Botulinum Neuromodulators: Clinical Data & Applications

Karol A Gutowski, MD, FACS

ENDLESS POSSIBILITIES.
CHICAGO
OCTOBER 10-14 2014
AMERICAN SOCIETY OF PLASTIC SURGEONS
THE PLASTIC SURGERY FOUNDATION
ASMS
plastic surgery
THE MEETING

Disclosures

Angiotech/Quill - Advisory Board

Suneva Medical - Instructor

Viora - Speaker

Will discuss off-label uses

Will use brand names for ease of understanding

Will refer to BOTOX *Cosmetic* as BOTOX

BoTN-A Product Information

FDA Approved

- BOTOX *Cosmetic* - **Ona**botulinumtoxin**A**
- DYSPORT – **Abo**botulinumtoxin**A**
- XEOMIN – **Inco**botulinumtoxin**A**

Not FDA Approved

- MYOBLOC - **Rima**botulinumtoxin**B**
- NEURONOX - Botulinum toxin **A**
- RT001- Botulinum toxin **A** (Topical)

FDA Cosmetic Approval

- **BOTOX *Cosmetic**** [Allergan]
  - Moderate to severe glabellar lines
  - Moderate to severe lateral canthal lines
- **DYSPORT** [Medicis/Valeant]
  - Moderate to severe glabellar lines
- **XEOMIN** [Merz Aesthetics]
  - Moderate to severe glabellar lines
- All for adults ≤ 65 years old

What FDA Wants You to Know

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

BoTN-A Mechanism of Action

Block neuromuscular junction transmission by inhibiting acetyl choline release

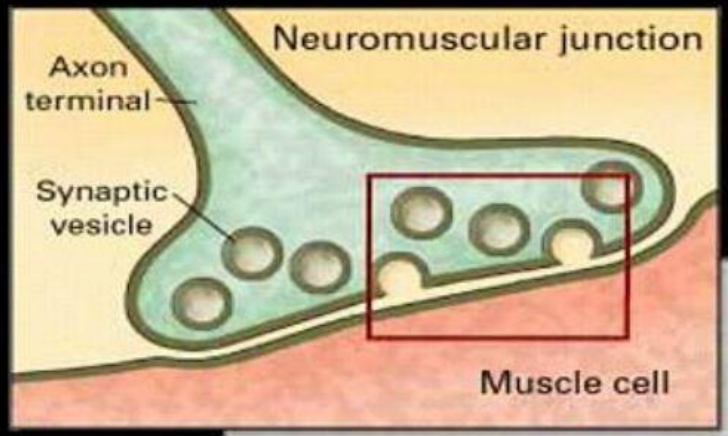
- BoTN-A binds to cholinergic nerve terminals
- Internalized into nerve
- Light-chain translocated into nerve cytosol
- Enzymatic cleavage of SNAP-25 (essential for ACh release)
- Impulse transmission re-established by formation of new nerve endings

