit BOTOX = 2 units DAXI
- Price improving?
- Slow rollout

Daxi Comparison

	Revance (DAXI)[1]	Allergan (Botox®)[2,7]	Ipsen (Dysport®)[3,7,8]	Merz (Xeomin®)[4,7]	Evolus (Jeuveau™)[5,6]
Manufacturing location(s)	USA	Ireland	UK	Germany	South Korea
BoNT/Complex Size	150 kDa	900 kDa	~400kDa	150 kDa	900kDa
Excipients	Buffers Sugar Polysorbate 20 RTP004	900 µg sodium chloride 500 µg HSA	2.5 mg lactose 125 µg HSA	4.7 mg sucrose 1 mg HSA	900 µg sodium chloride 500 µg HSA
Drying process	Lyophilized	Vacuum Dried	Lyophilized	Lyophilized	Vacuum Dried
Core 150 kDa neurotoxin (GL dose)	0.18 ng	0.18 ng	0.27 ng	0.08 ng	0.12 ng
Storage (pre-reconstitution)	Room temperature	Refrigerate	Refrigerate	Room Temperature	Refrigerate

Safety & Efficacy Reported in SAKURA Studies



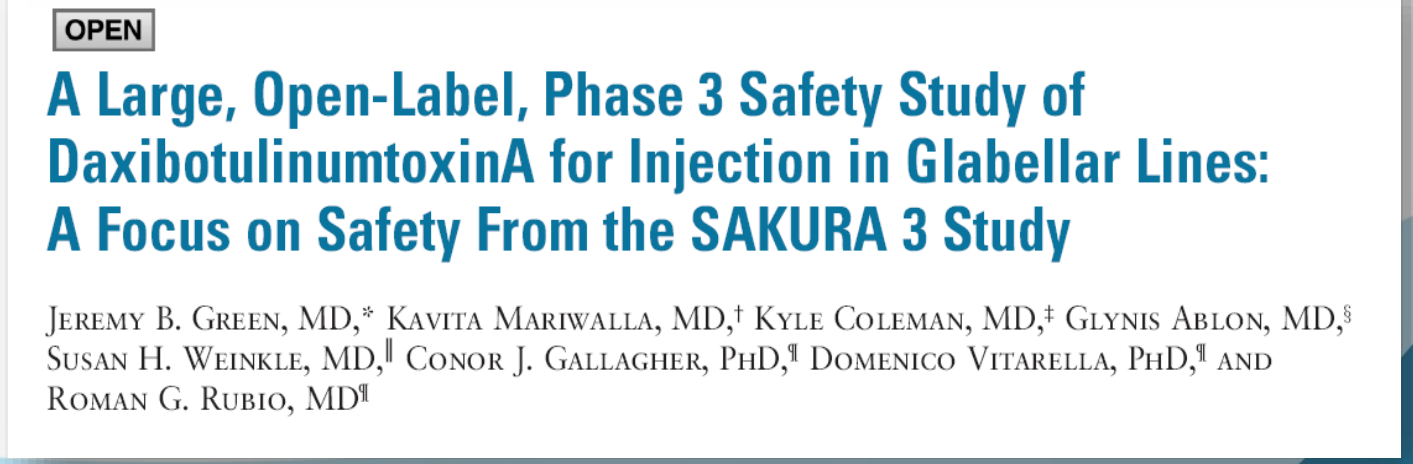
COSMETIC

OPEN

DaxibotulinumtoxinA for Injection for the Treatment of Glabellar Lines: Results from Each of Two Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Studies (SAKURA 1 and SAKURA 2)

Jean D. Carruthers, M.D.
Steve Fagien, M.D.
John H. Joseph, M.D.
Shannon D. Humphrey,

Background: DaxibotulinumtoxinA for Injection (DAXI) is a novel botulinum toxin type A formulation in clinical development. A phase 2 dose-ranging study identified an optimal dose and demonstrated efficacy with a median duration of 24 weeks.



OPEN

A Large, Open-Label, Phase 3 Safety Study of DaxibotulinumtoxinA for Injection in Glabellar Lines: A Focus on Safety From the SAKURA 3 Study

Jeremy B. Green, MD,* Kavita Mariwalla, MD,† Kyle Coleman, MD,‡ Glynis Ablon, MD,§ Susan H. Weinkle, MD,‖ Conor J. Gallagher, PhD,¶ Domenico Vitarella, PhD,¶ and Roman G. Rubio, MD¶

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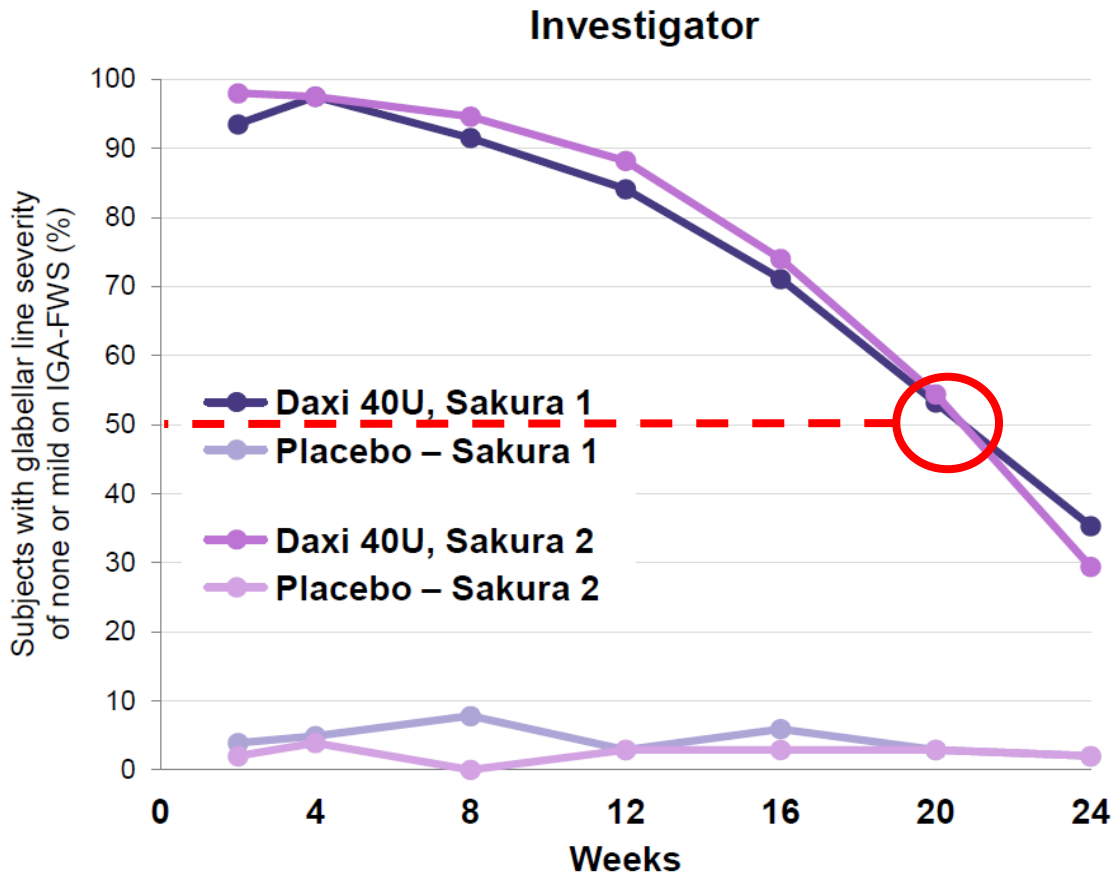
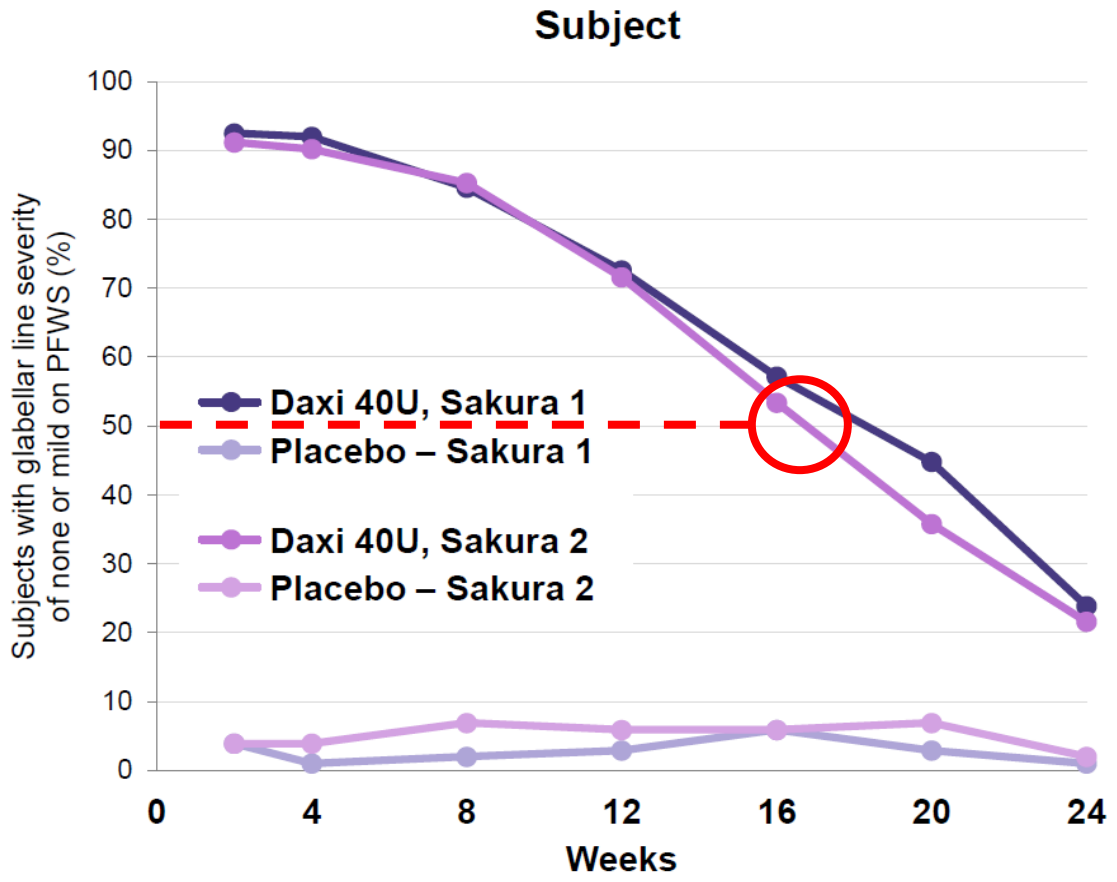
Daxi Duration

SAKURA 1 & 2: Secondary Endpoint

None or Mild Response on IGA-FWS and PFWS through Week 24

revance® MEDICAL AFFAIRS

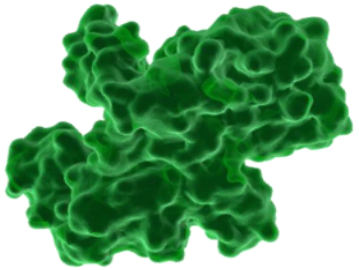
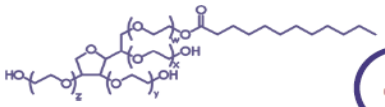
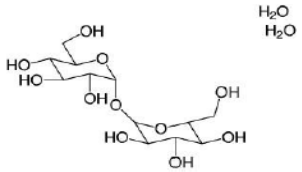




Daxi Formulation

revance MEDICAL AFFAIRS

DAXI's Novel Formulation: Key Properties

150 kD Neurotoxin type A	Stabilizing Peptide Excipient	Polysorbate 20	Buffers, Sugar	DaxibotulinumtoxinA for Injection
				
	Prevents Aggregation		Protects During Drying	

Prevents Adsorption to vial

Allows for Formulation without HSA

Allows for Room Temperature Stability

BTA Resistance & Accessory Proteins

- Some patients develop less effect or non-response
- May be due to development of antibodies (Ab)
  - BTA Ab very rare in cosmetic uses
  - Some secondary non-responders 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 BTA itself
  - Antibodies directly against BTA may effect result

BTA 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 BTA
  - Presence of antibody ≠ no response
  - Absence of antibody ≠ response
- Antibodies may disappear over time
- May respond to BTB (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

- BTA is zinc dependent
- Phytates block zinc absorption

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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 BTA 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?

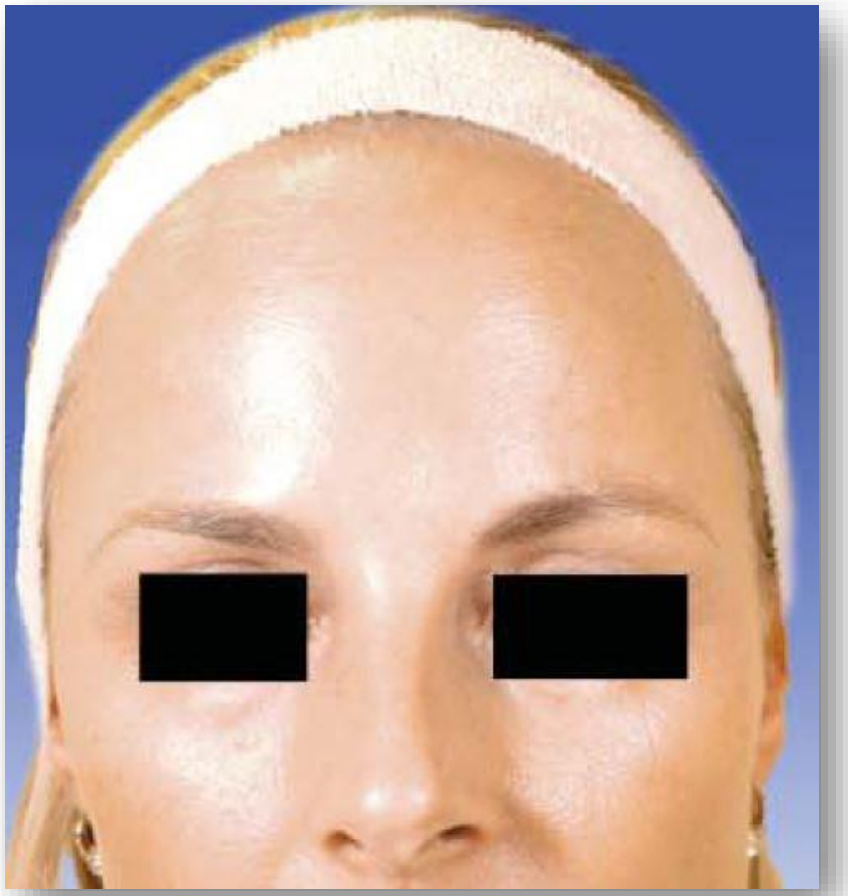
Injecting Botulinum Toxin at Different Depths Is Not Effective for the Correction of Eyebrow Asymmetry

JASON SNEATH, MD,* SHANNON HUMPHREY, MD,* ALASTAIR CARRUTHERS, MD, FRCPC, FAAD,* AND JEAN CARRUTHERS, MD, FRCSC†

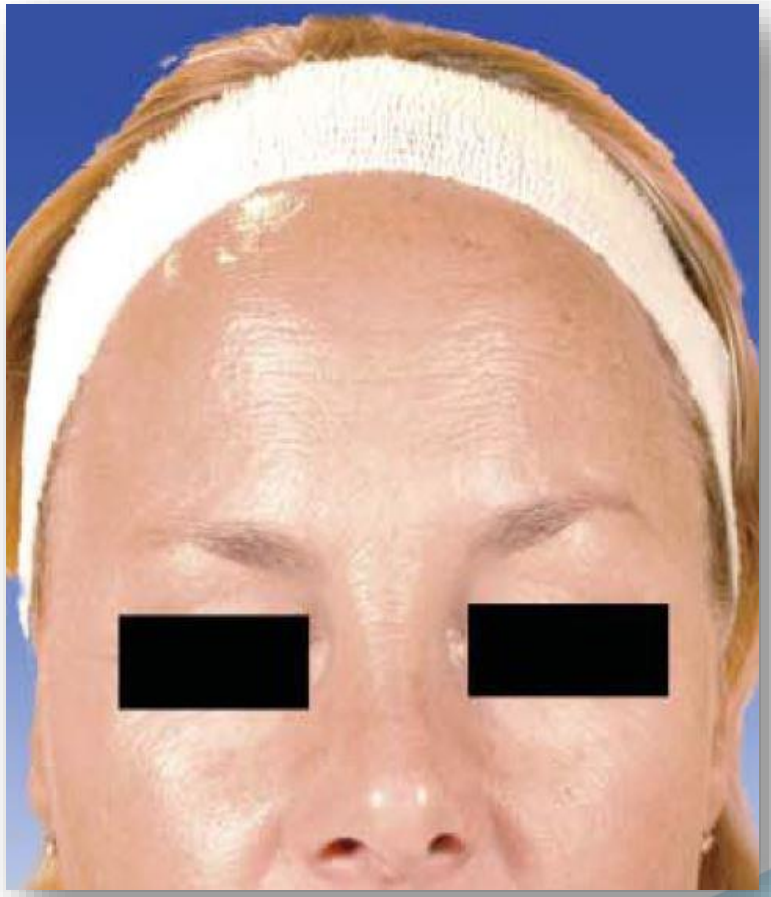
Selective eyebrow depressors cannot be targeted due to BTA diffusion radius

Subject to debate

BTA 44 yo Twins Case Report



Regular BTA injections every 4 to 6 months for 19 years



4 BTA injections over 19 years

Regular BTA treatments may prevent long-term skin changes

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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

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Personal Experience

• Accessory proteins	Do they matter?
• Interchangeable	Maybe (more similar than different)
• Split face	Not much difference
• Patient cross-over	Not much difference
• BTA non-responders	True non-responders won't respond to all of them

In Your Practice

- Consider your overall BTA 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

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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 Re-lift

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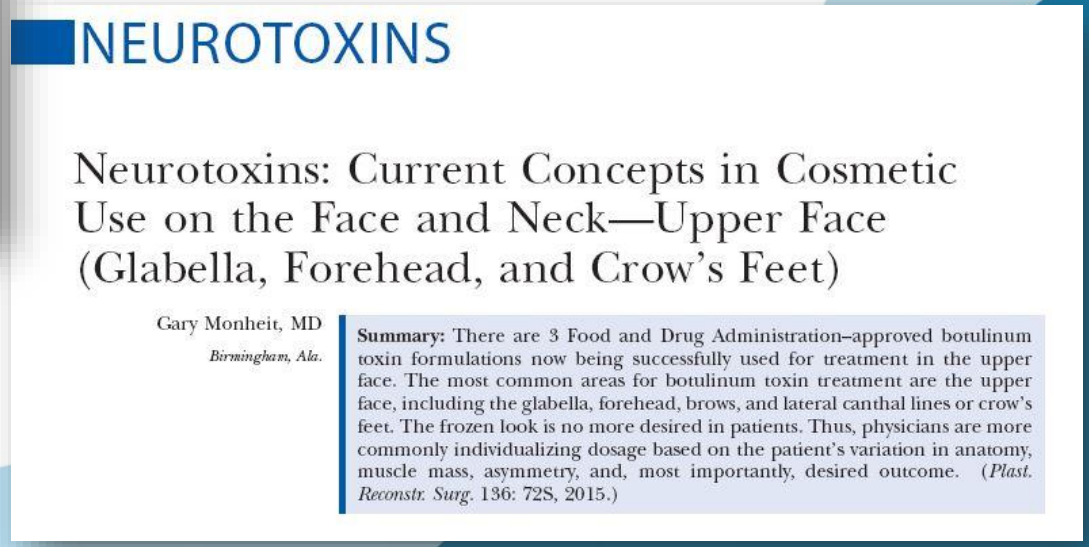
Natural vs Unnatural Results

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

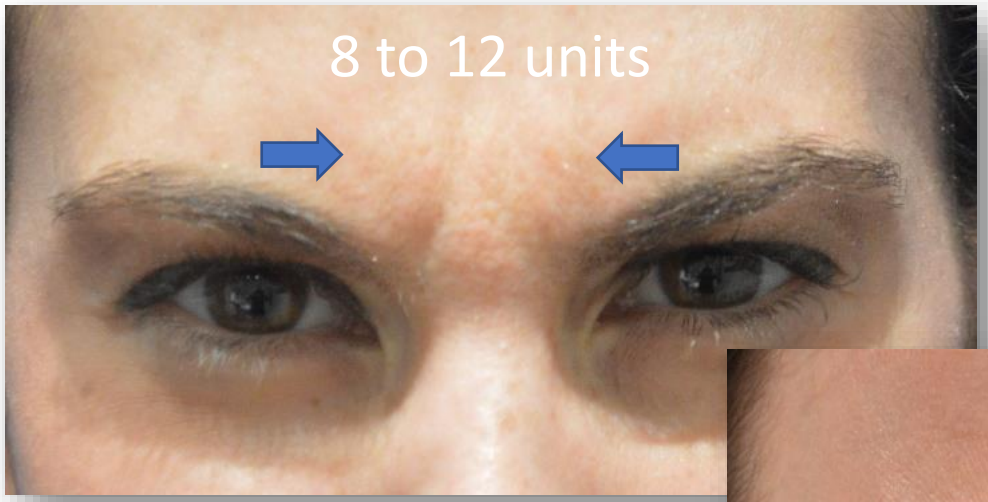

NEUROTOXINS

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

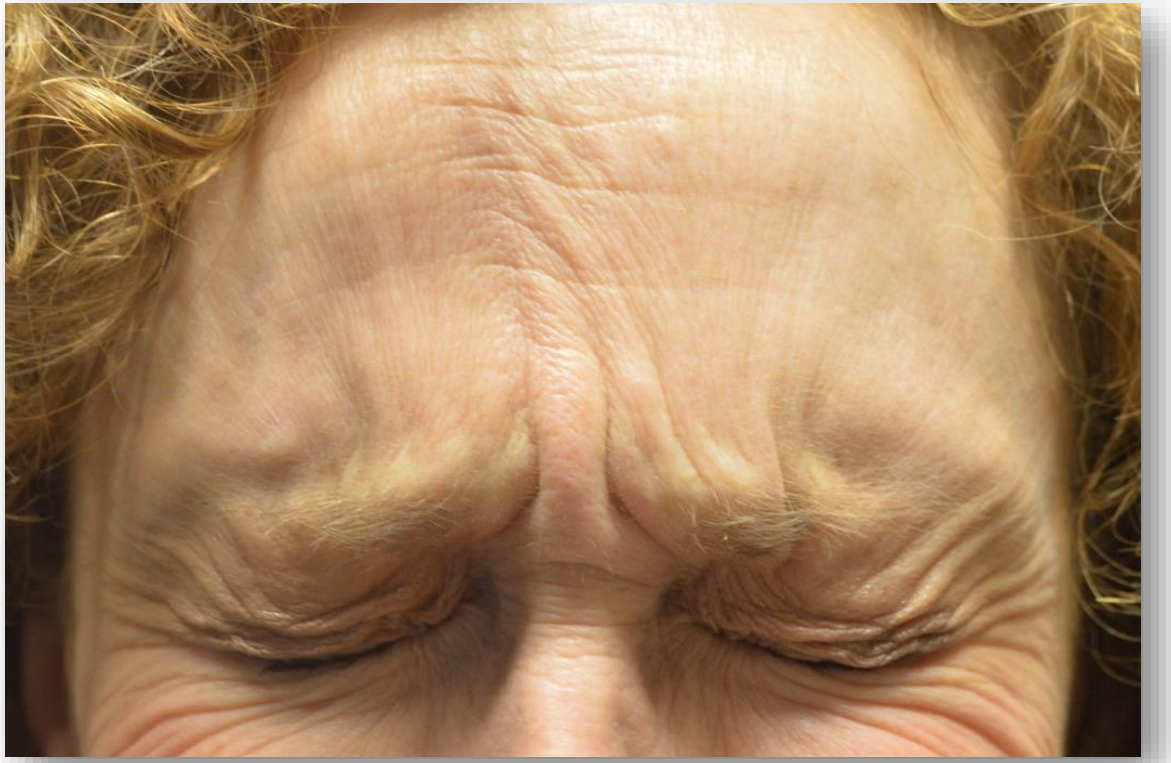
Gary Monheit, MD
Birmingham, Ala.