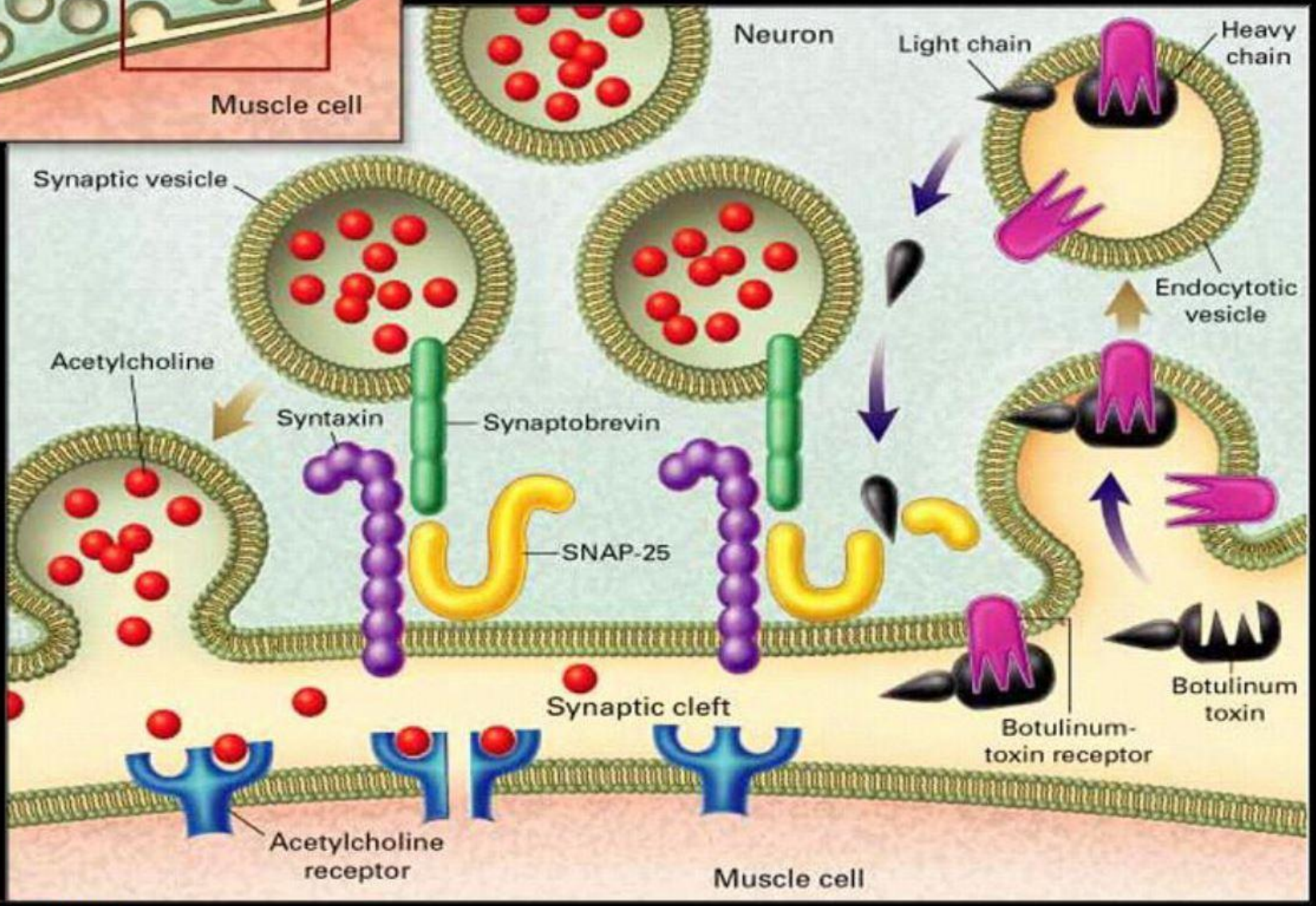
Mechanism of Action

Types A and B bind to distinct acceptors

Botulinum Type A cleaves SNAP-25

Botulinum Type B cleaves synaptobrevin (VAMP)





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

Product Comparison

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

Product Composition

	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)

Product Composition

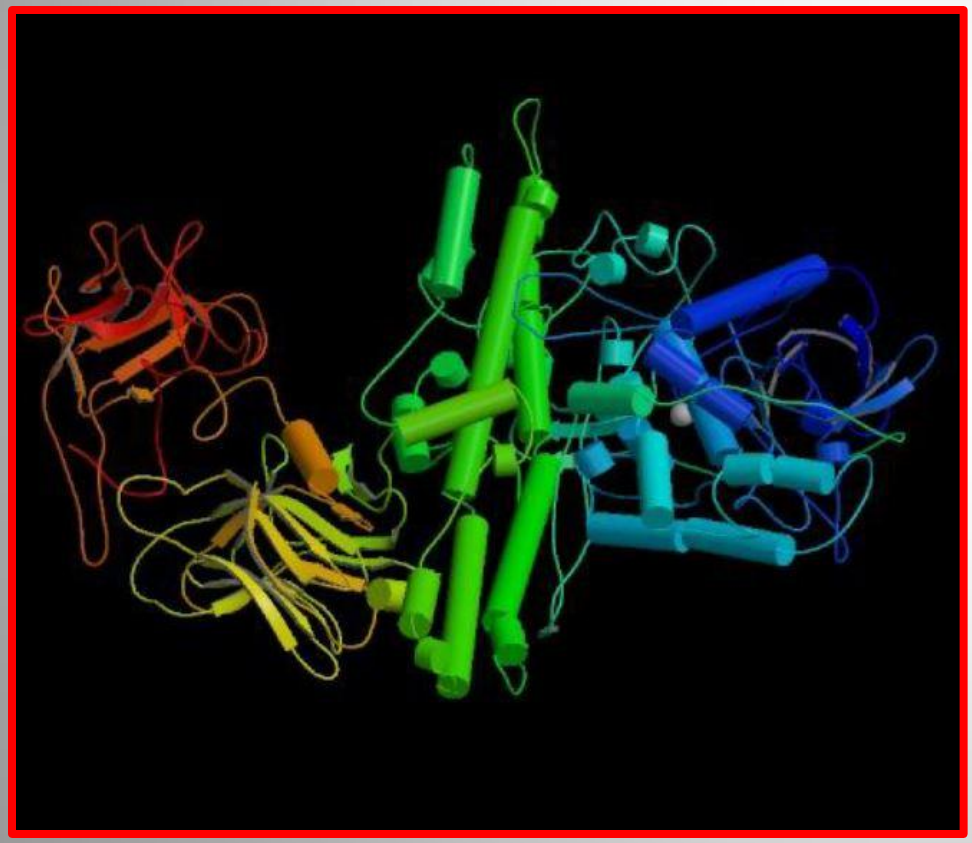
	BOTOX® Cosmetic[1]	*DYSPORT®*[2]	*XEOMIN®*[3]
Non-Proprietary Name	**onabotulinumtoxinA**	**abobotulinumtoxinA**	**incobotulinumtoxinA**
First Approval	• 1989 (US)	• 1991 (UK)	• 2005 (Germany)
Serotype	• A	• A	• A
Strain	• Hall (Allergan)	• Hall¥	• Hall
Receptor/Target	• SV2/SNAP-25	• SV2/SNAP-25	• SV2/SNAP-25
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)

Product Composition

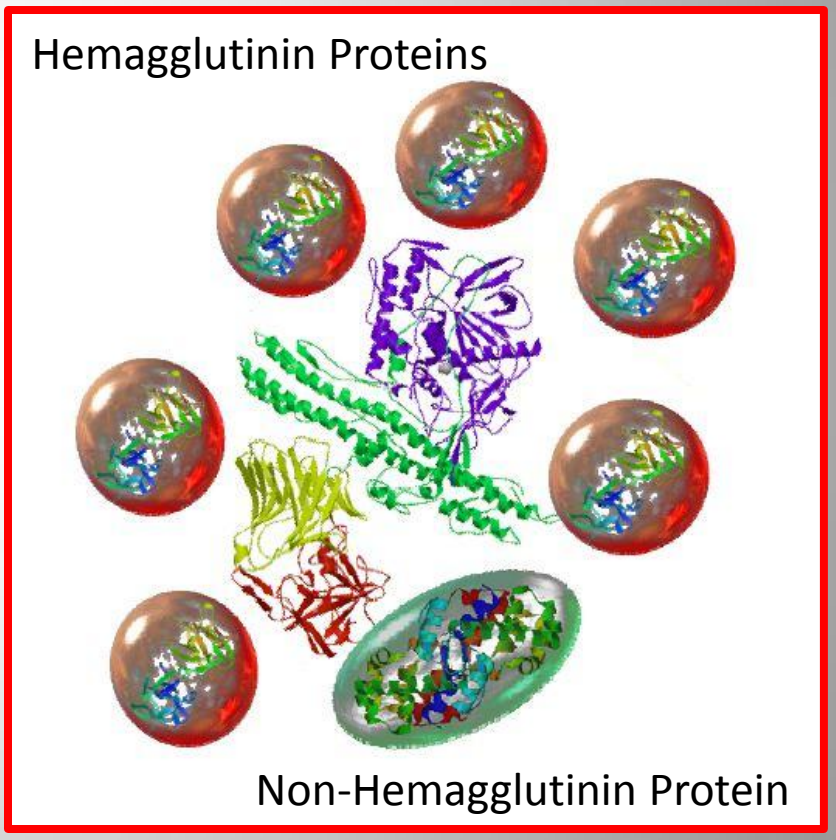
	BOTOX® Cosmetic[1]	*DYSPORT®*[2]	*XEOMIN®*[3]
Non-Proprietary Name	**onabotulinumtoxinA**	**abobotulinumtoxinA**	**incobotulinumtoxinA**
First Approval	• 1989 (US)	• 1991 (UK)	• 2005 (Germany)
Serotype	• A	• A	• A
Strain	• Hall (Allergan)	• Hall¥	• Hall
Receptor/Target	• SV2/SNAP-25	• SV2/SNAP-25	• SV2/SNAP-25
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)