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



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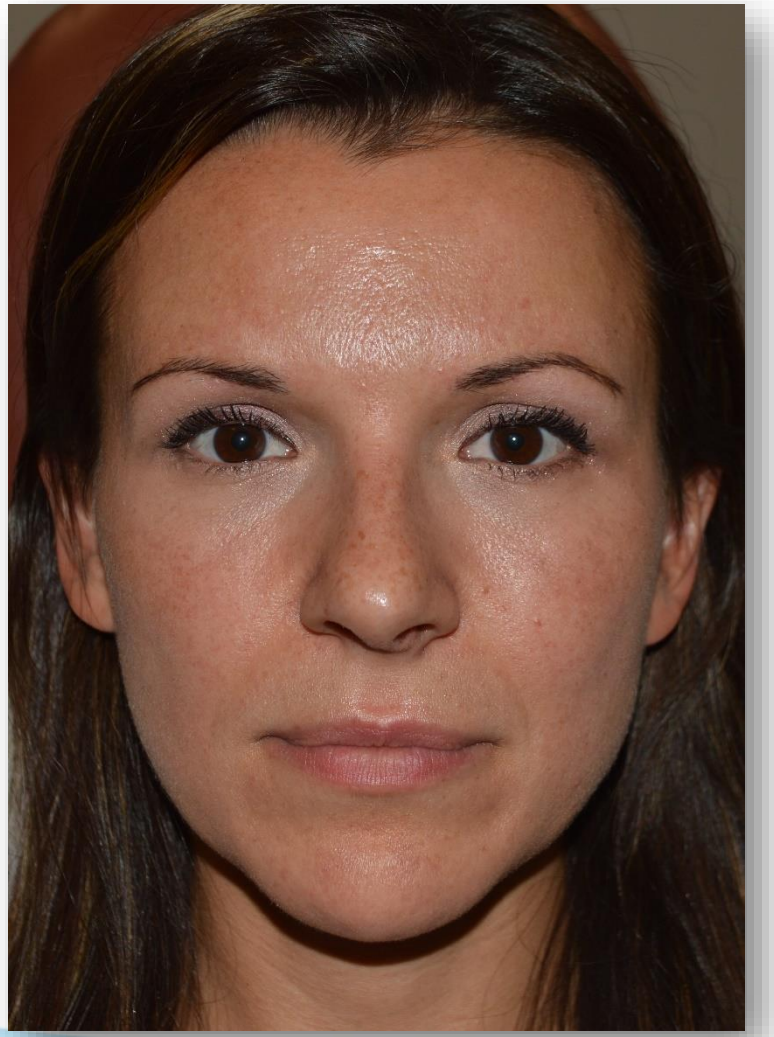
Size of Treatment Area

Dollars per Unit or Number of Units?



"Can you do my Botox?"

"I had 60 units last time"

"But is was only $10 per unit!"

"Why do you charge so much more?"

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Dollars per Unit or Number of Units?

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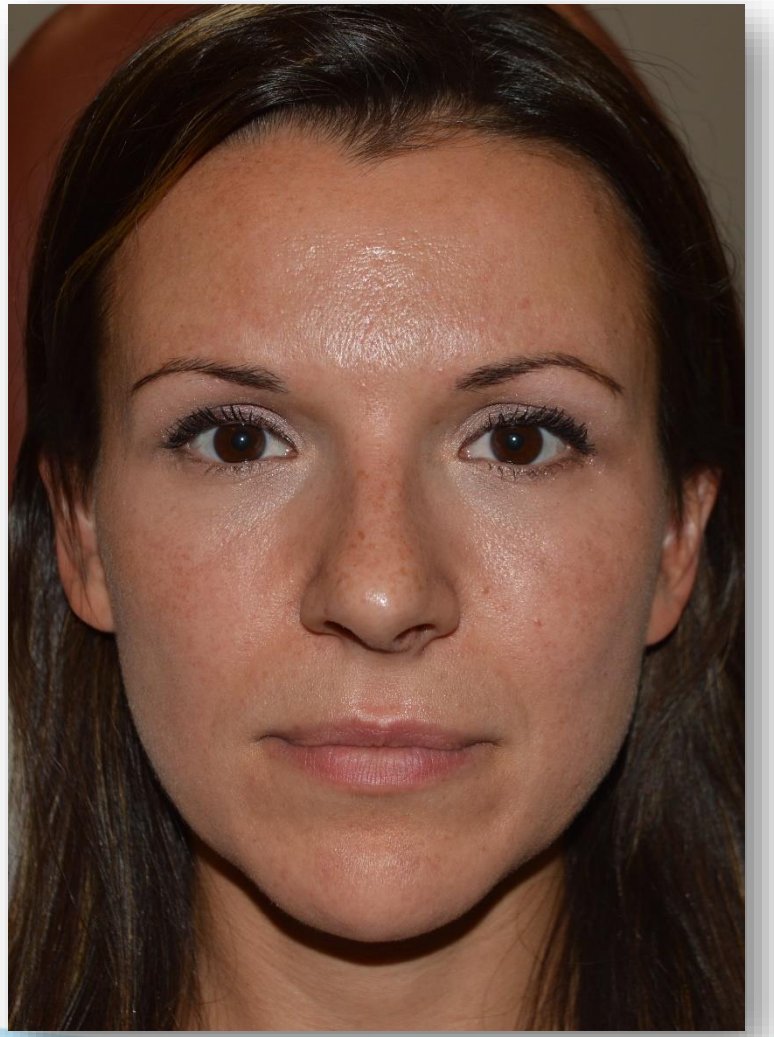
Dollars per Unit or Number of Units?



Why do I charge more?

Because you will pay LESS!

Needed only 32 units

- Paid $16/unit
- Saved $88

Third party trainers “over” educating novice injectors

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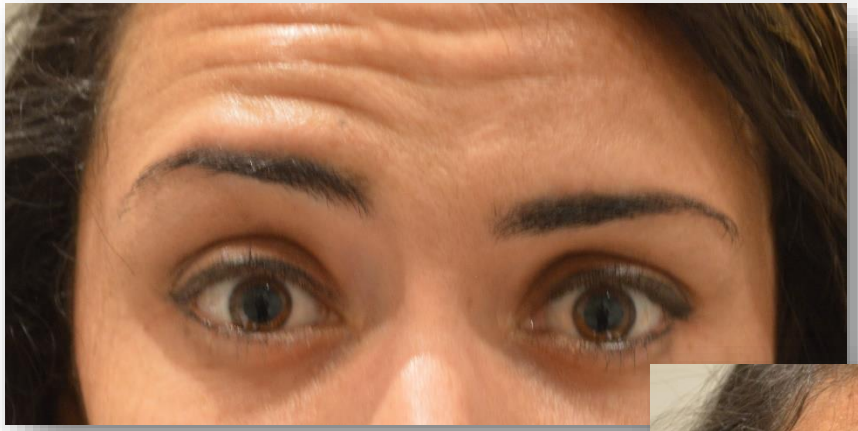
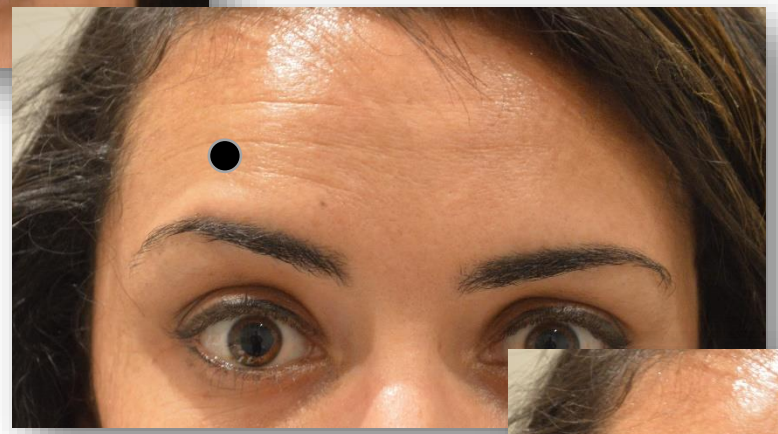
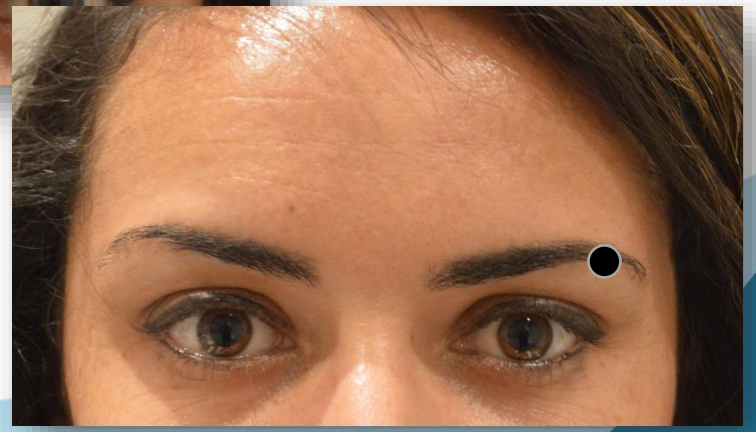
Watch for Asymmetry



6 units per side

+ Right 2 units





Consider 2 units
Left lateral brow

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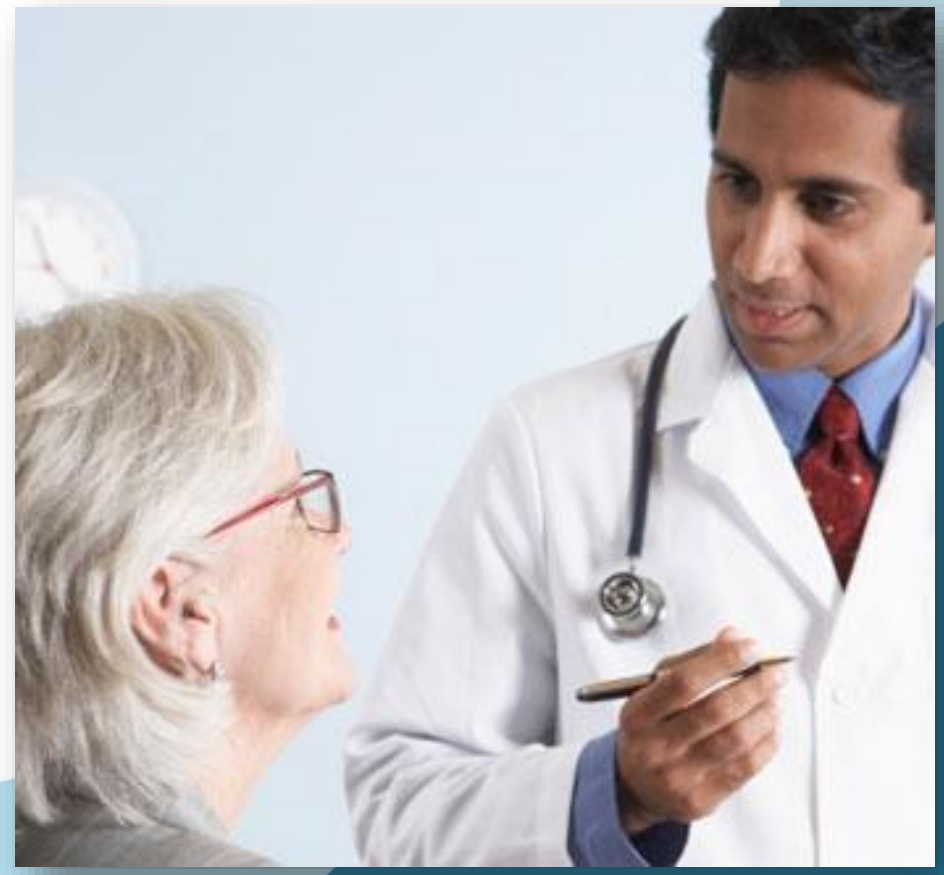
New Patients

- Informed consent & “off-label” use
- Photo documentation
- Start with lowest doses needed
- Need for 2 week follow up visit
  - Assess results
  - Add more if needed

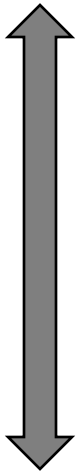


Product Dilutions

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

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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)

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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
V 1% Lido + Epi at injection sites
___ Nerve block
___ Topical
___ Ice

Treatment outcomes: _____

Complications: None

Place Product Stickers Here

C 32 1578

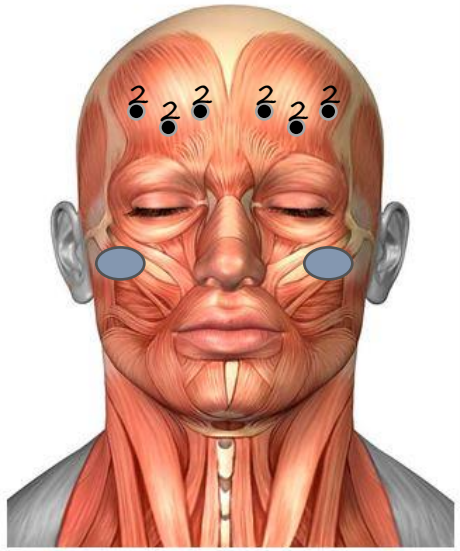
Voluma 13-578

Additional Notes

F= 2u x6 = 12u

Malar = 0.5cc per side

May need more in 2 weeks



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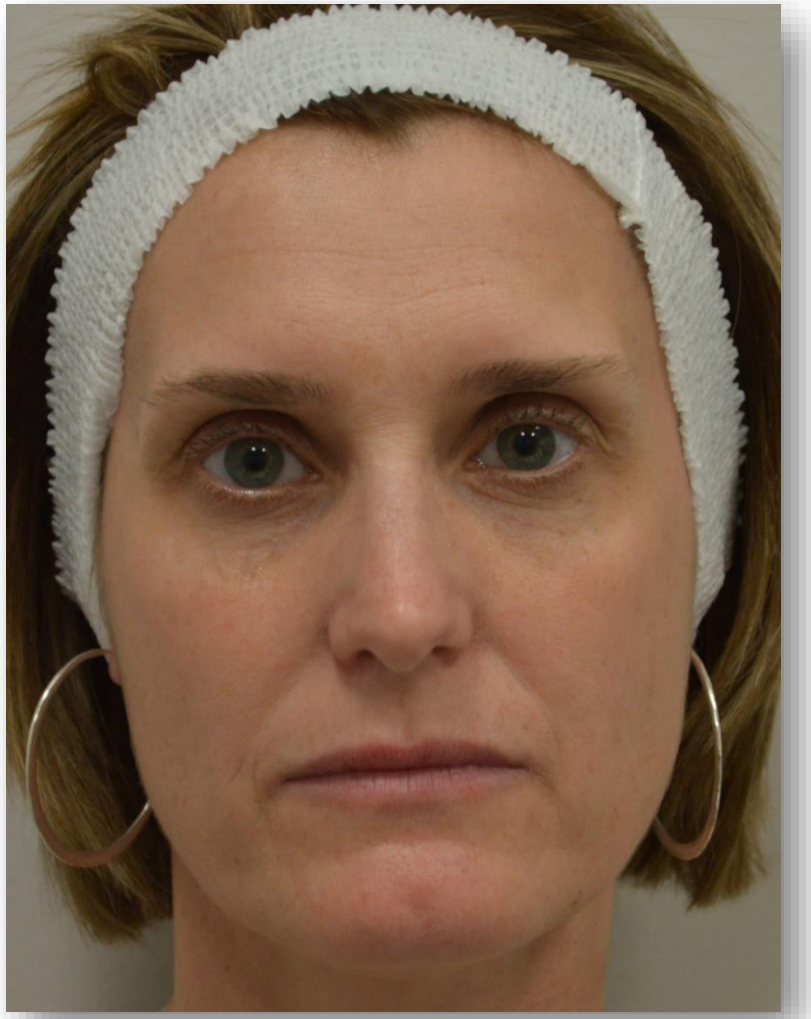
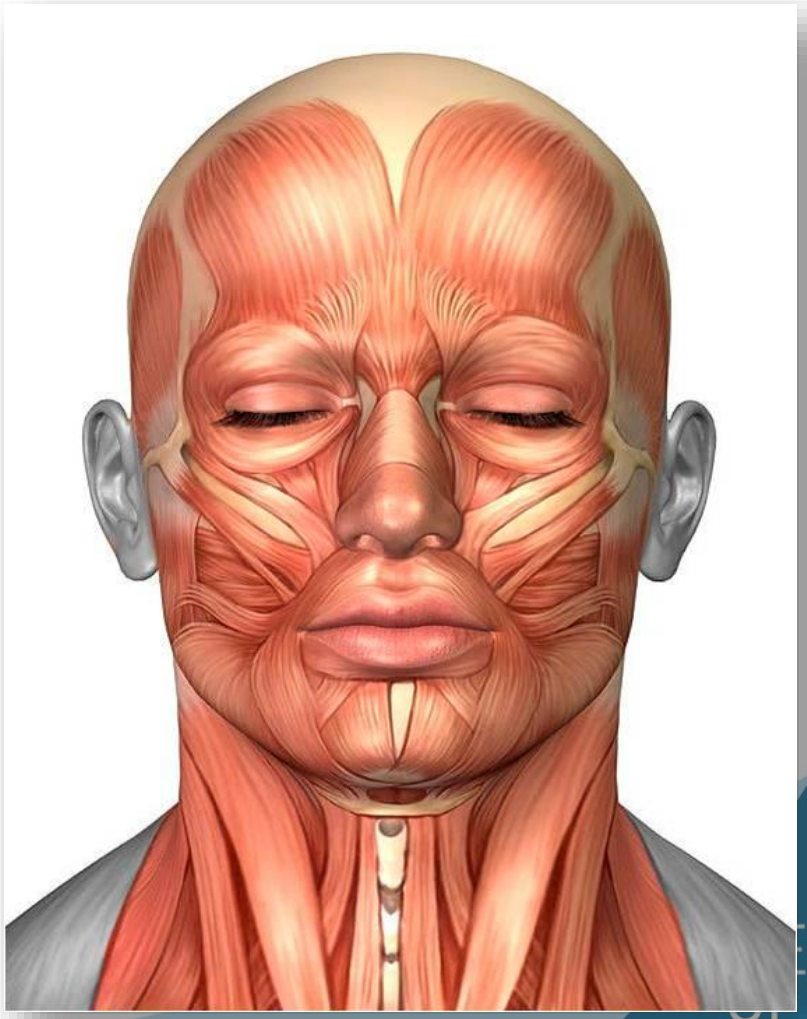
Injection Sites

Assume Botox Units & First Treatment





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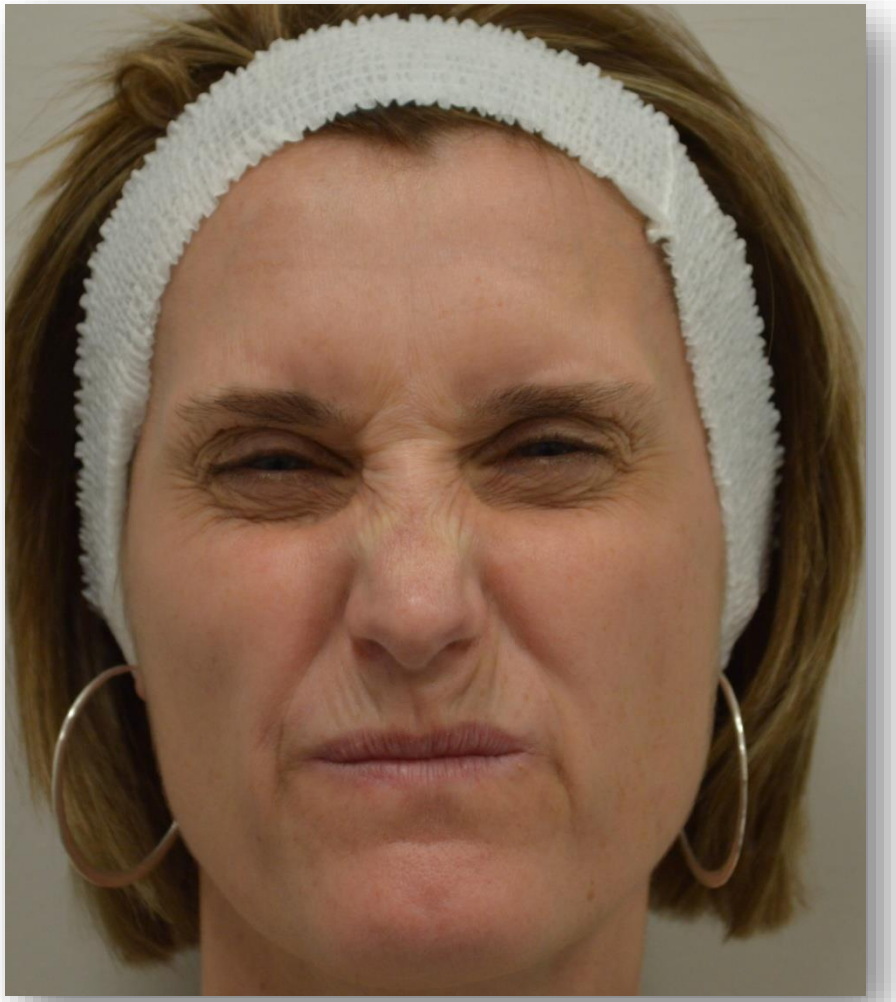
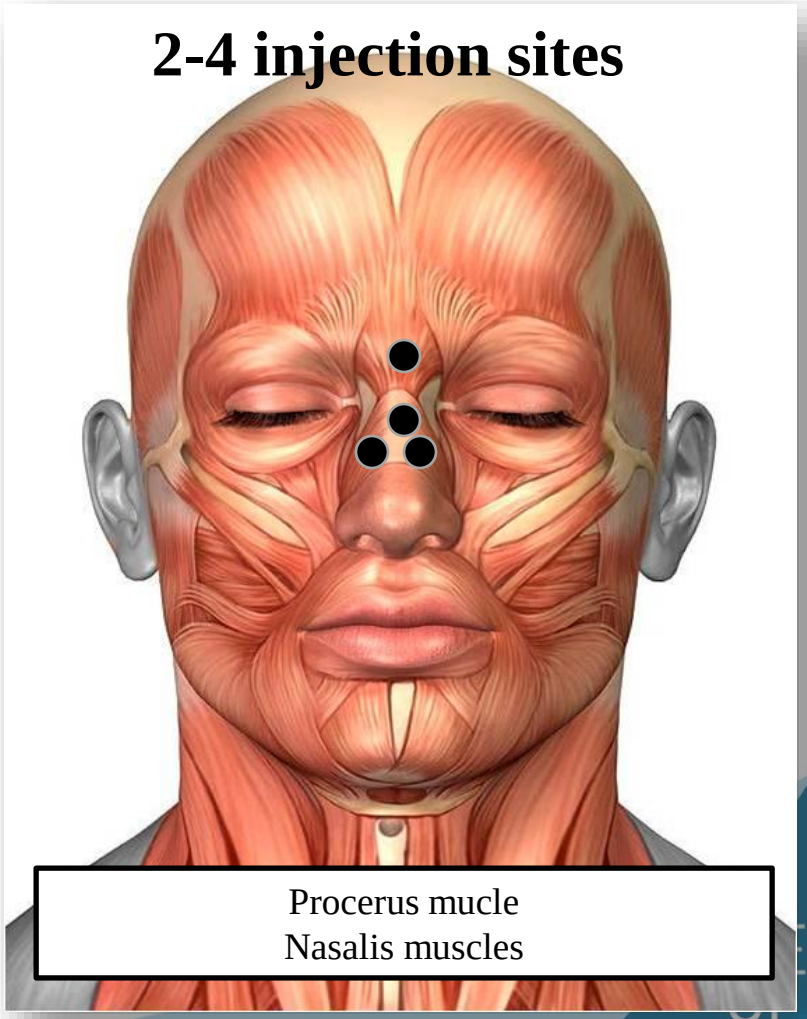
Bunny Lines