BoTN-A Molecule

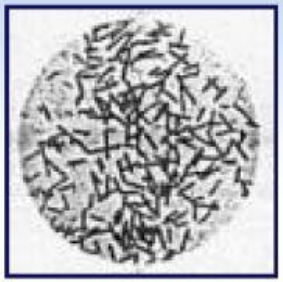
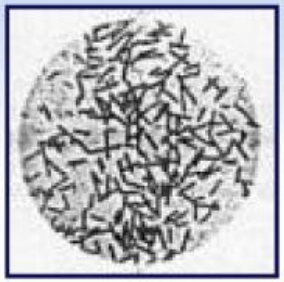
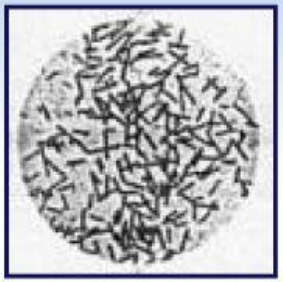
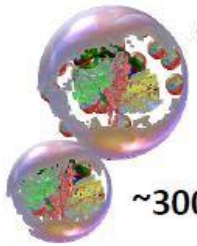
BoTN-A



BoTN-A + Accessory Proteins



BoTN-A Protein Comparison

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

Pivotal Study Doses

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

Dilution and dosage may vary as determined by clinician

Adjusting dose to target muscle mass may improve outcome and duration