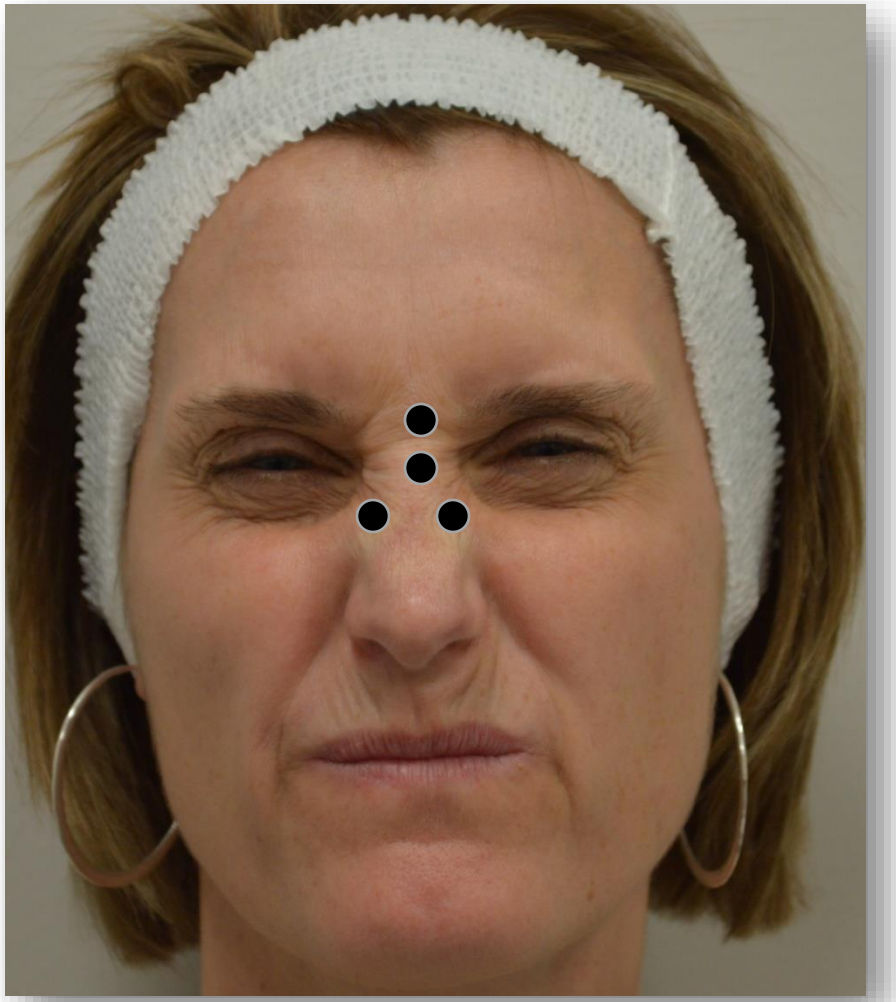
2 Units per Injection Site

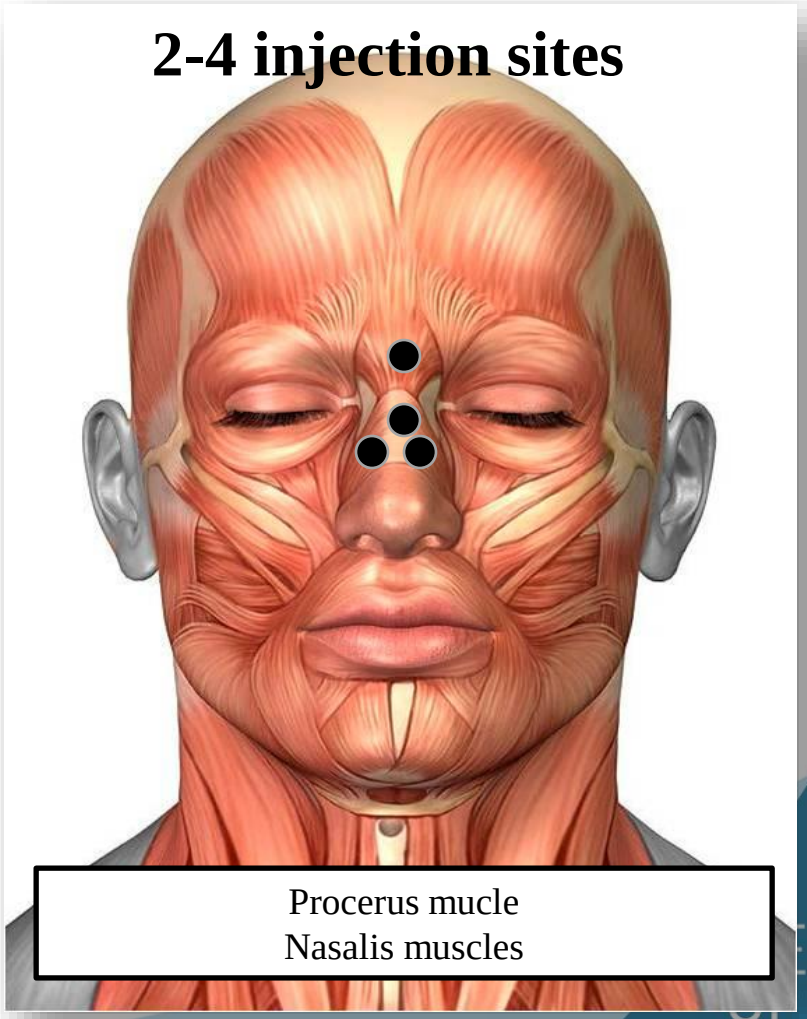




Bunny Lines

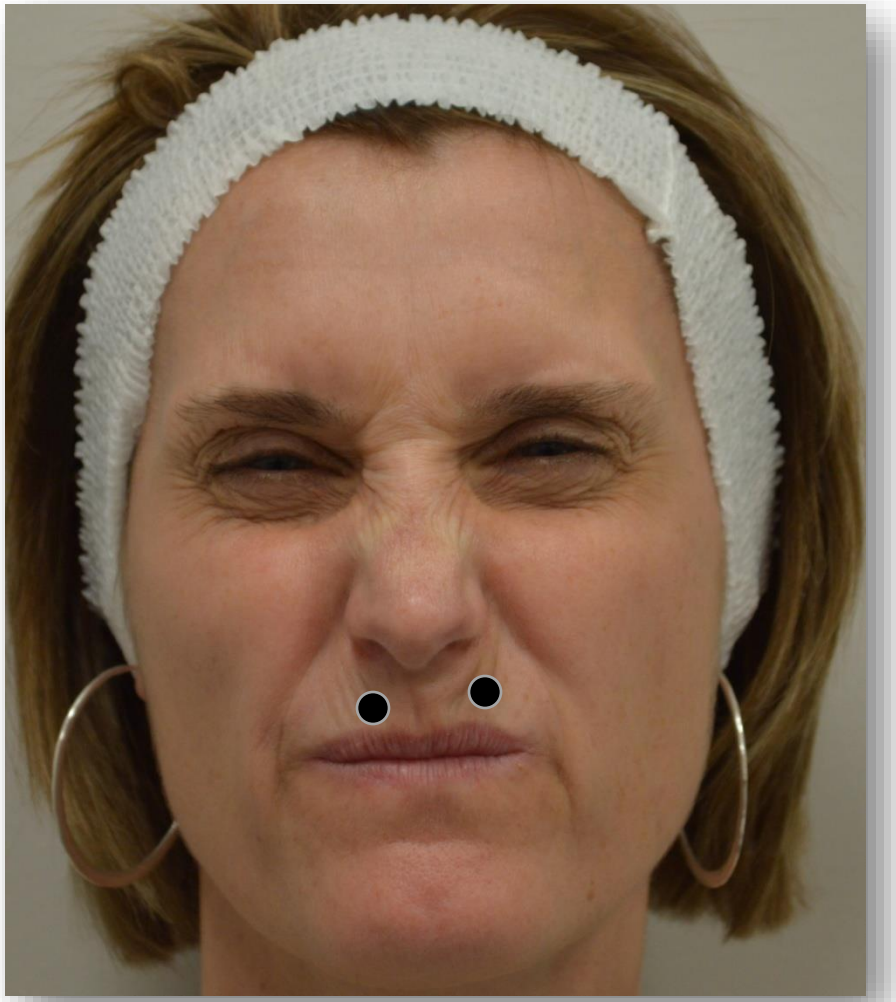
2 Units per Injection Site

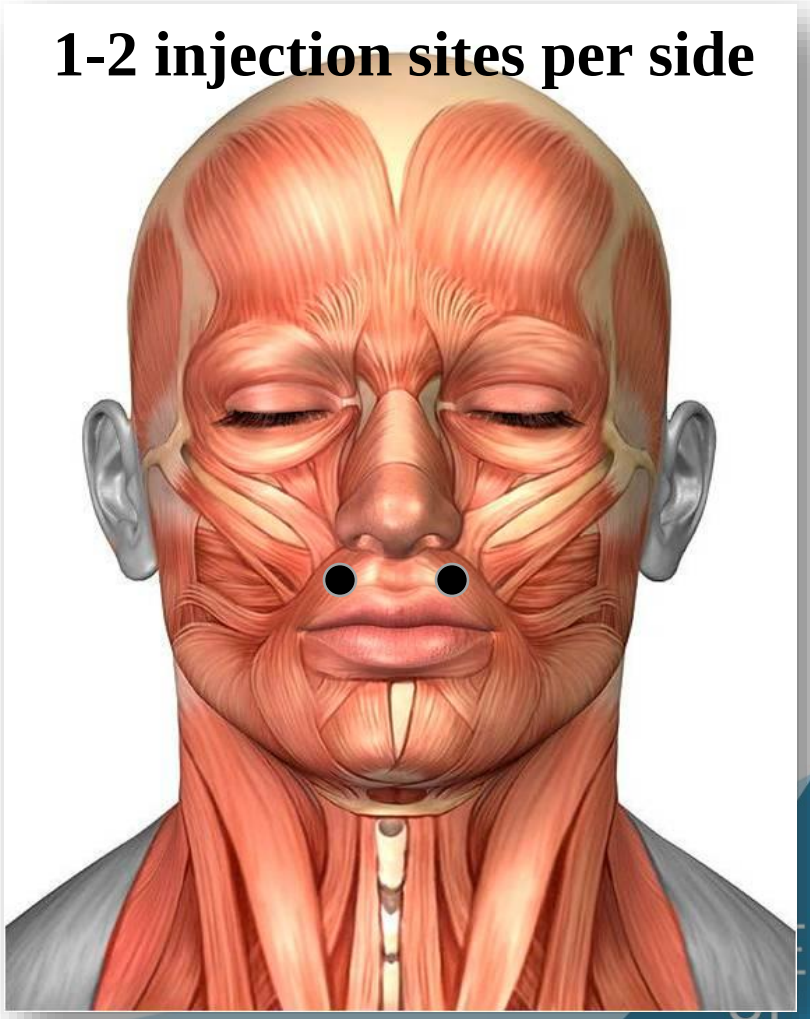




Upper Lip Lines

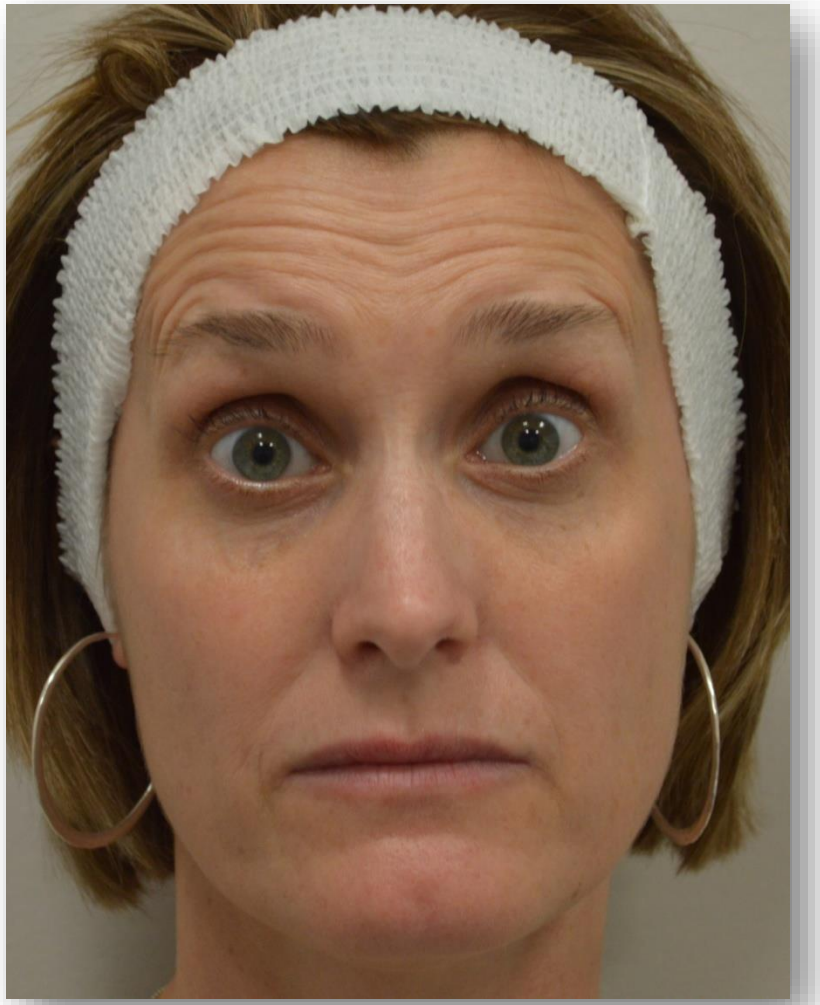
2 Units per Injection Site

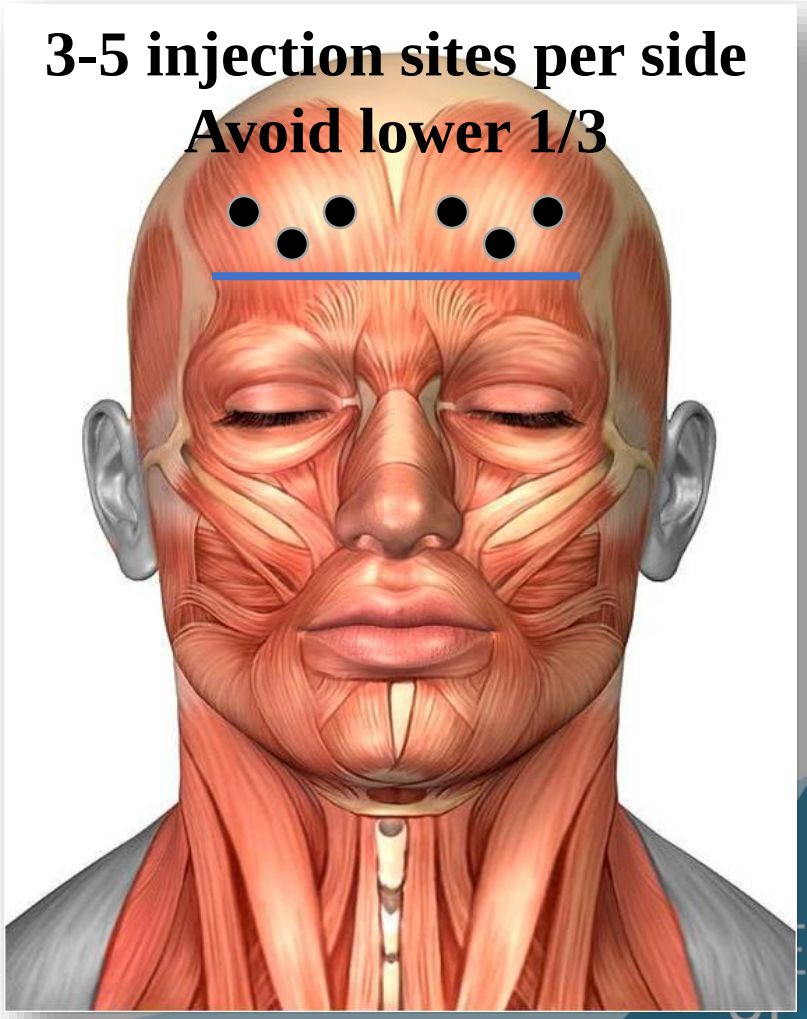




Forehead

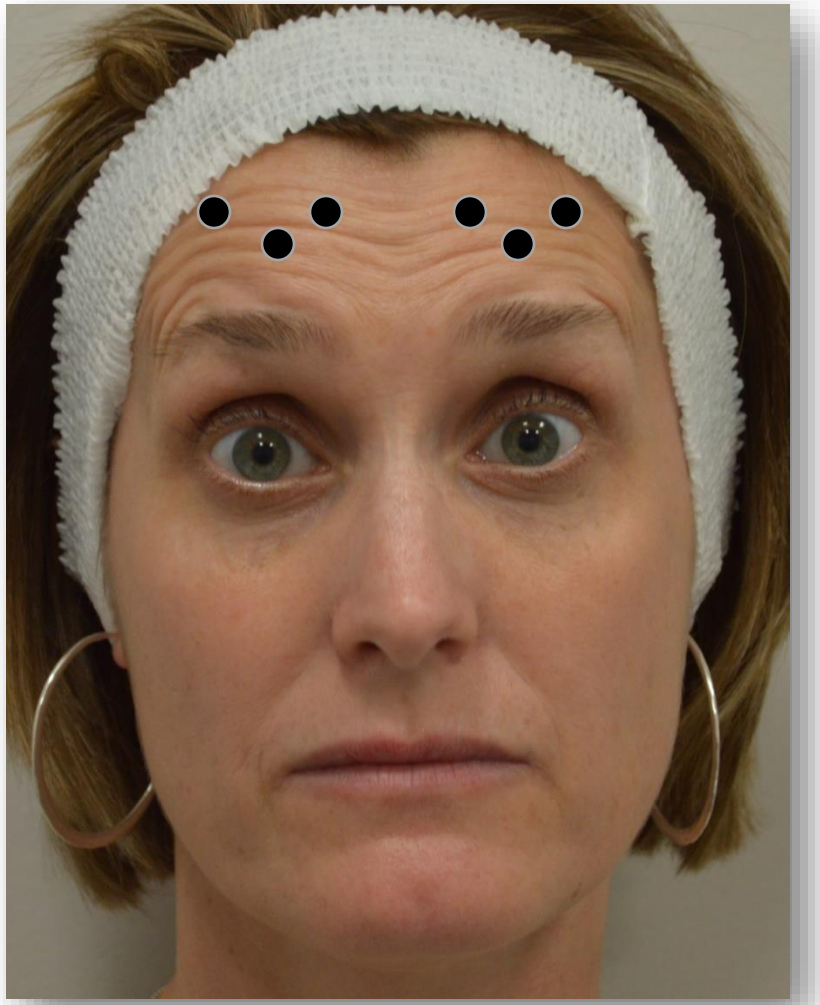
2 Units per Injection Site

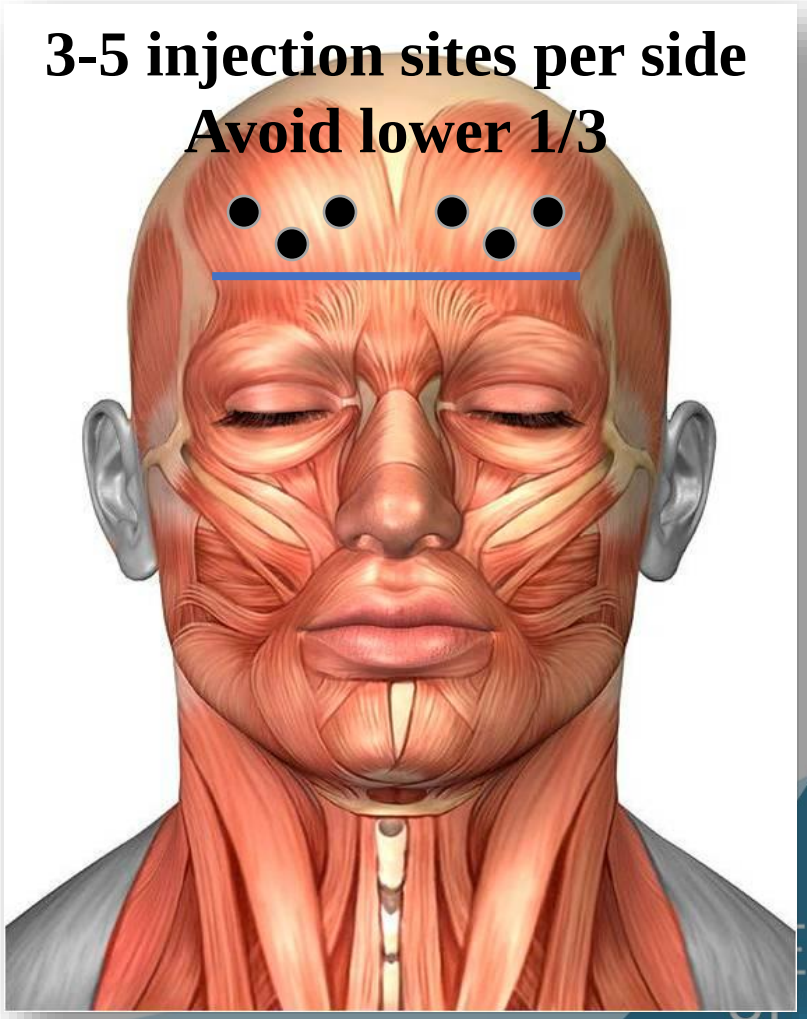




Forehead

2 Units per Injection Site

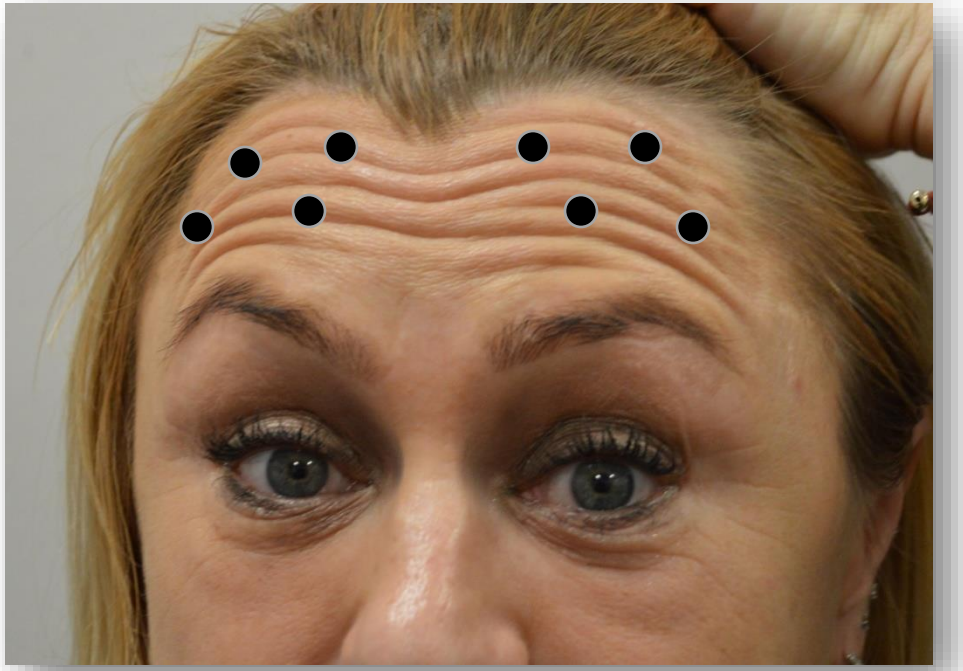


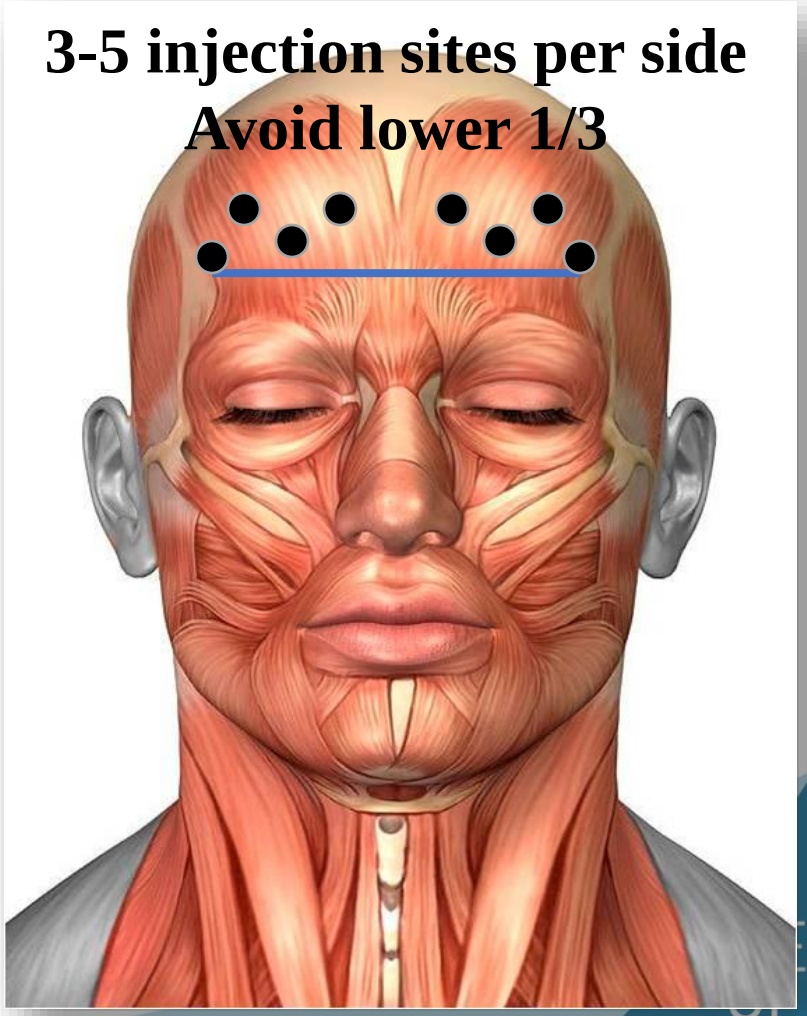


Forehead

2 Units per Injection Site

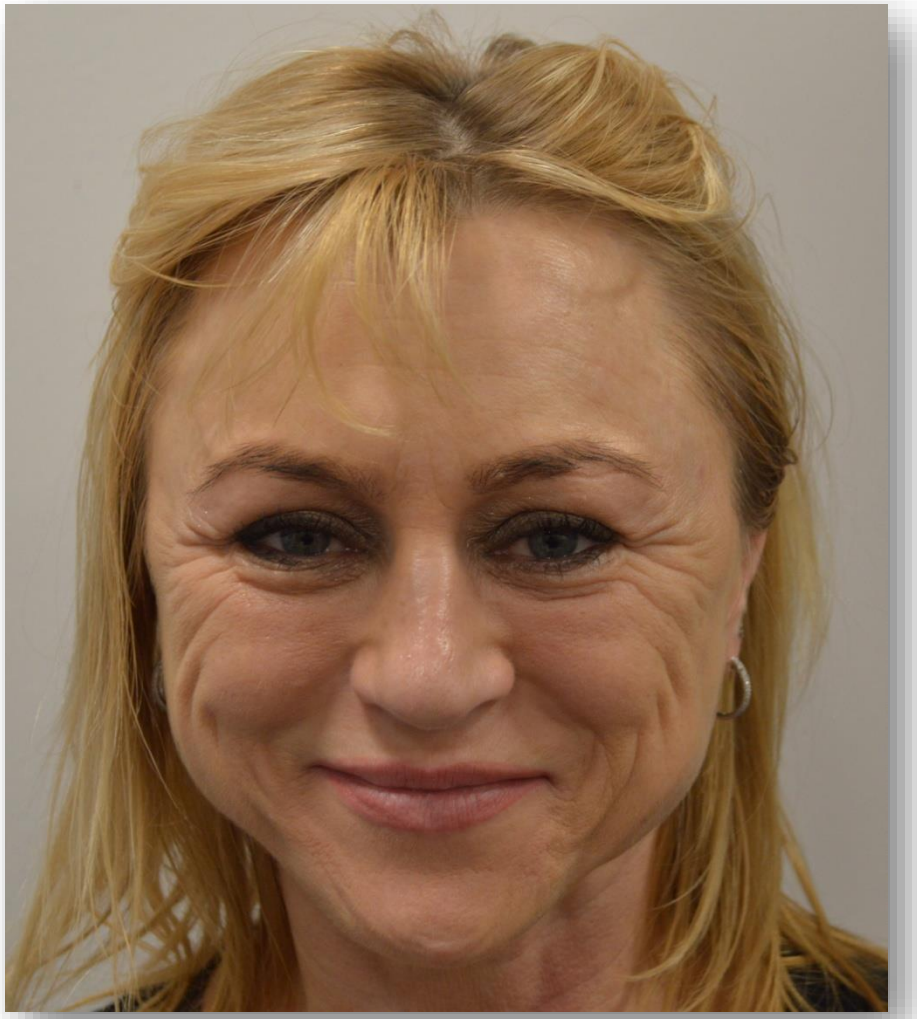
16 to 20 units

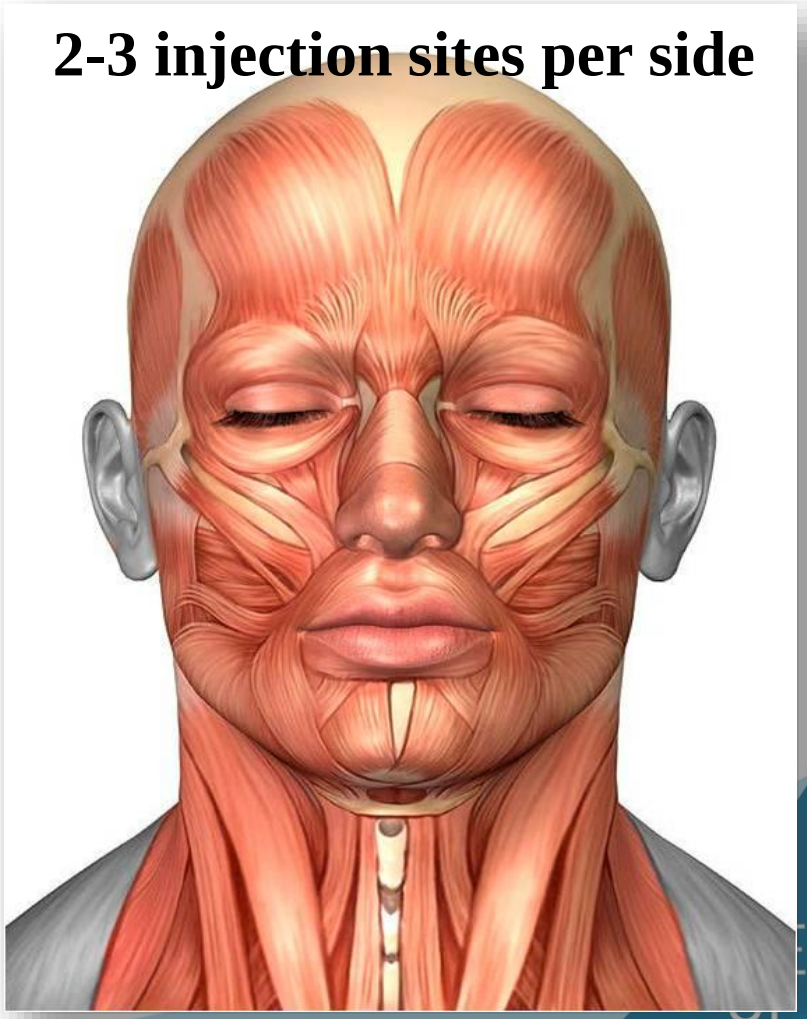




Crow’s Feet & Laugh Lines

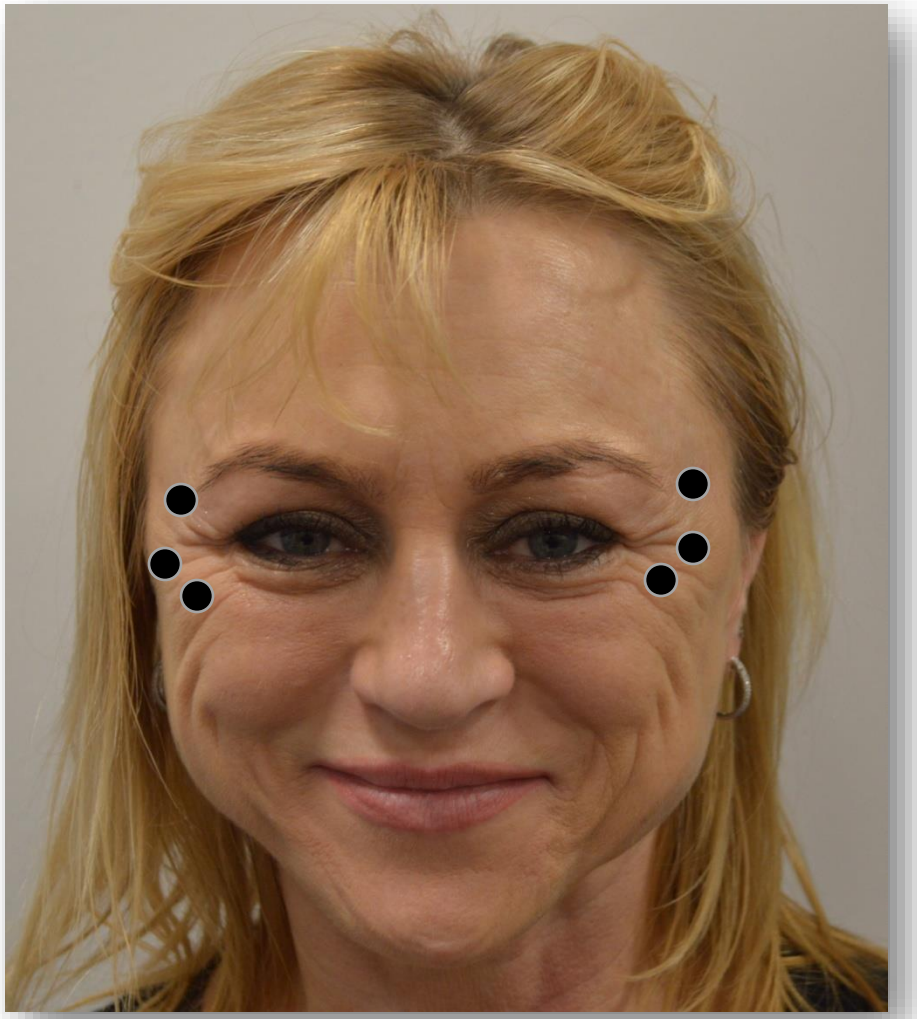
2 Units per Injection Site

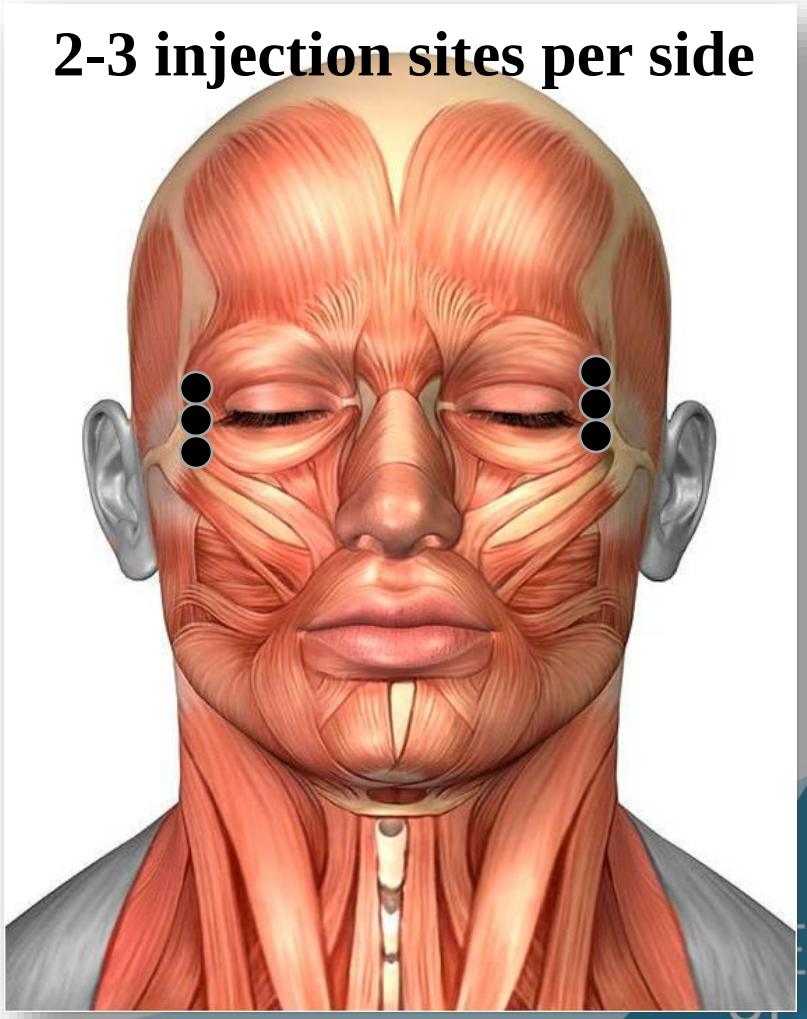




Crow’s Feet & Laugh Lines

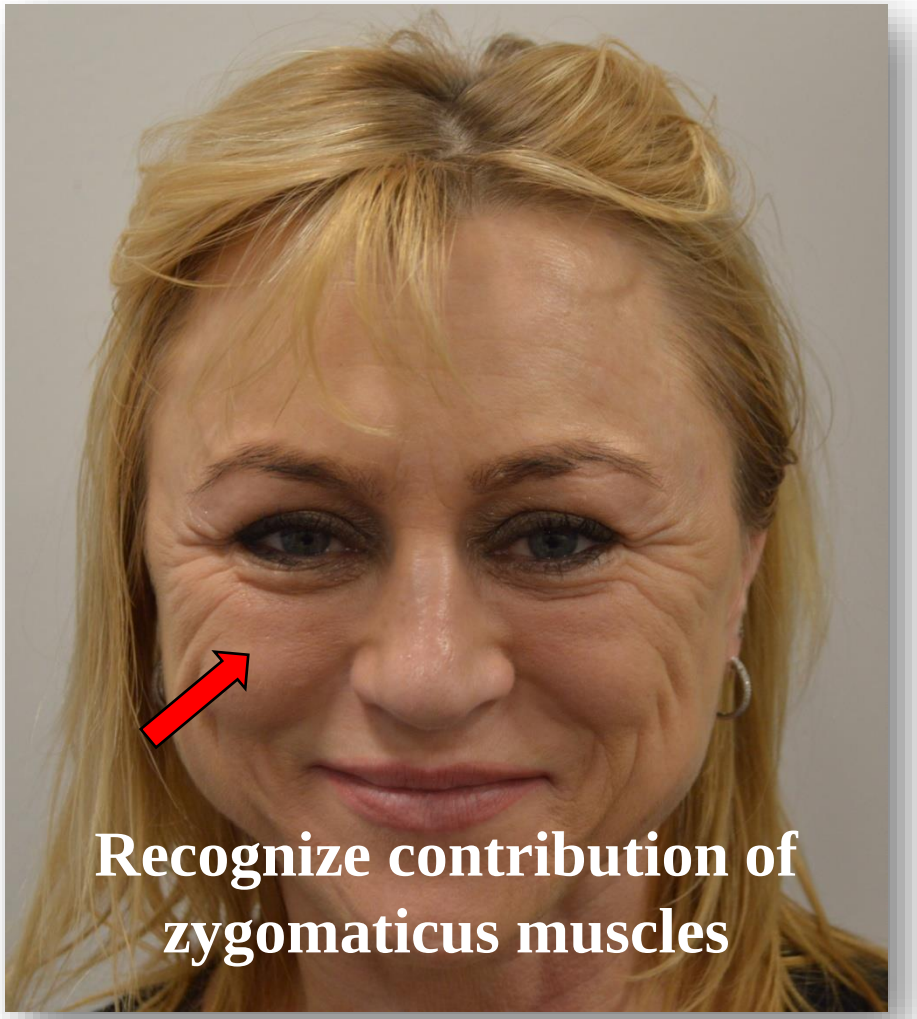
2 Units per Injection Site

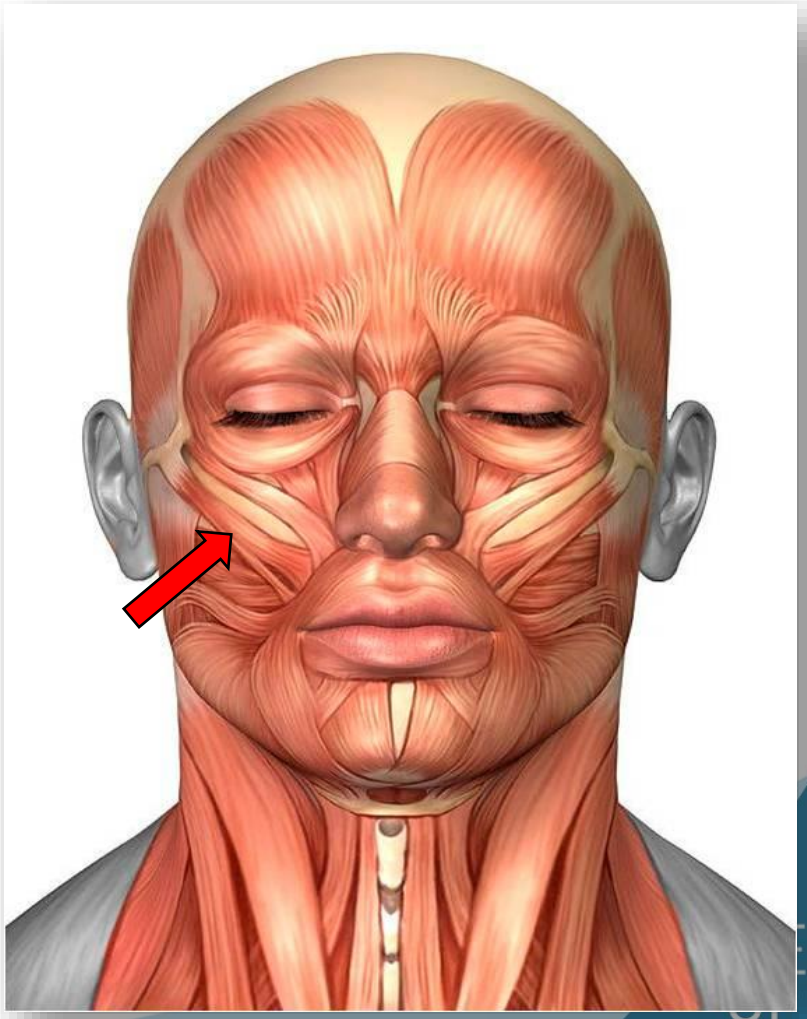




Crow’s Feet & Laugh Lines

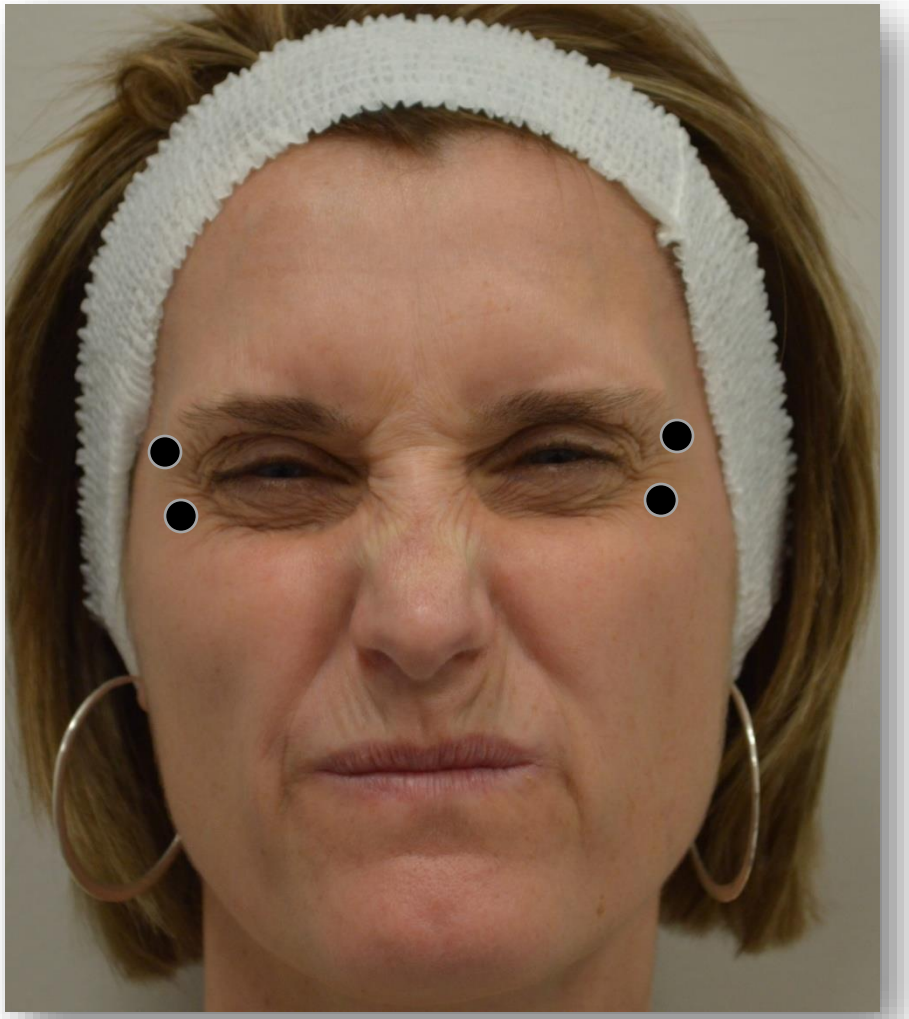
Limitations due to Contributing Muscle Groups