Pivotal Study Doses

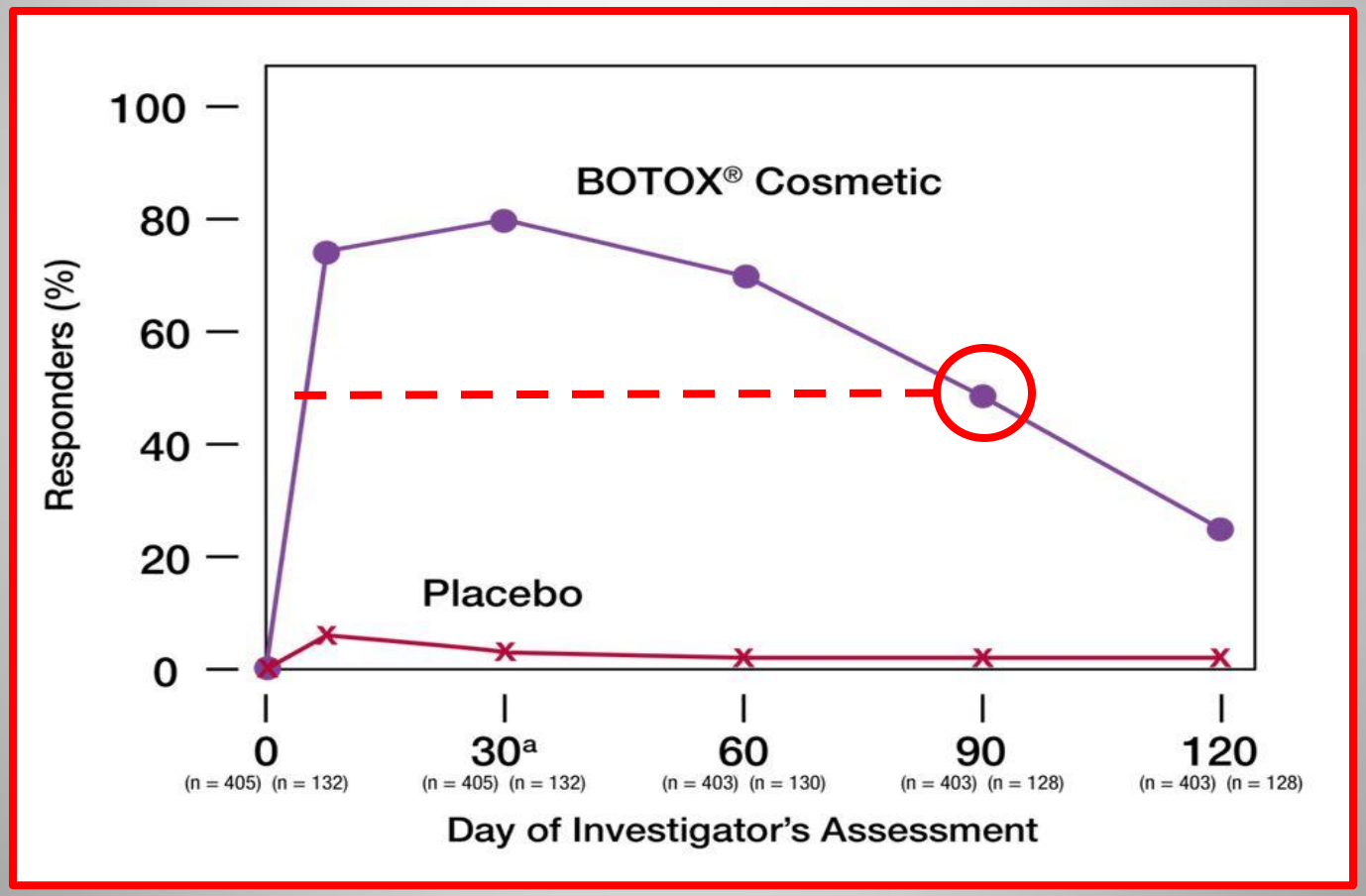
BoTN-A	Dilution	Glabella	Duration
BOTOX	4u/0.1 cc	4 u at 5 sites	3-4 months
DYSPORT	10u/0.08 cc	10 u at 5 sites	3-4 months
XEOMIN	4u/0.1 cc	4 u at 5 sites	3 months

Dilution and dosage may vary as determined by clinician

Adjusting dose to target muscle mass may improve outcome and duration

BOTOX Pivotal Studies

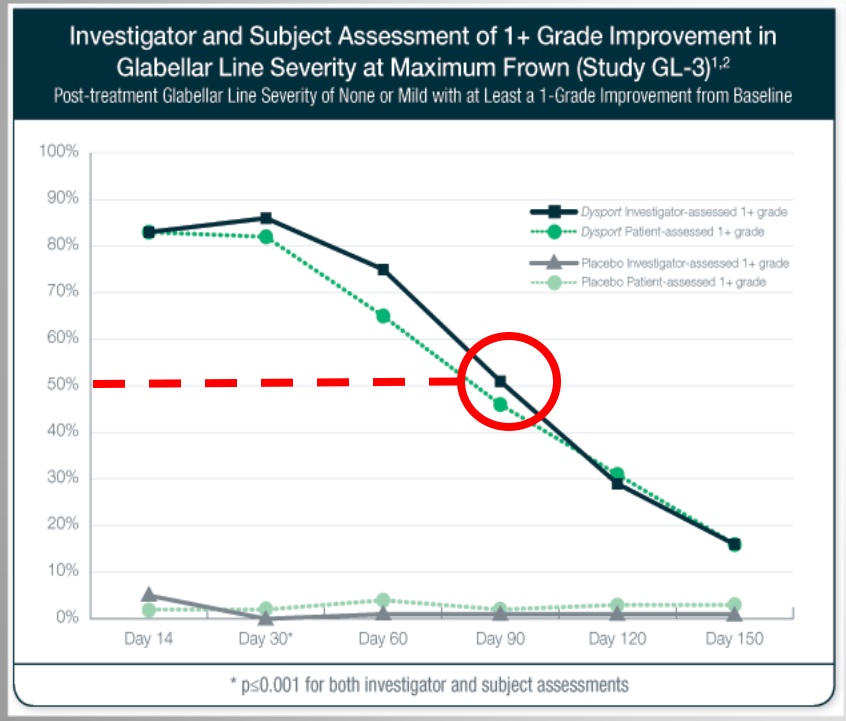
50% of patients maintain improvement at 3 months