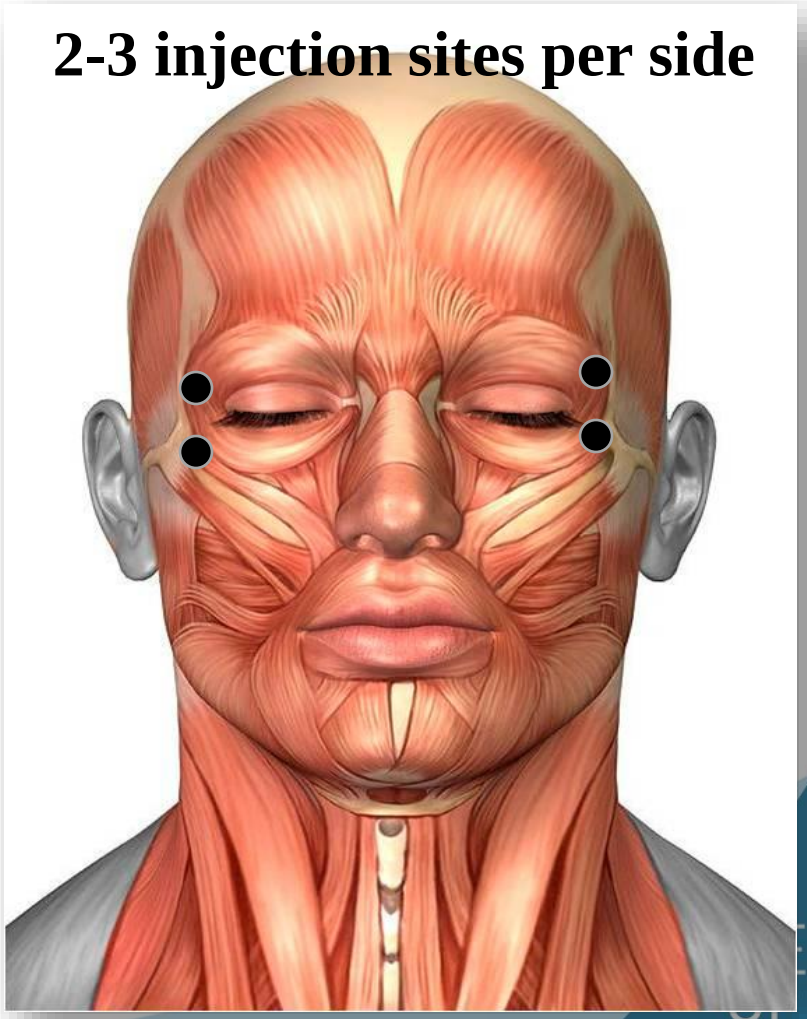




Crow’s Feet & Laugh Lines

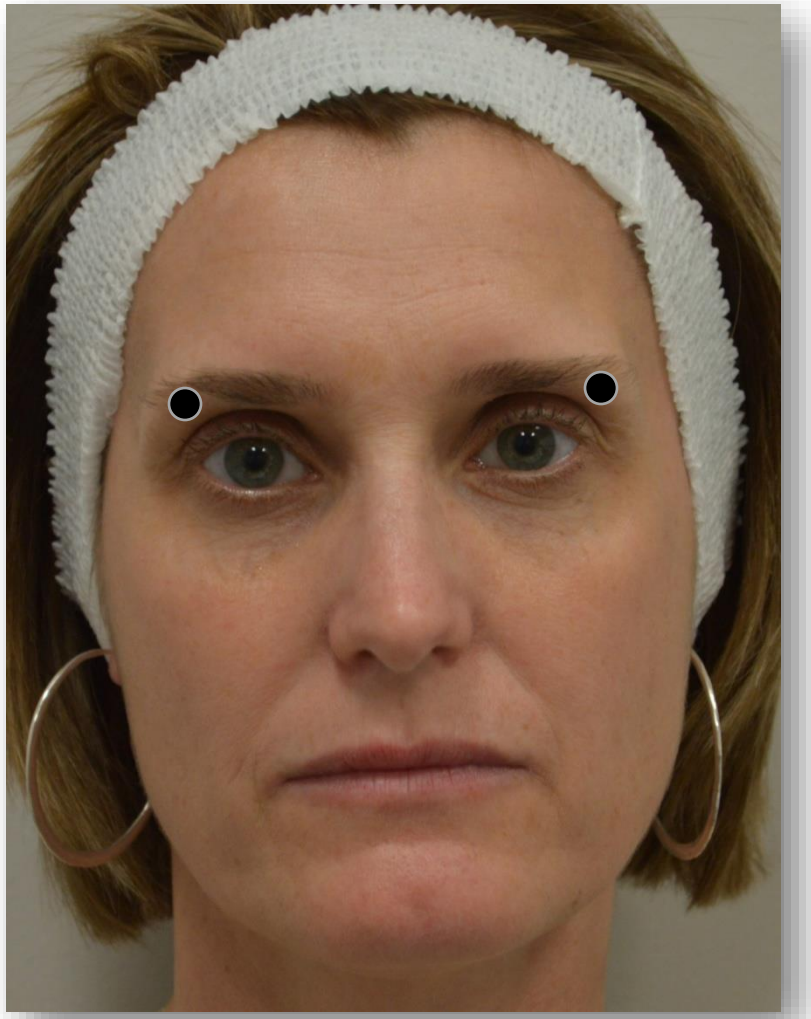
2 Units per Injection Site

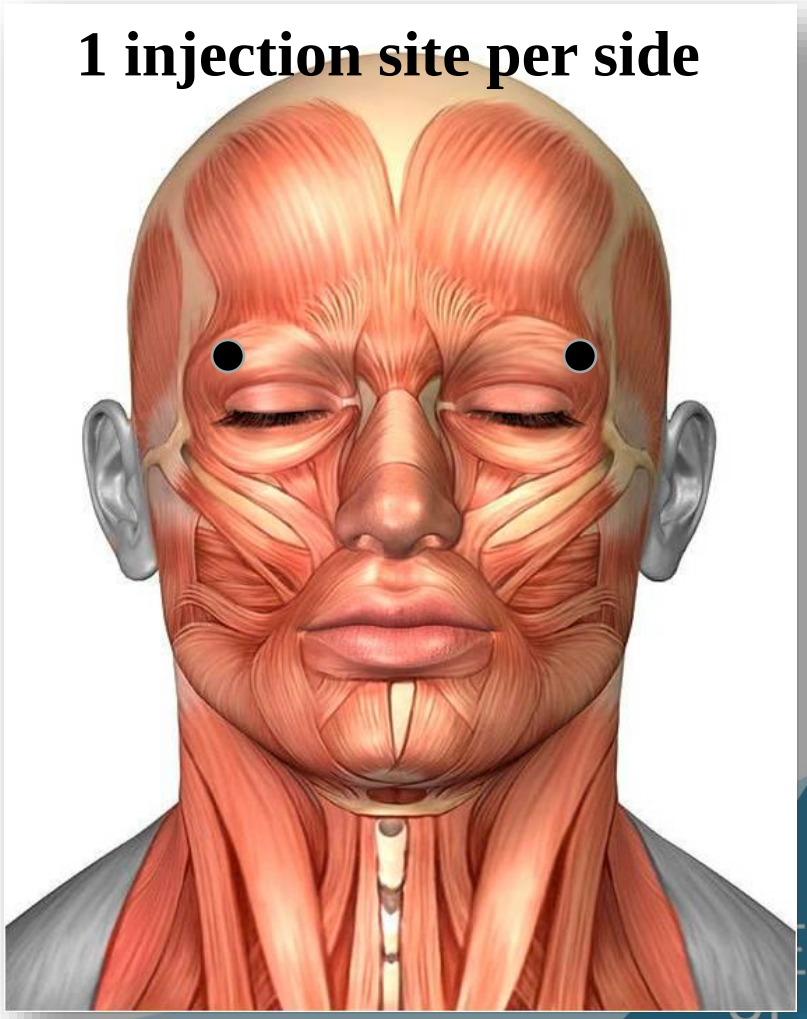




Lateral Brow Lift

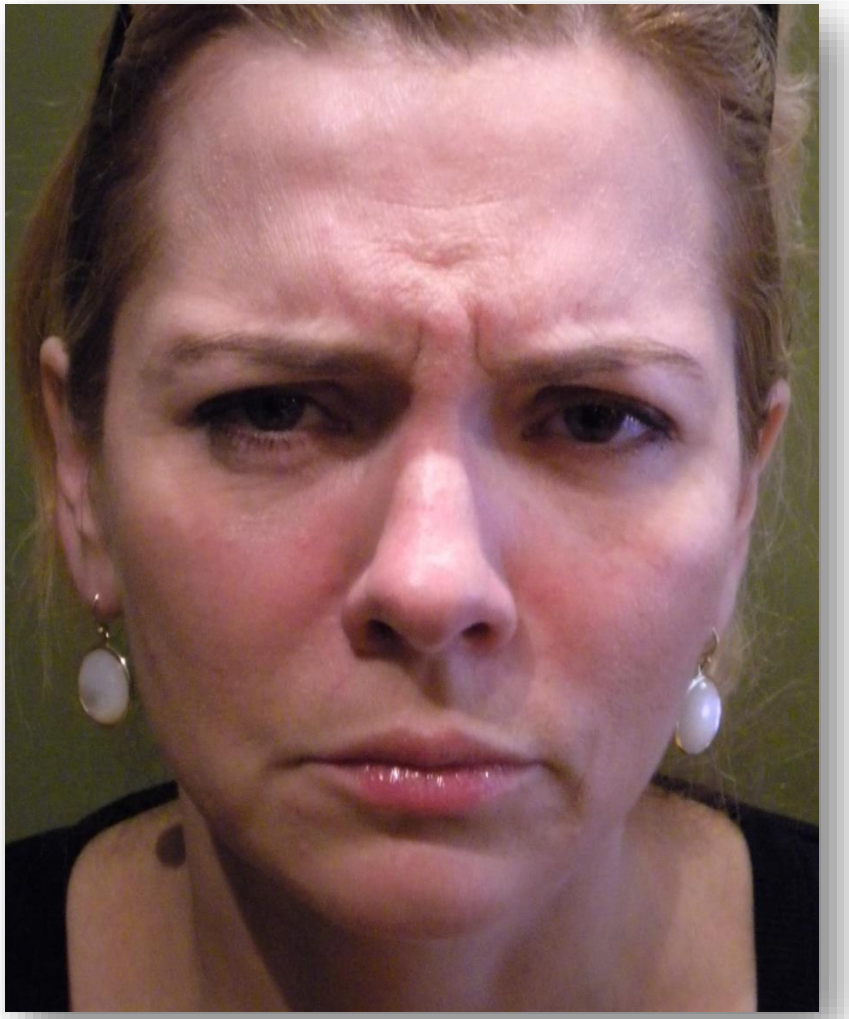
2 Units per Injection Site

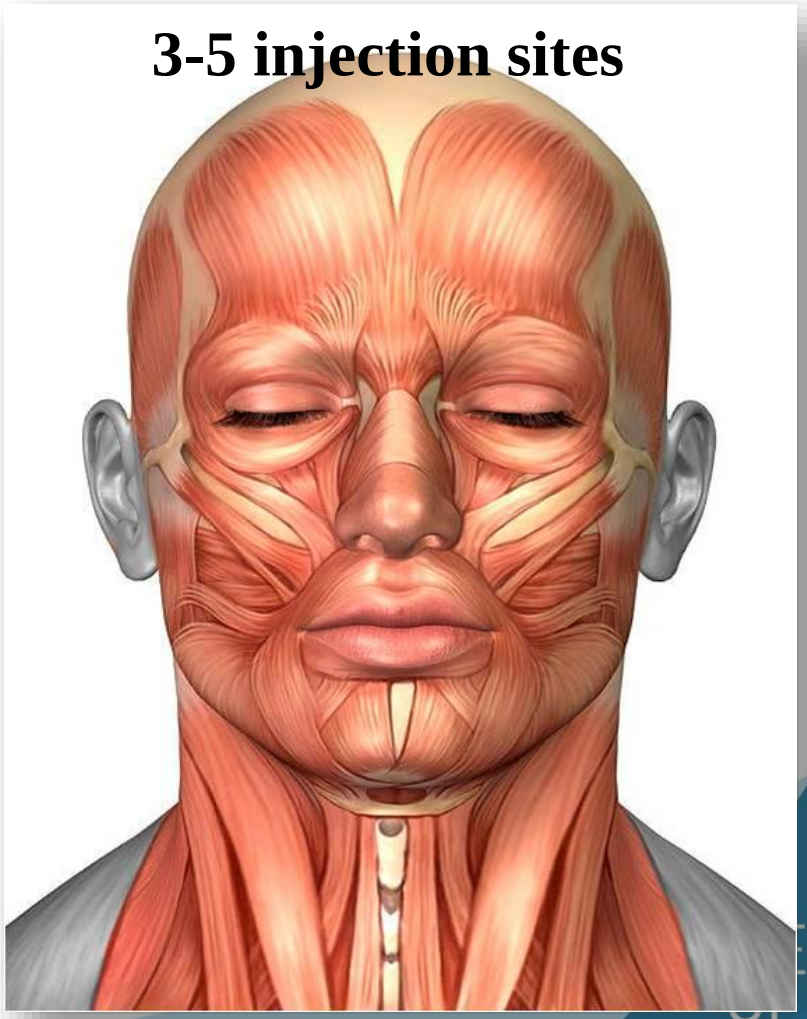




Glabella

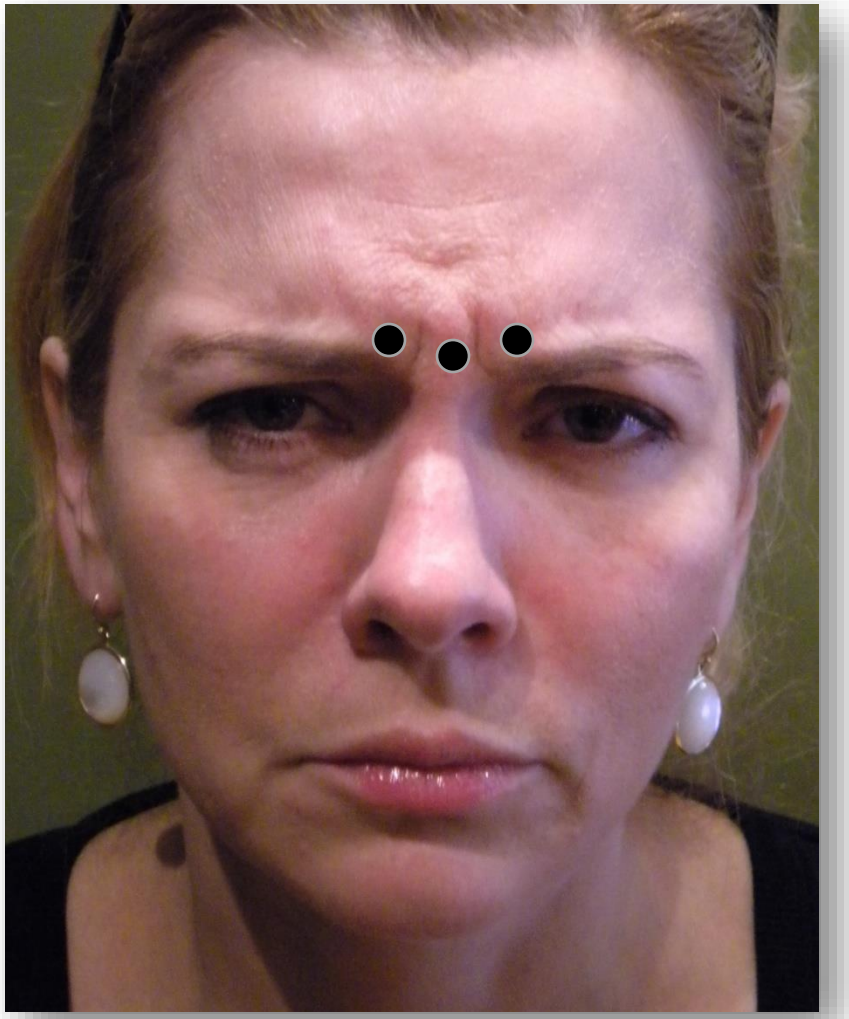
4-5 Units per Injection Site

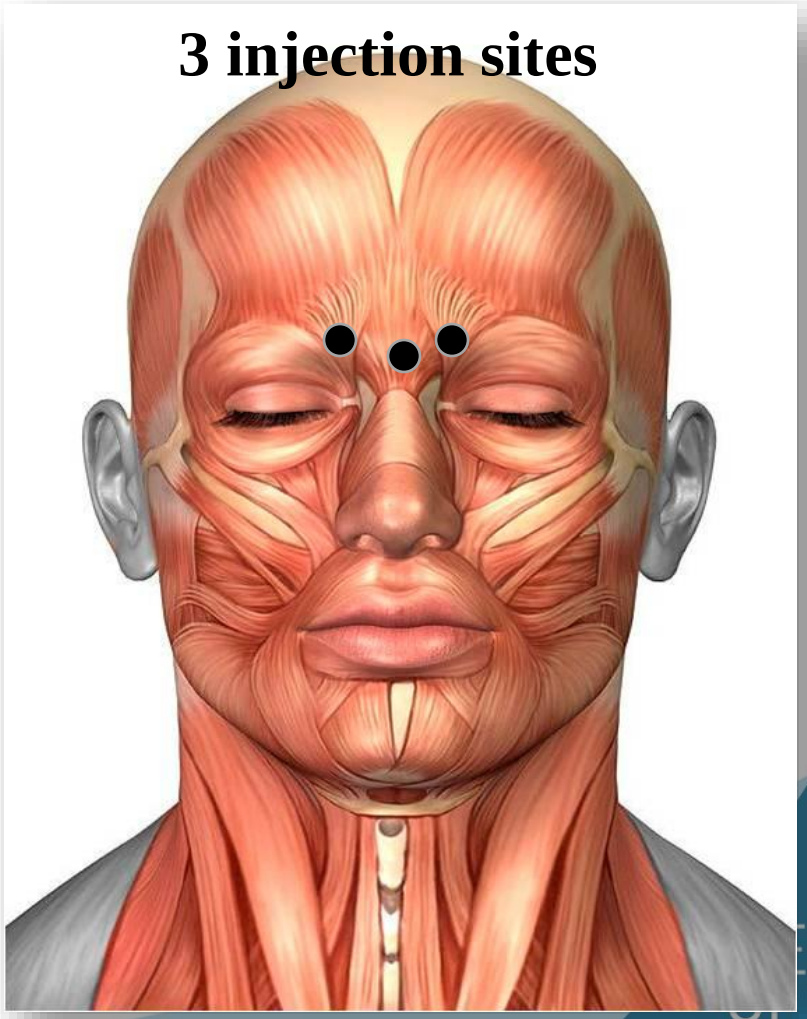




Glabella

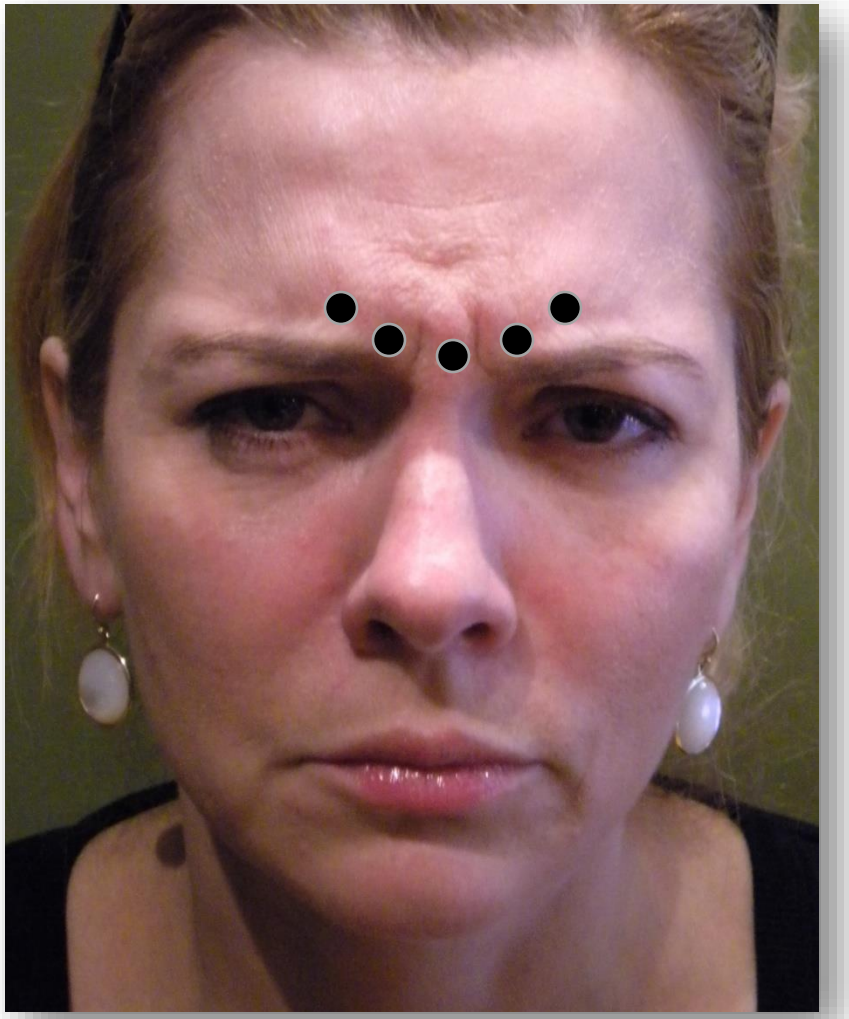
4-5 Units per Injection Site

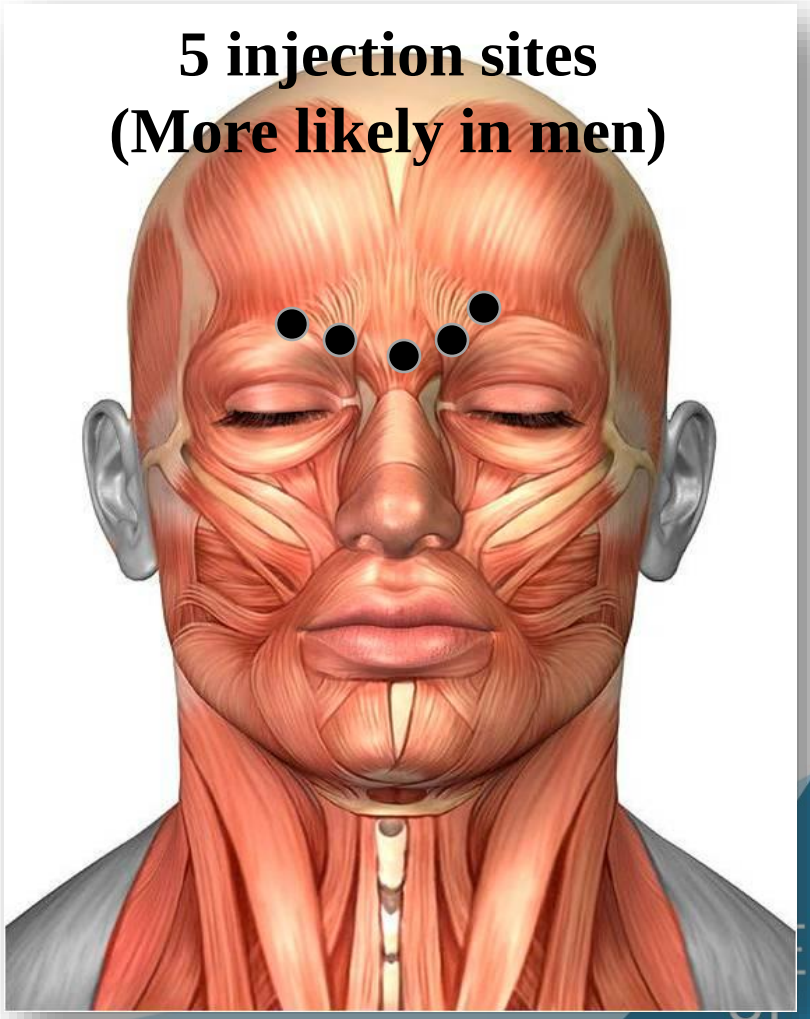




Glabella

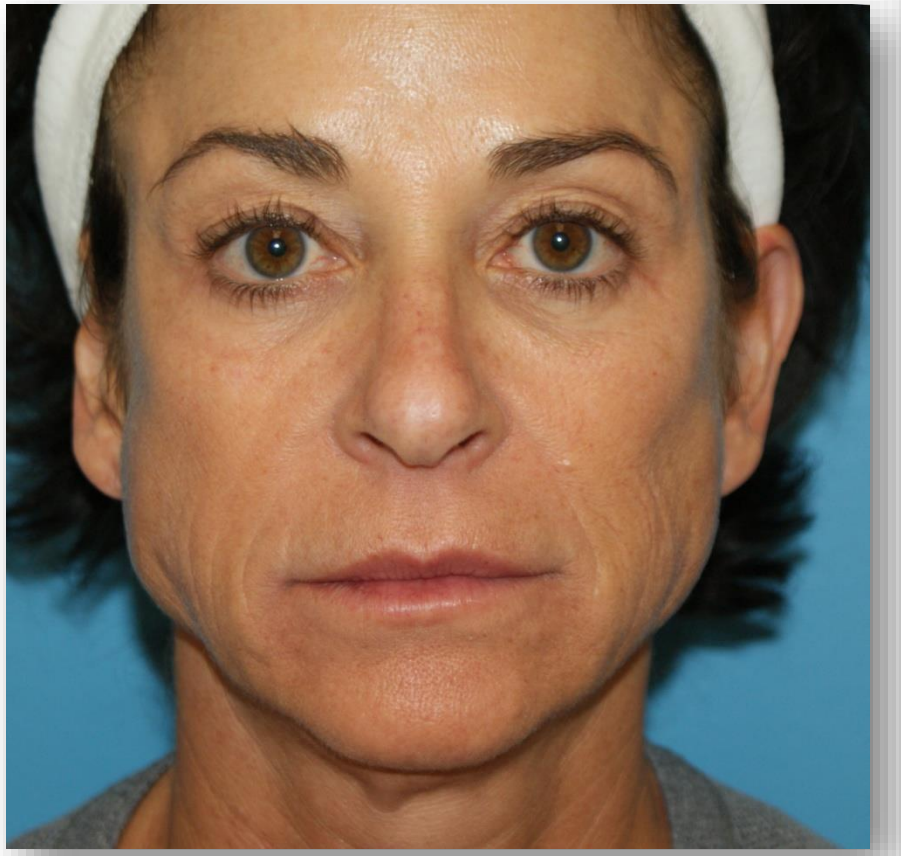
4-5 Units per Injection Site

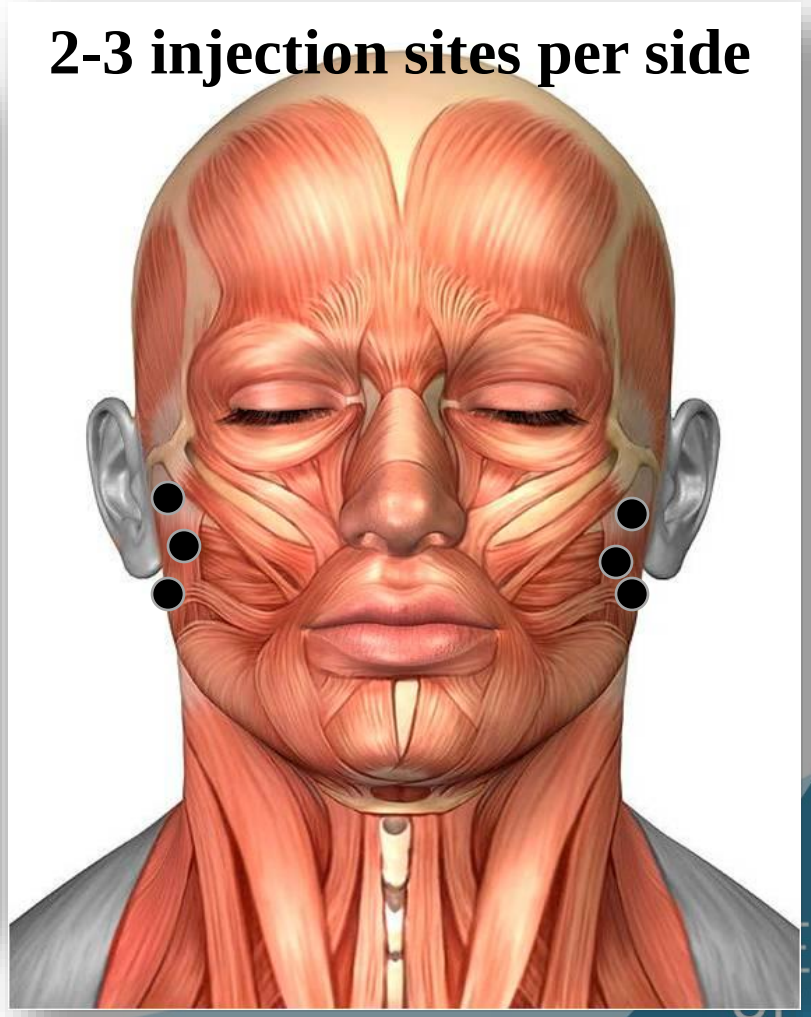




Masseter Hypertrophy

5-10 Units per Injection Site





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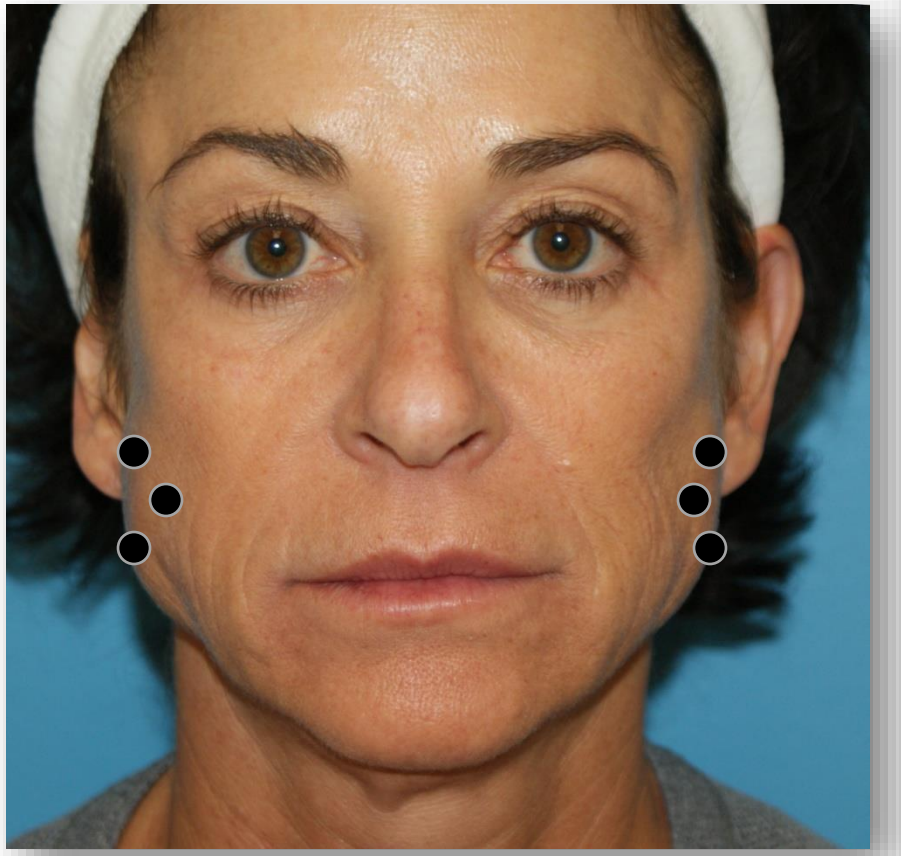