DYSPORT Pivotal Studies

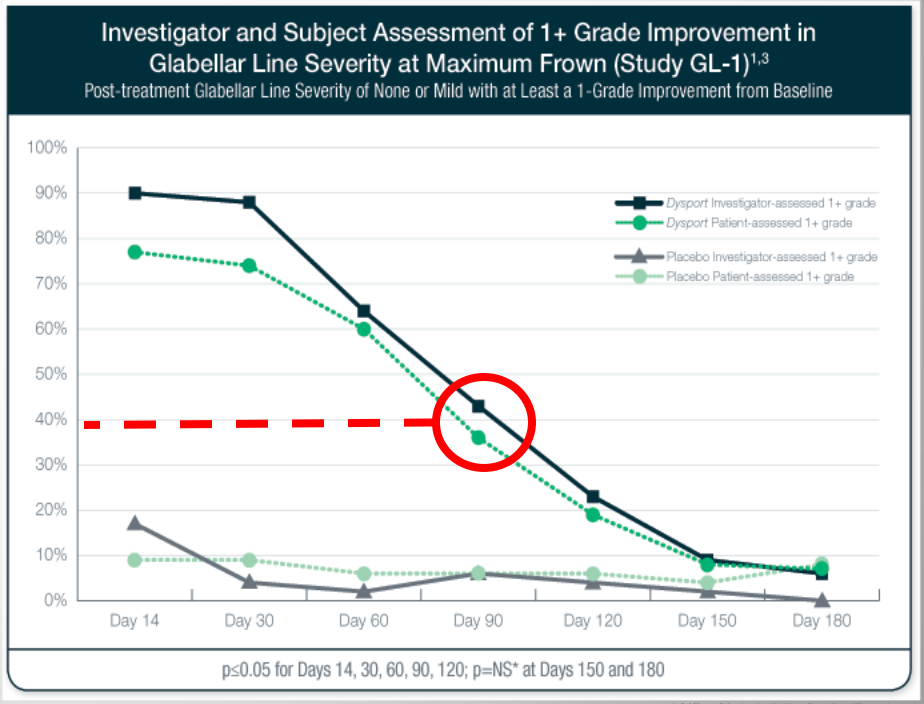
40% - 50% of patients maintain <u>1-Grade</u> improvement at 3 months

Improvement at every time point[2]



GL-3 was a 5-month, single-dose, double-blind, multicenter, randomized, placebo-controlled study (N=300) to assess the safety and efficacy of 50 Units of *Dysport* vs placebo in subjects with moderate to severe glabellar lines at maximum frown.[1] 60% (120/200 *Dysport* patients versus 0% treated with placebo) met the primary endpoint.

Improvement demonstrated for up to 4 months[3]