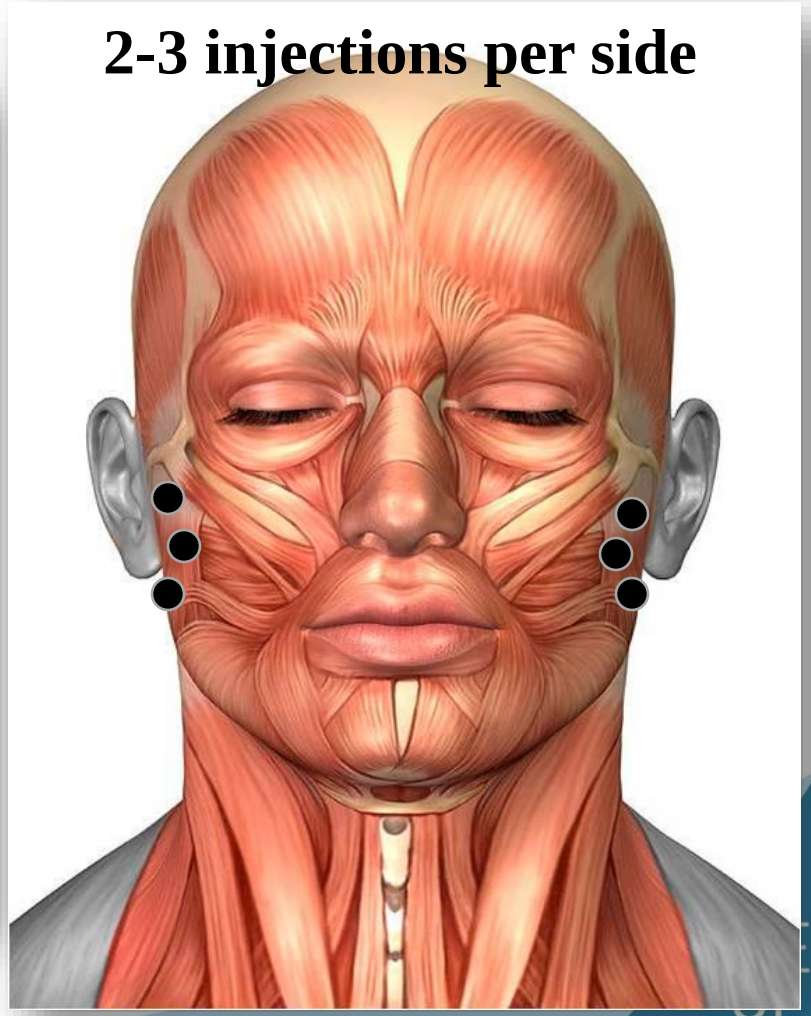
Masseter Hypertrophy

5-15 Units per Injection Site



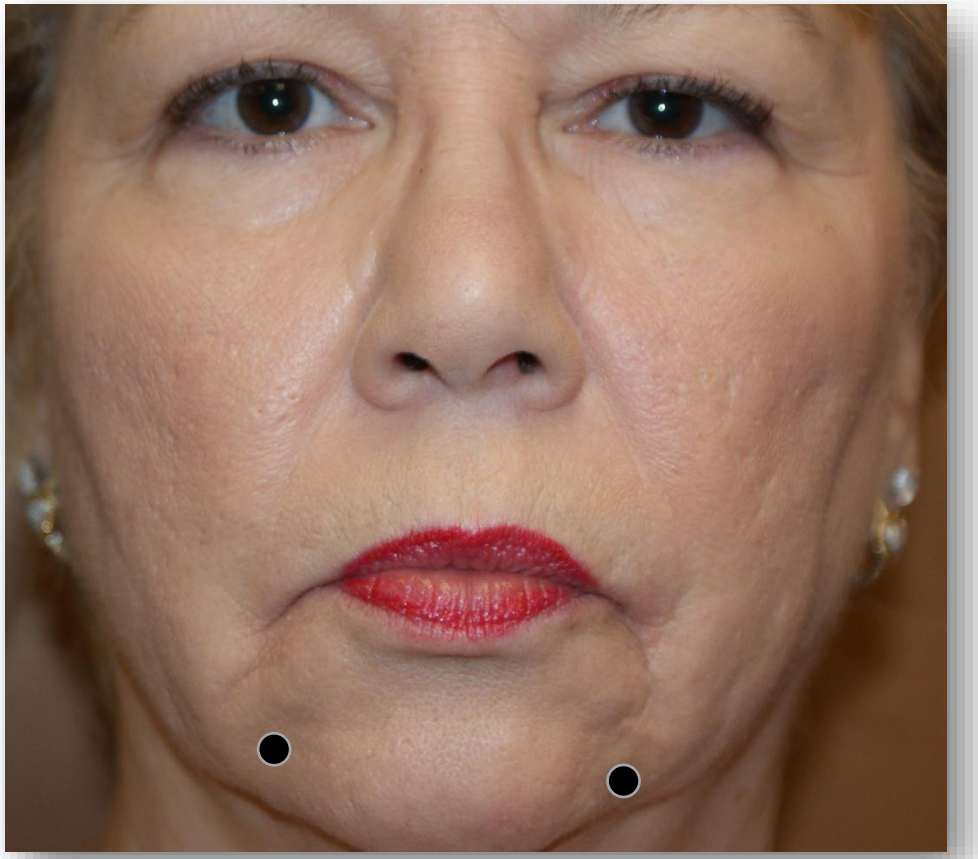
Avoid medial injection to risorius muscle



Smith, ASJ 2014

Lip Corner Elevation

3 to 5 Units per Injection Site



Inject lateral to commissure to avoid central lip depression

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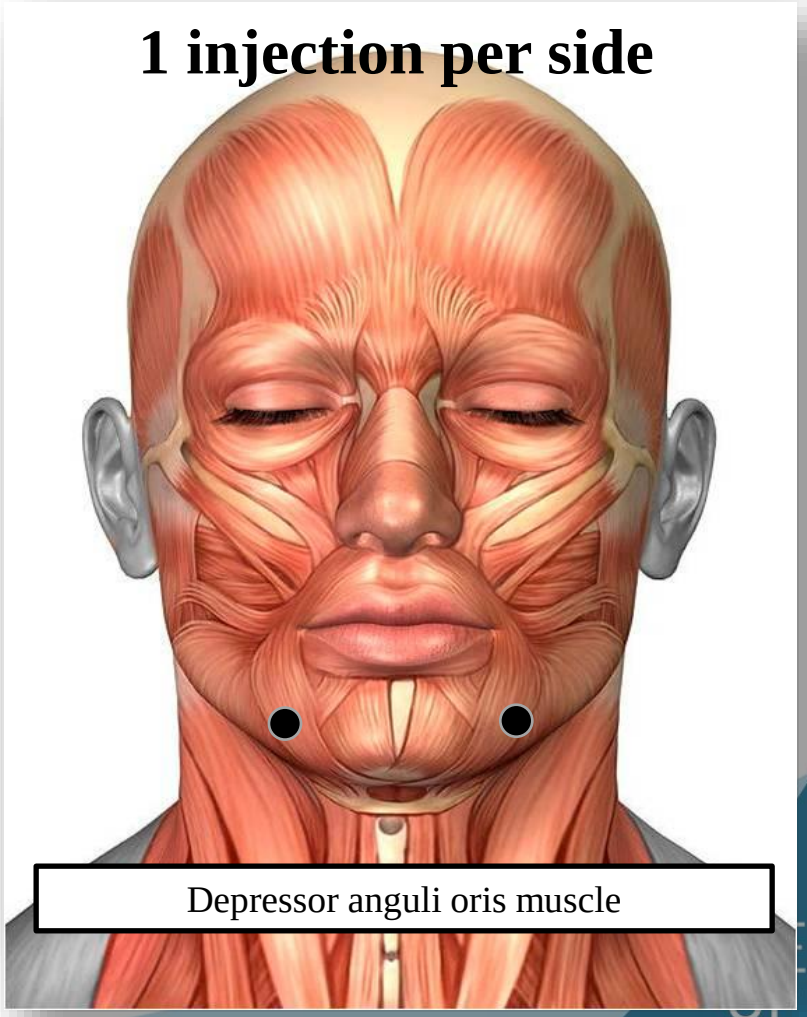
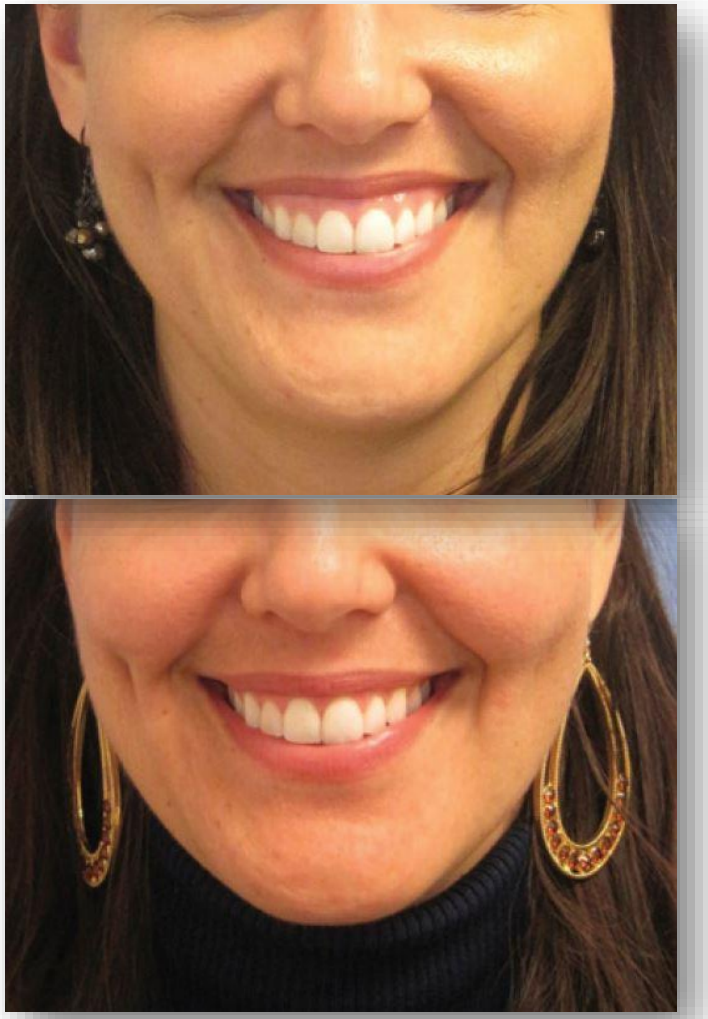
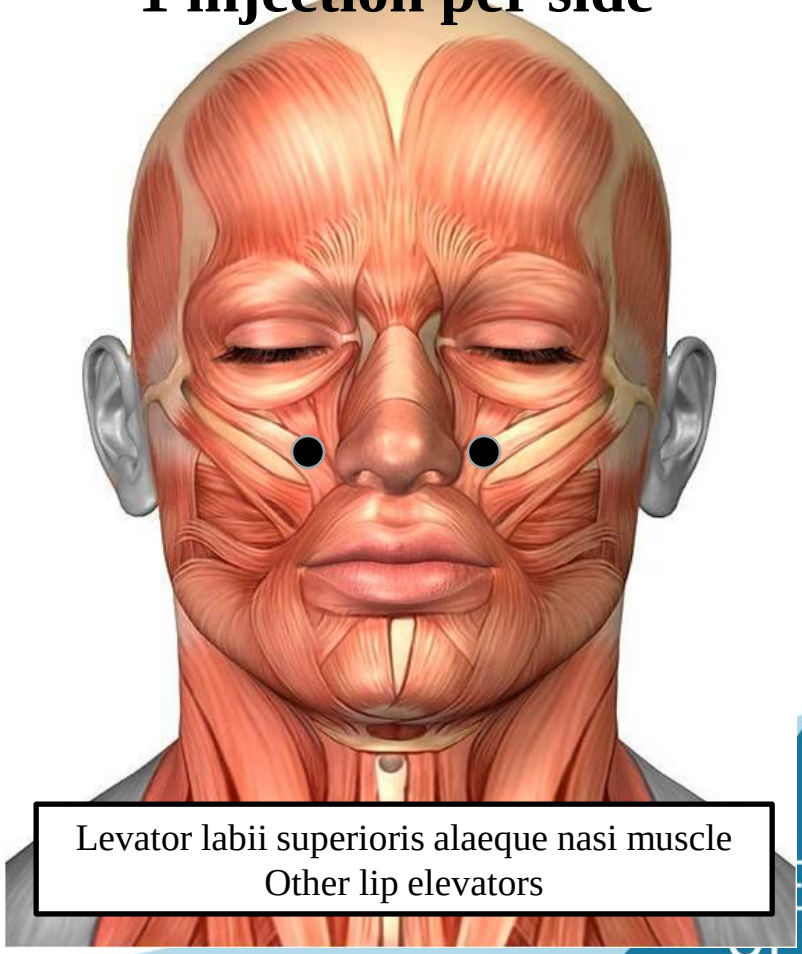


Gummy Smile

4-5 Units per Injection Site



1 injection per side



Levator labii superioris alaeque nasi muscle
Other lip elevators

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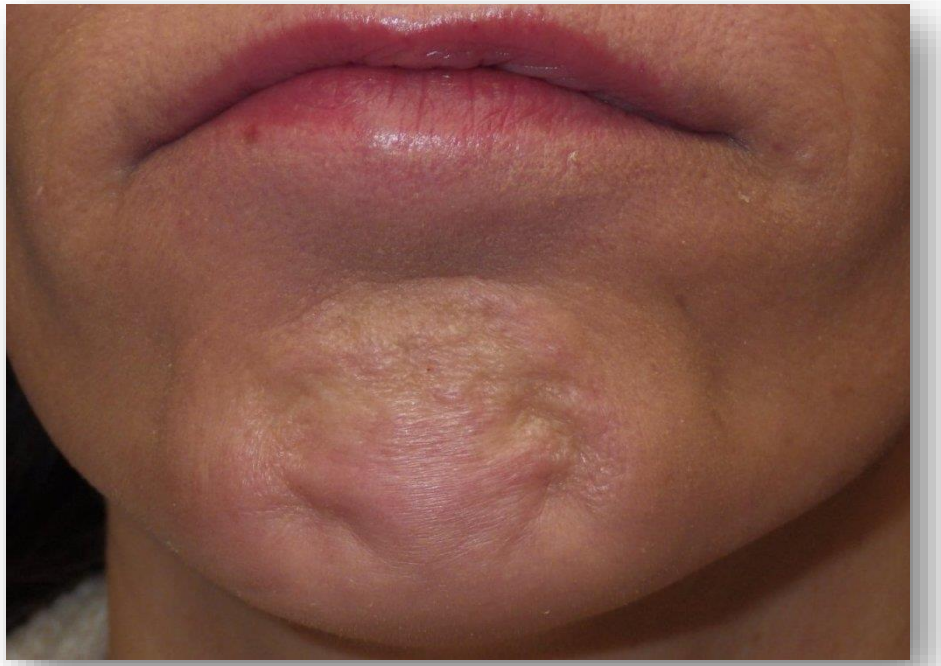
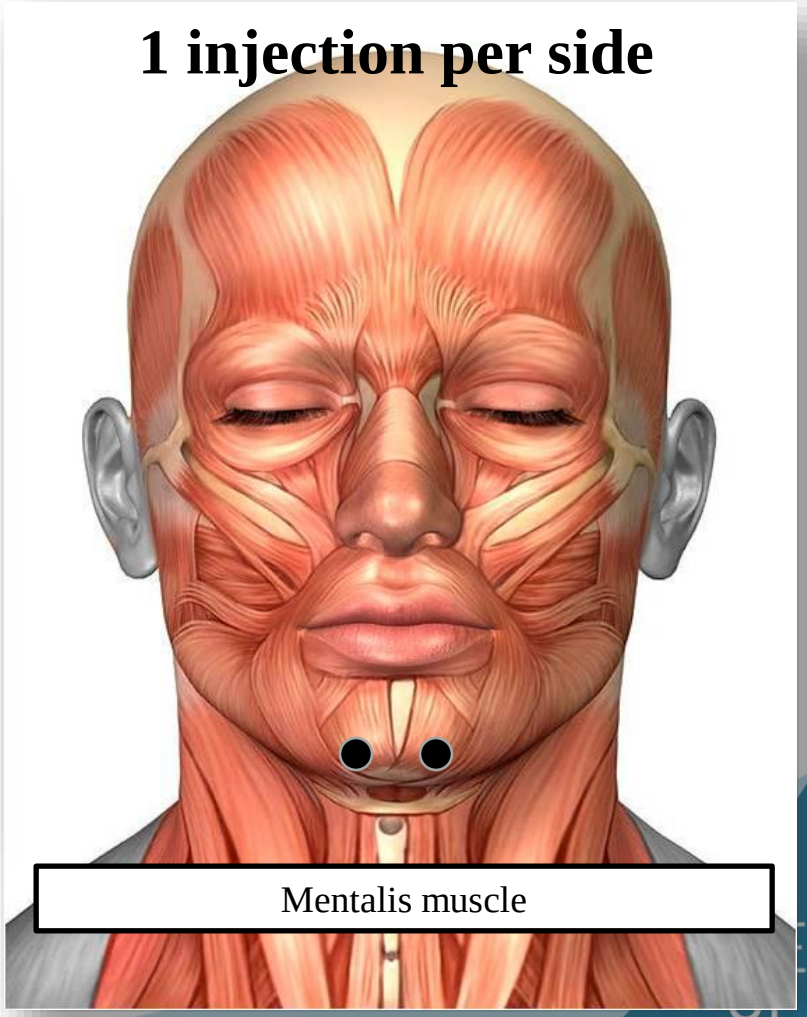
Chin Dimples

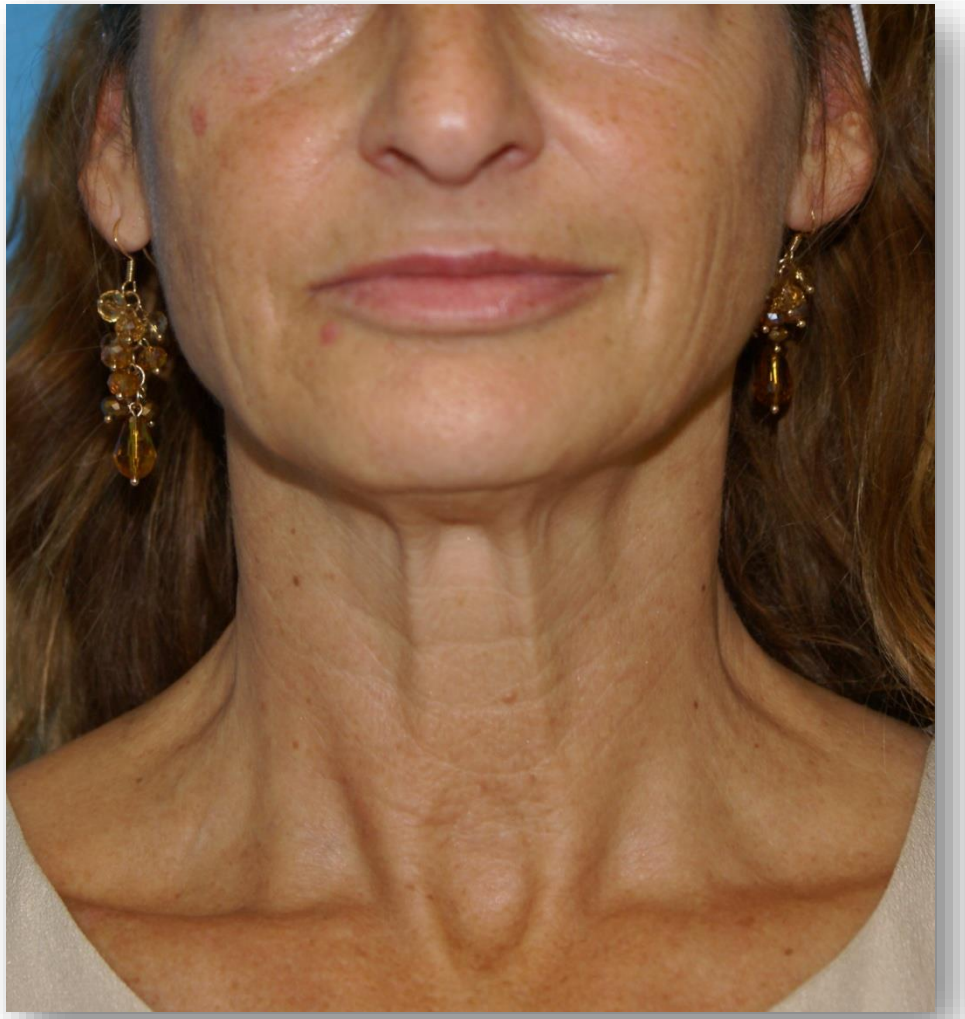
4-5 Units per Injection Site

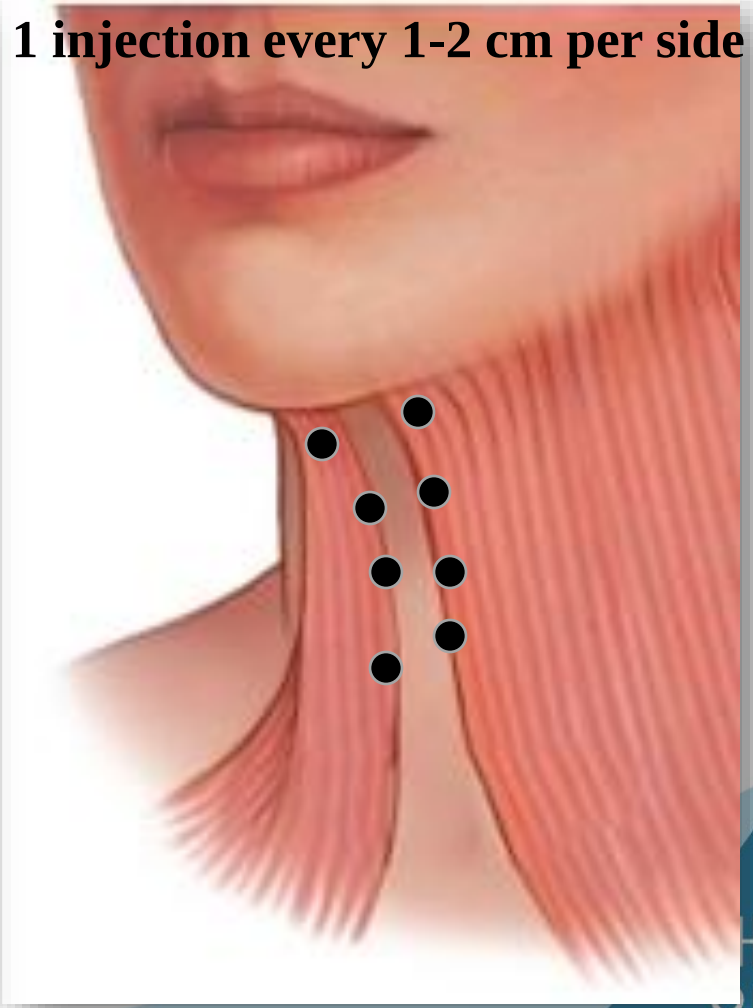




Platysmal Bands

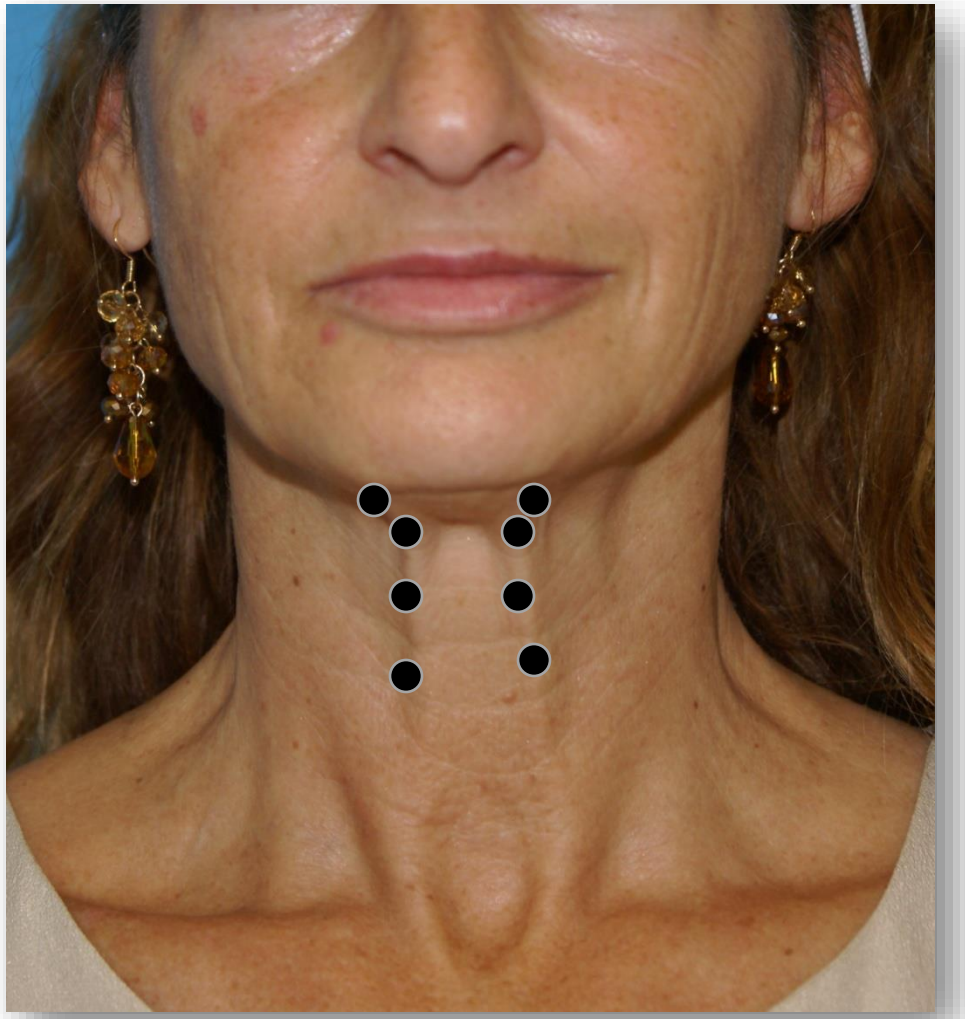
4 Units per Injection Site



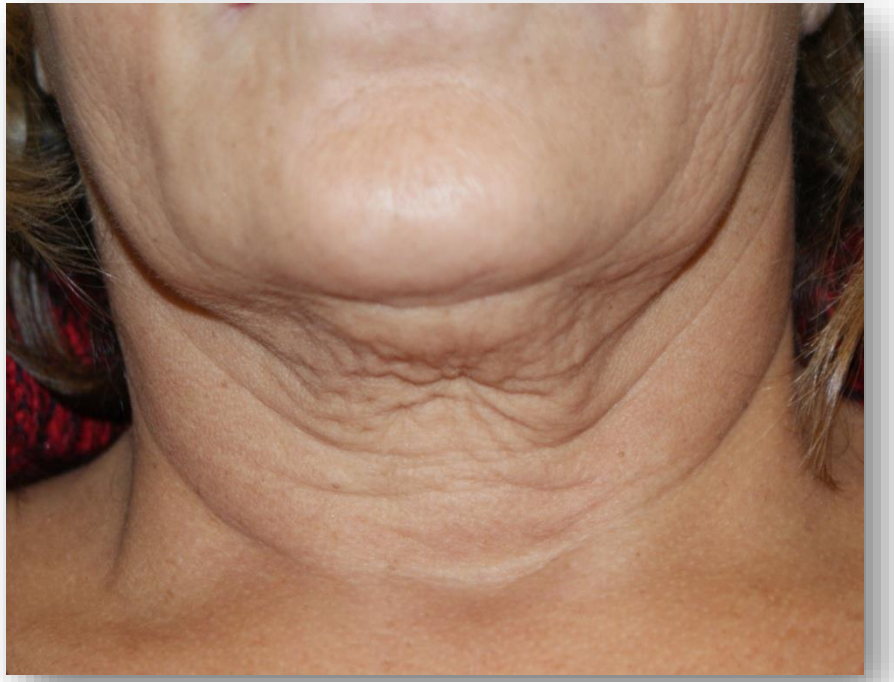


Platysmal Bands

4 Units per Injection Site

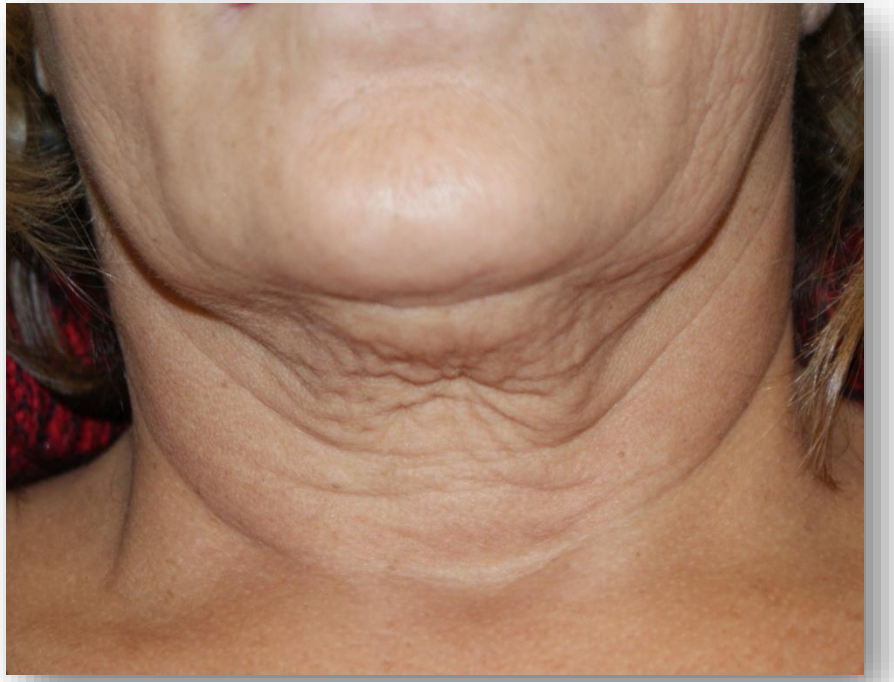


Annoying Platysma

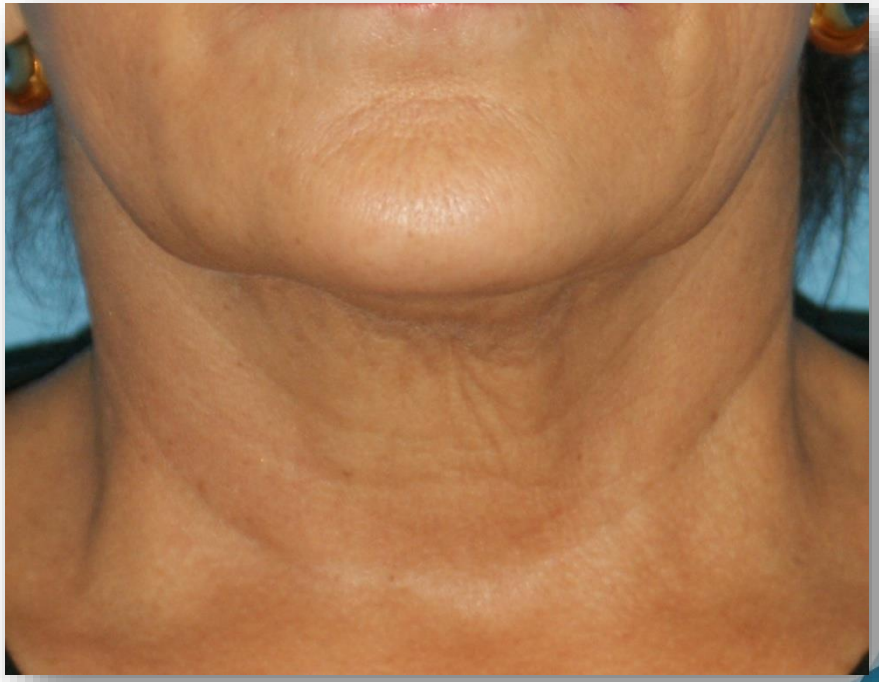


Loose Neck Skin

Annoying Platysma

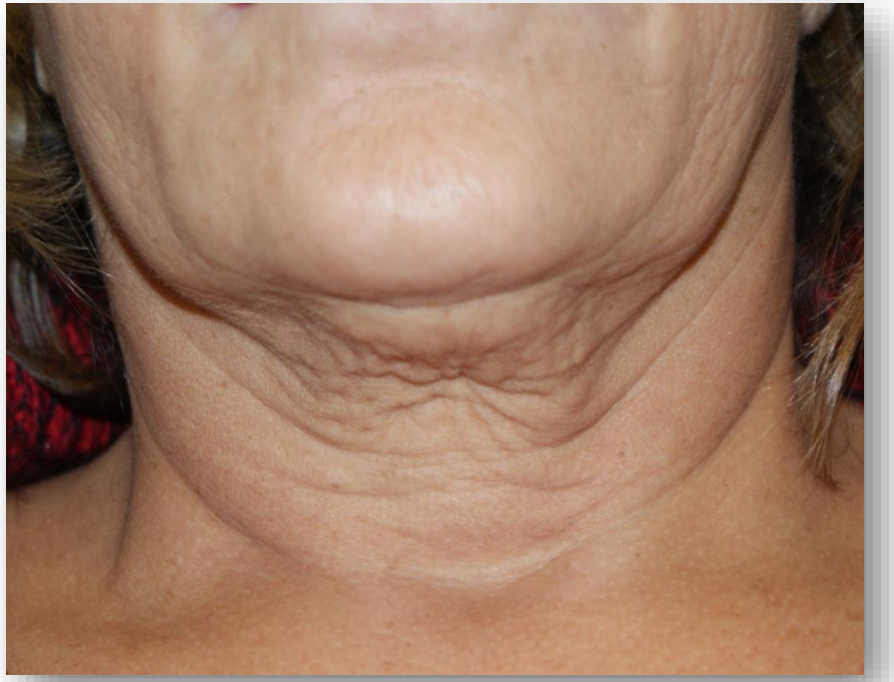


Loose Neck Skin

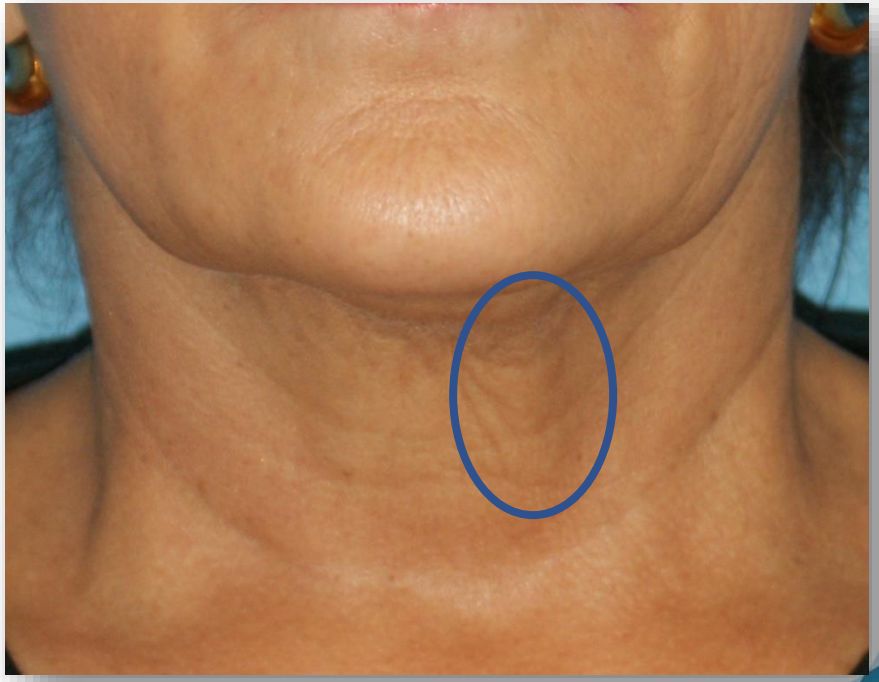


After External Radiofrequency Skin Tightening

Annoying Platysma

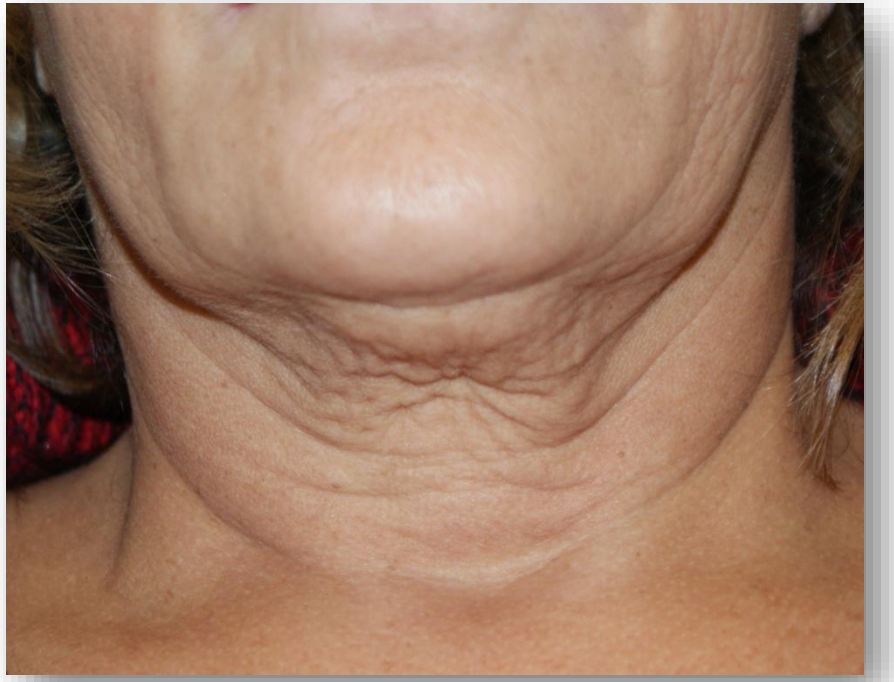


Loose Neck Skin

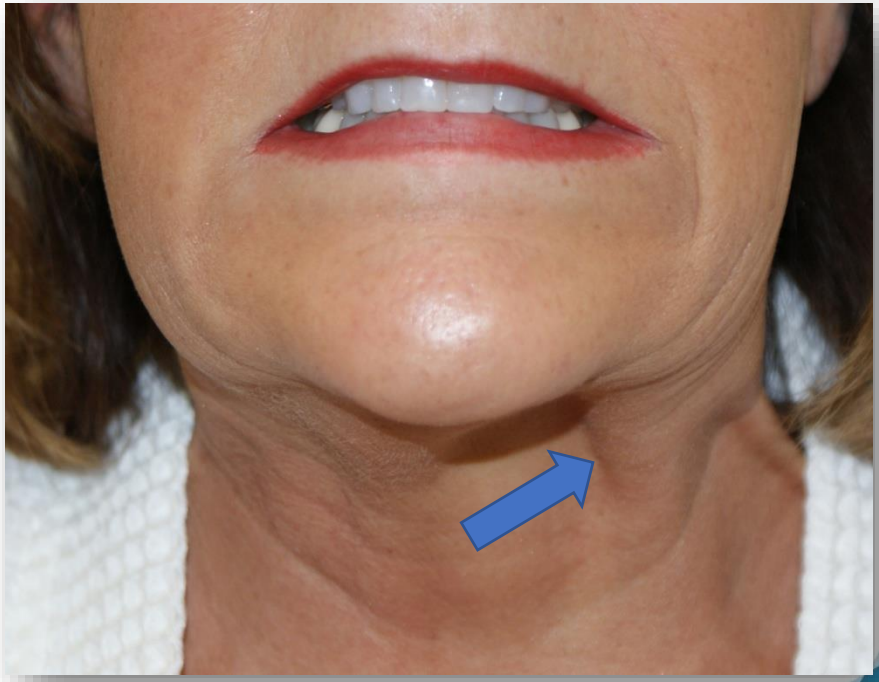


After External Radiofrequency Skin Tightening

Annoying Platysma

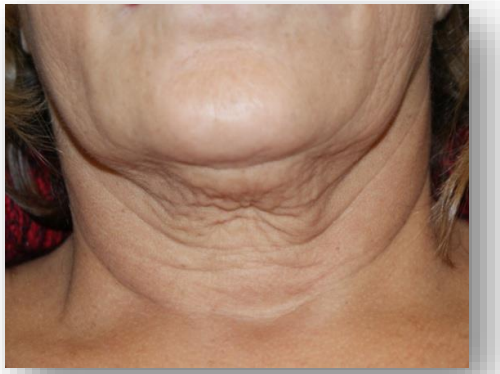


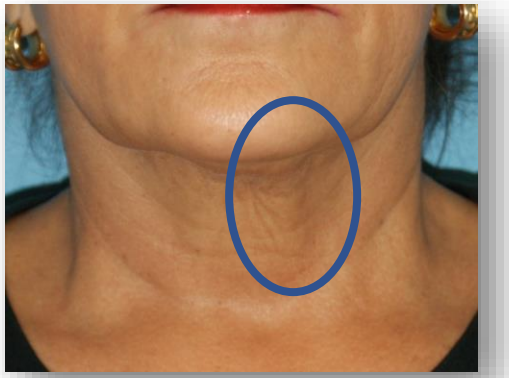
Loose Neck Skin

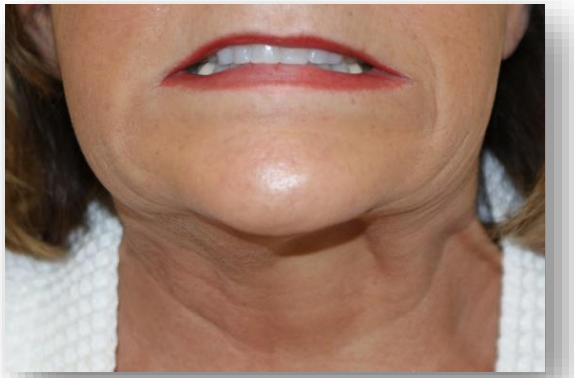


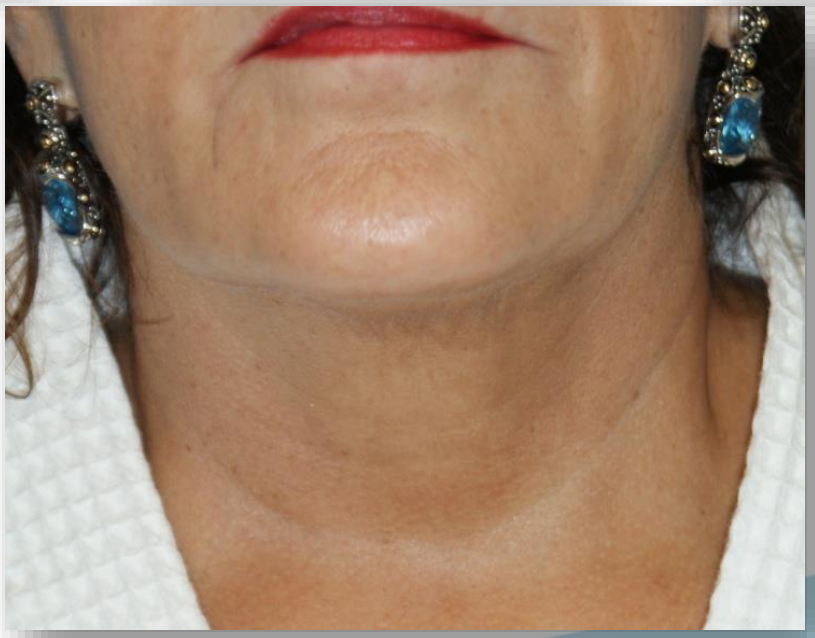
Active Medial Platysmal Band

Annoying Platysma

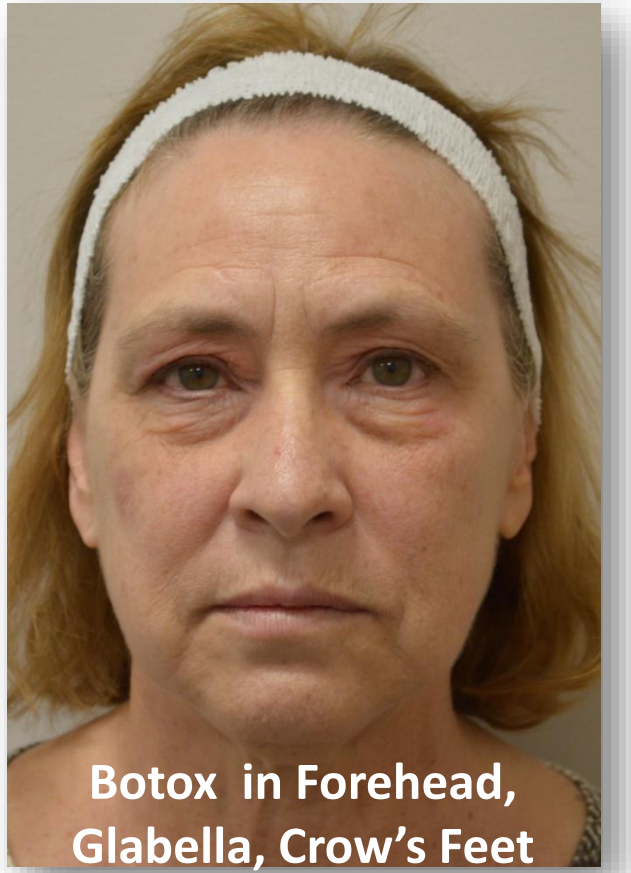


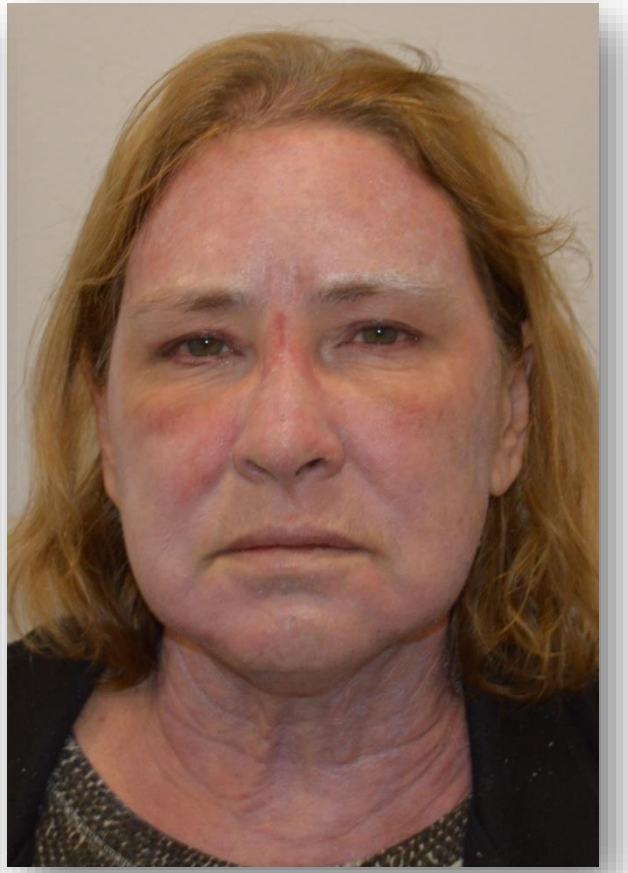






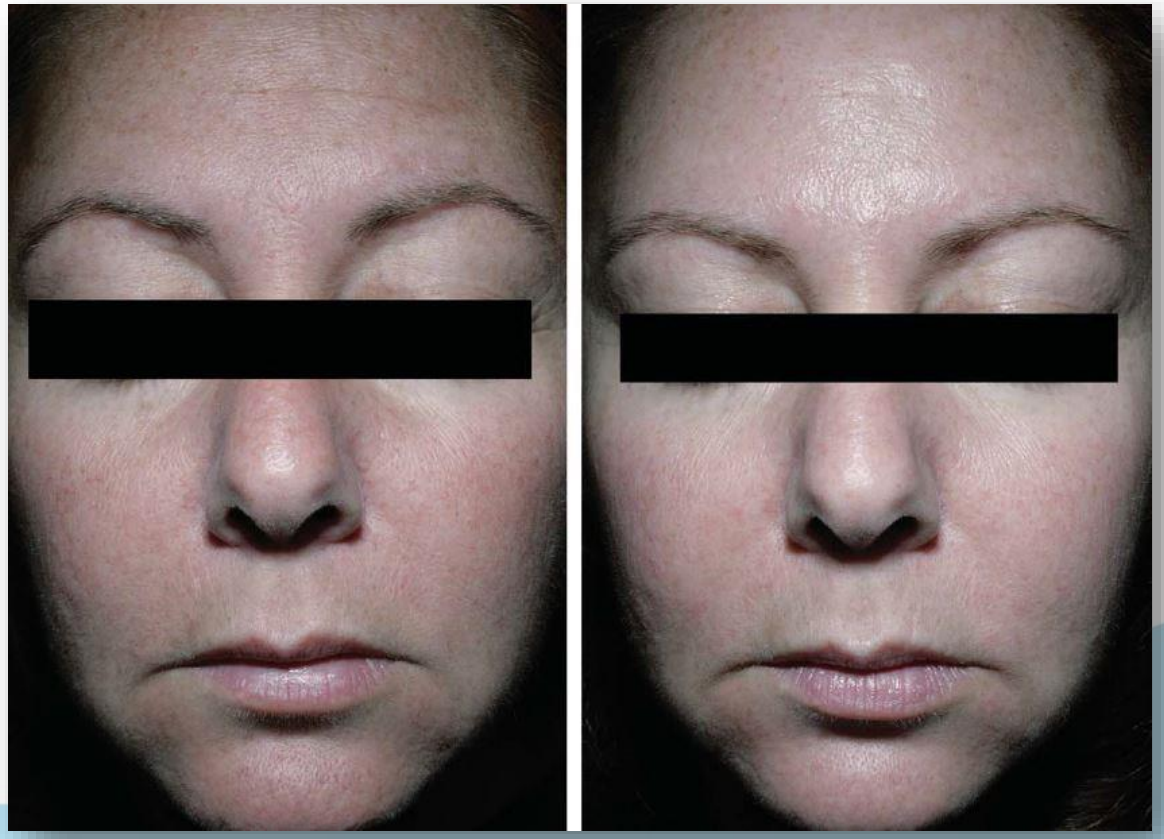
Prior to Skin Resurfacing



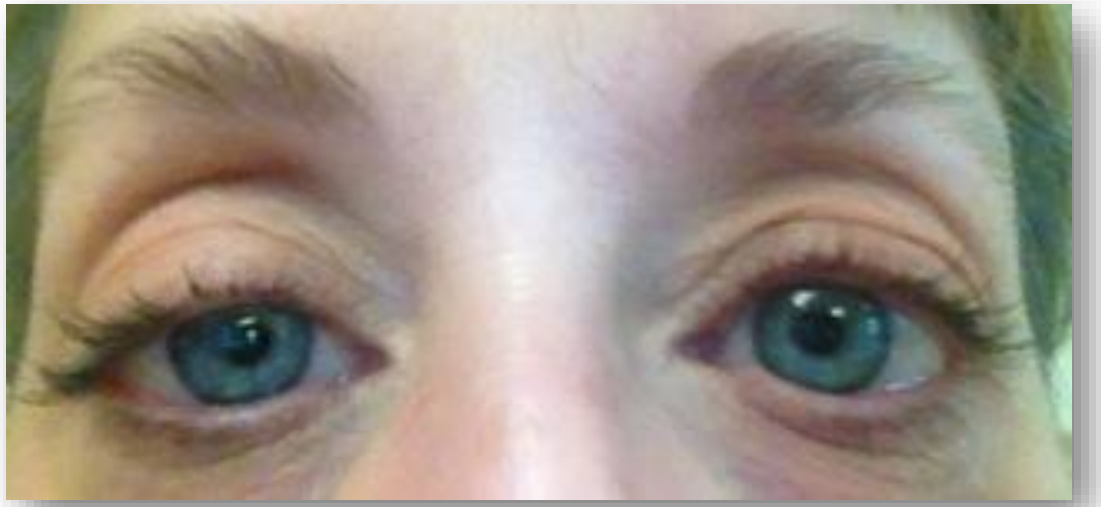


BoTN-A for Rosacea

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

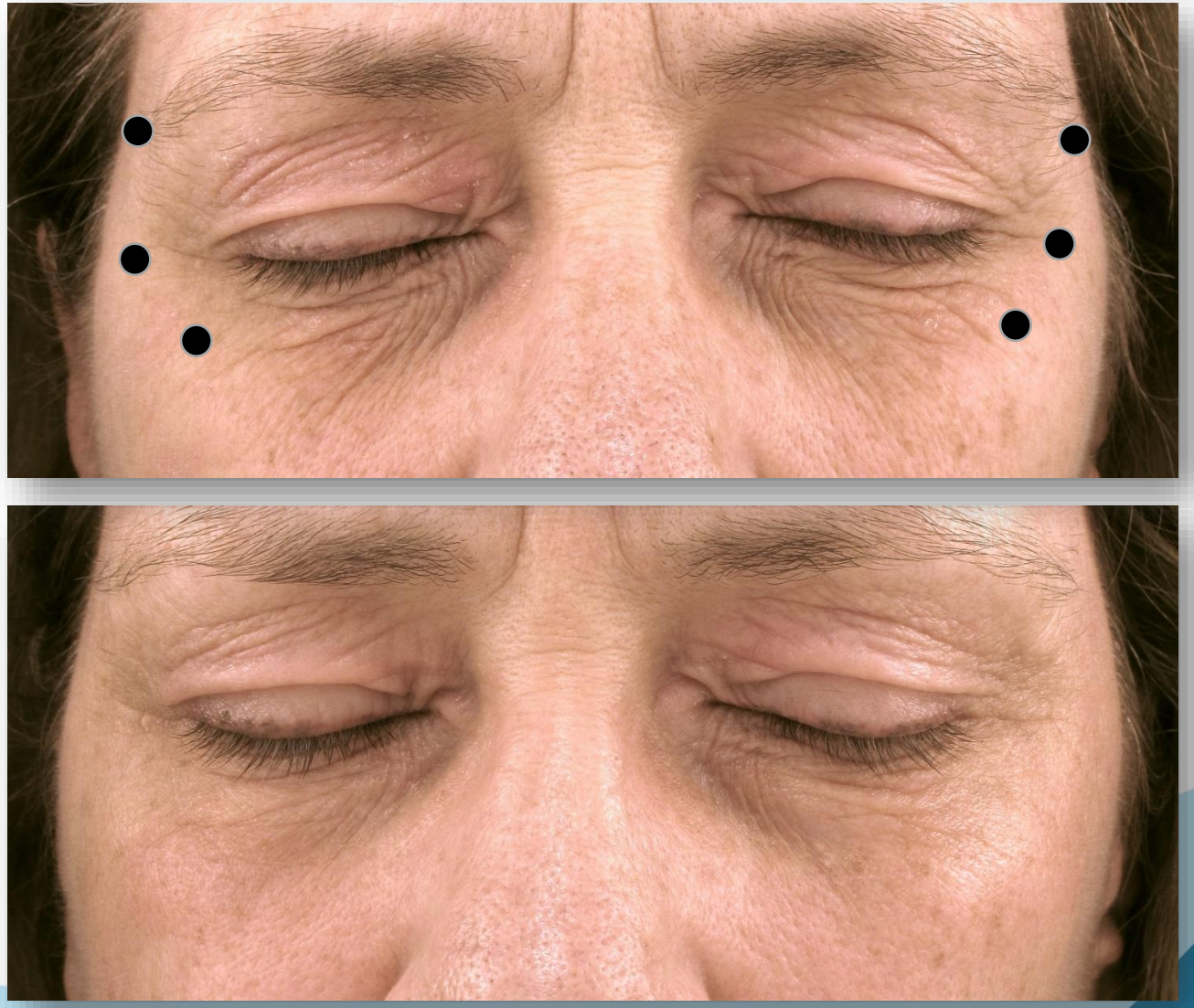


Eyelid Ptosis Reversal



- 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

BTA + Fractional CO_2 Laser



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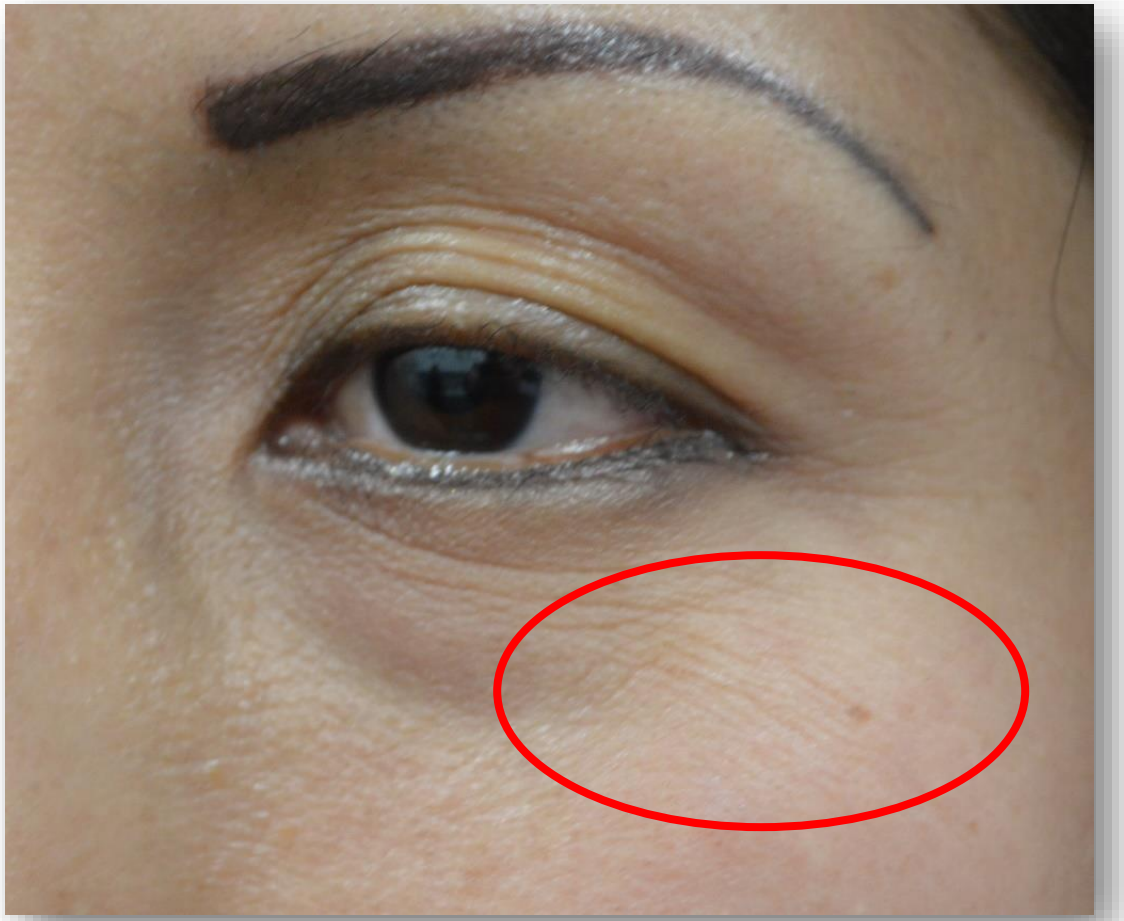
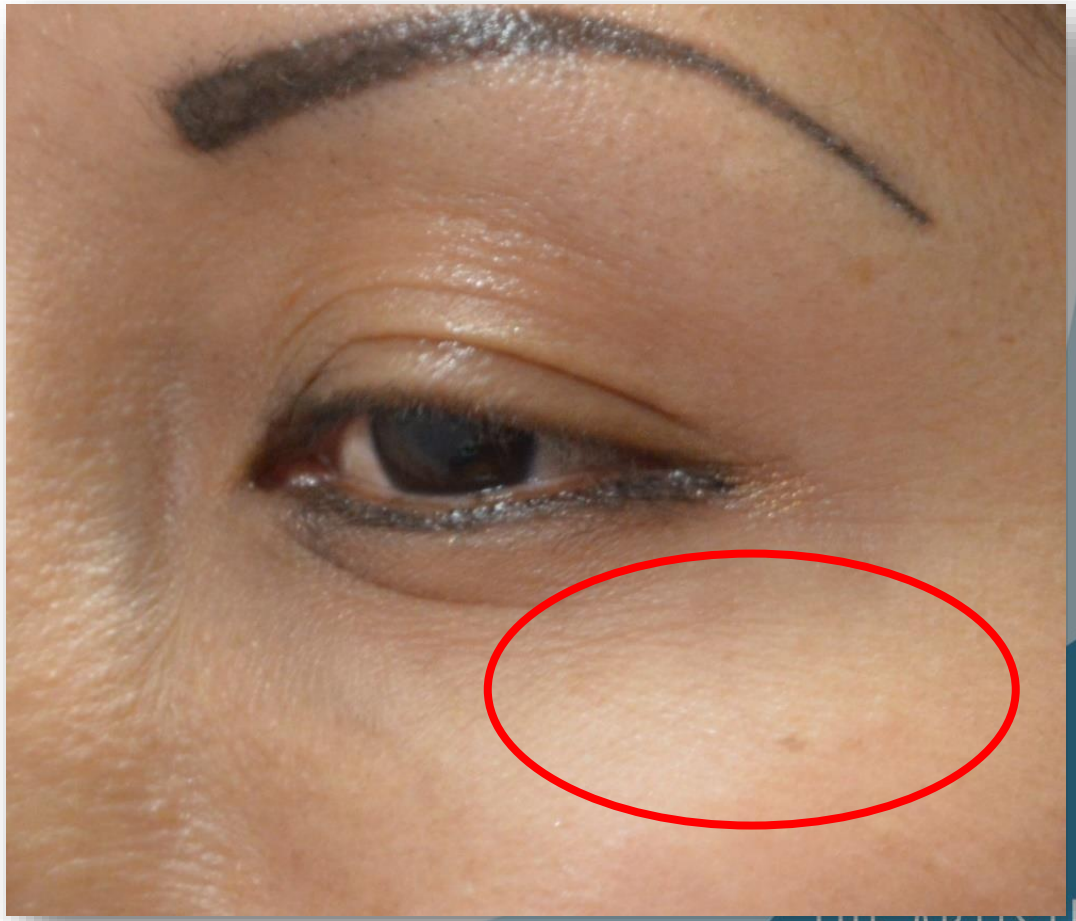
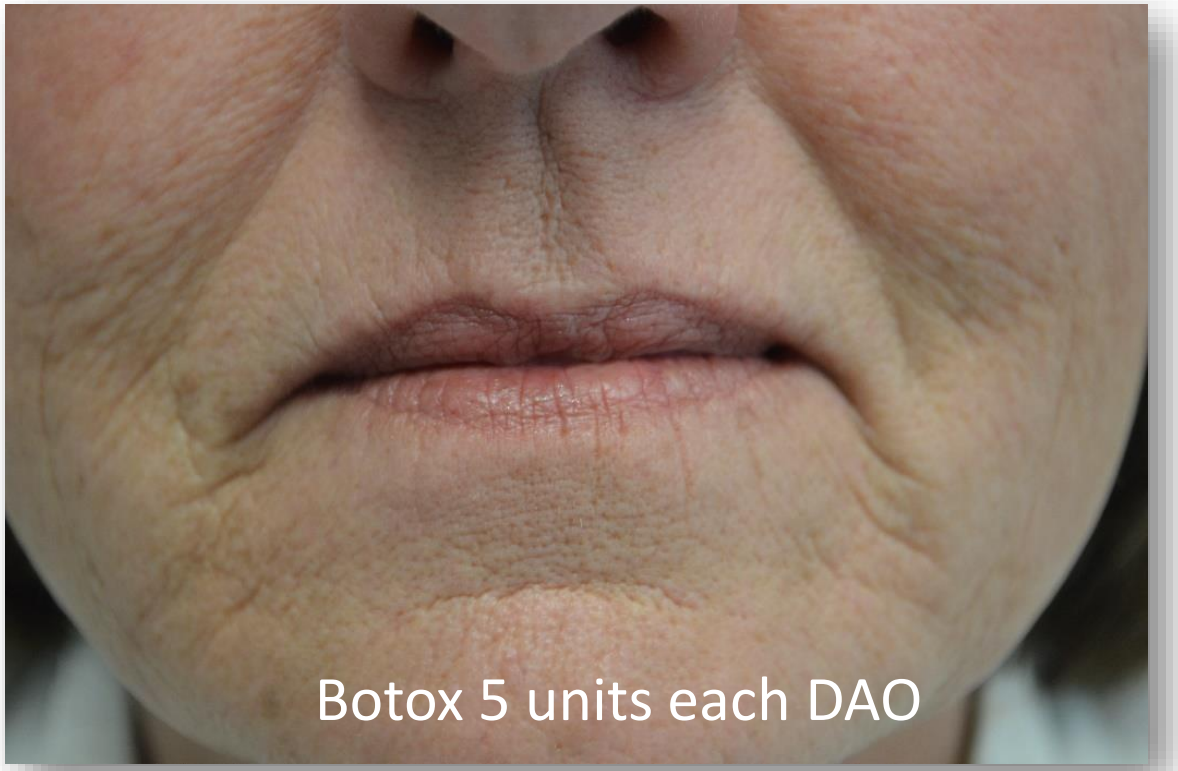
BTA + Filler

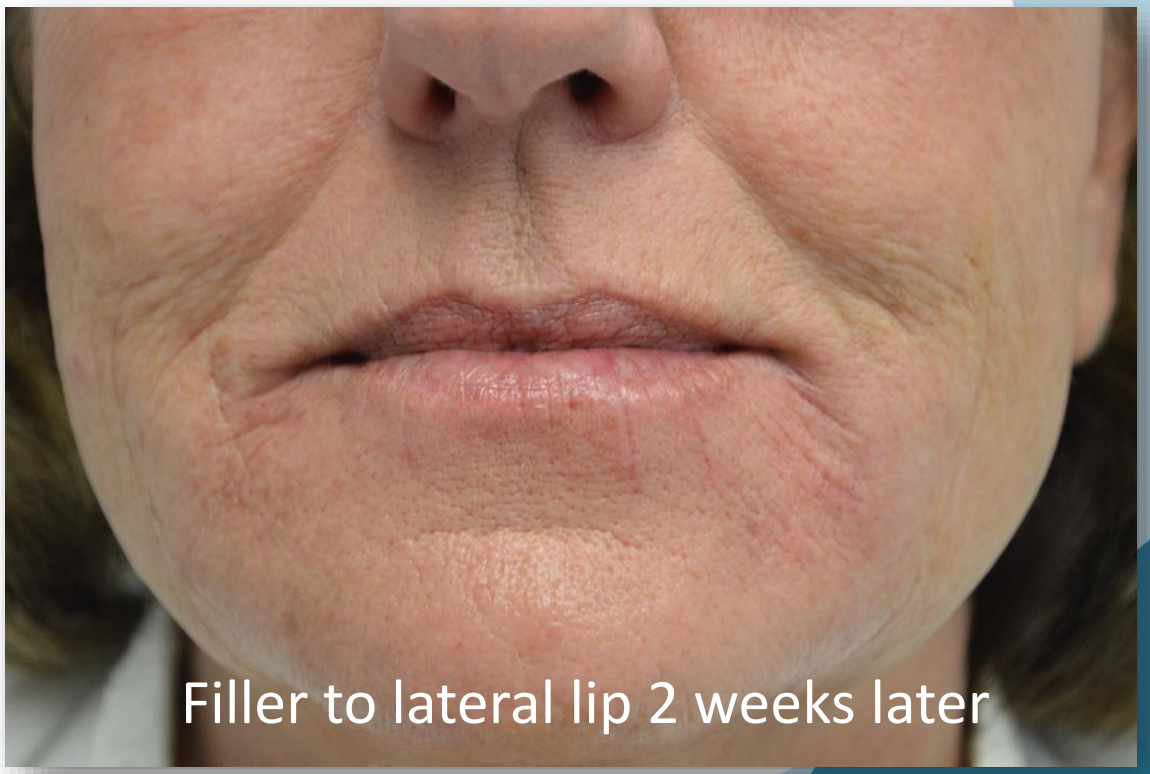
BTA + Filler





BTA + Filler





What to do when BTA not working

Short Duration

- Increase dose
- Increase frequency
- Try another BTA
- Zinc/Phytase supplement?

Minimal or No Effect

- Check product
- Injector error
- Increase dose
- Try another BTA
- Consider **neutralizing antibodies** (NAb) after log-term use

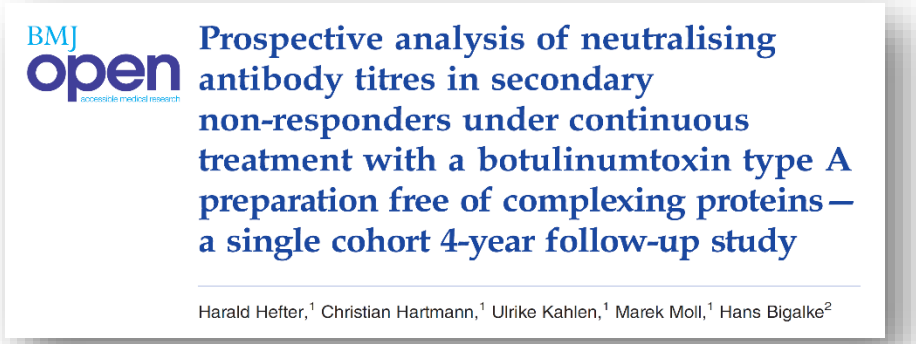
Neuromodulator Treatment Failure

- Up to 20% for cervical dystonia
  - High doses used
- More being reported in aesthetic use
  - Higher doses being used
  - Patient being treated > 10 years
  - May present as shorter duration
  - Changing to another BTA rarely works
- Military (others) who have been vaccinated

Immunologic Cause for Poor or No Response

- The accessory proteins seem to play a role in NAb formation
- Cervical dystonia treatment failure due to neutralizing antibodies, usually in 2 to 3 years
  - Dysport 0 to 2.5%
  - Botox 0 to 1.2% (was higher when more protein)
  - Xeomin 0 to 1.0% in patients who had other BTA
  - BTB much higher
- NAb may take 1 to 4 years to become undetectable after stopping BTA

Decreased NAb during BTA Treatment



- Cohort of cervical dystonia patients treated with Botox or Dysport who are now non-responders & have high NAb levels
- Given Xeomin every 3 months for 4 years
- NAb became undetectable in most patients in 3 years
  - Would have expected high NAb during BTA treatment
- Can a BTA with less protein load and no accessory proteins prevent NAb response?

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Neutralizing Antibody Assay

- Mouse bioassay is better than *in vitro* assay
- Send blood sample for testing
- Results in 2 weeks
- 185 Euros
- But, lack of NAb does not predict a good response in the future

toxogen GmbH

Recommendations

- Reduce BTA load whenever possible
  - Use lowest does needed
  - Avoid touch ups
  - Avoid injection before effect worn off
  - Use less immunogenic BTA (minimal proteins)
- If neutralizing antibodies suspected
  - Consider serum assay
  - BTA “holiday” for 1 to 2 years
- Total lifetime BTA dose may predispose to NAb
- Patients have been exposed for many years
- If your BTA is not having the same effect, consider NAb
  - Stop for 1 to 2 years, then try again
- Less antigenic BTA may have less risk for NAb

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Basics of Neuromodulators

Karol A Gutowski, MD, FACS

Questions?

Karol@DrGutowski.com