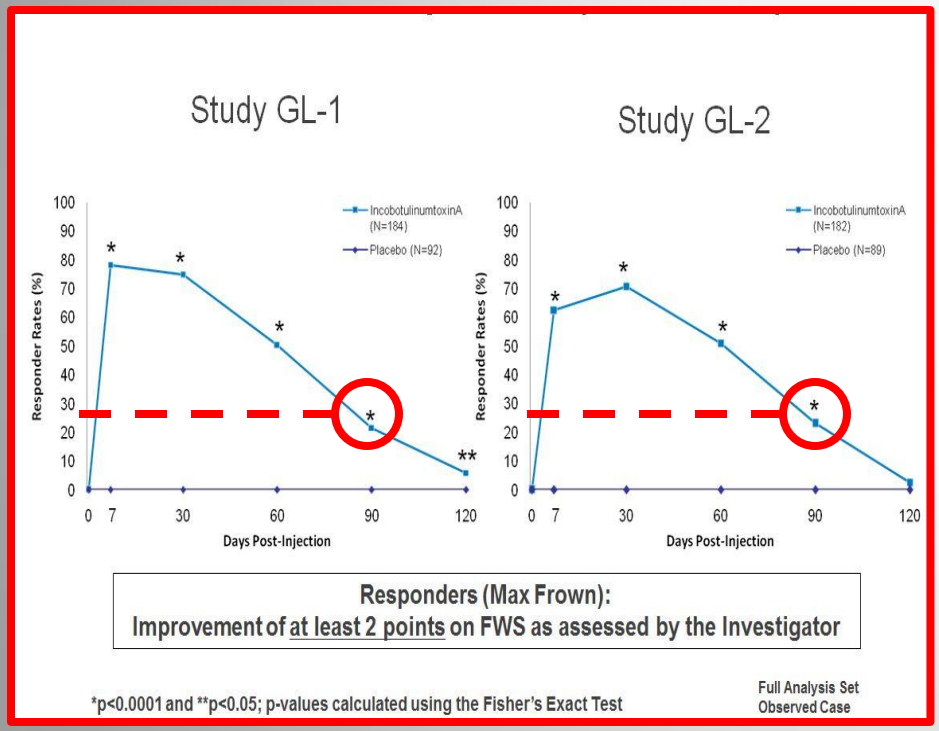


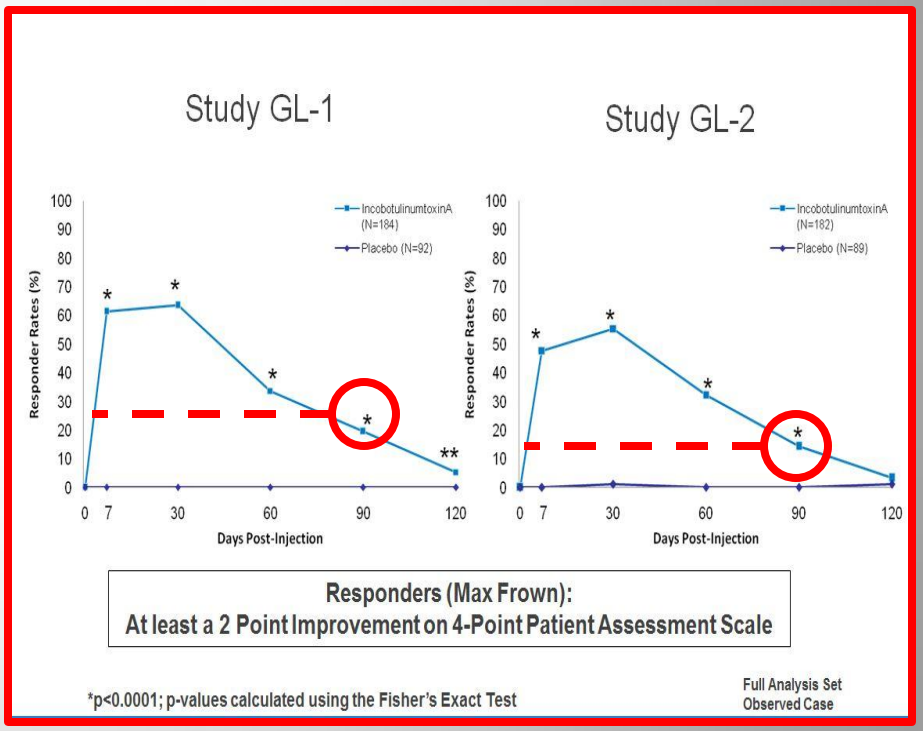
* NS = Not statistically significant

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

XEOMIN Pivotal Studies

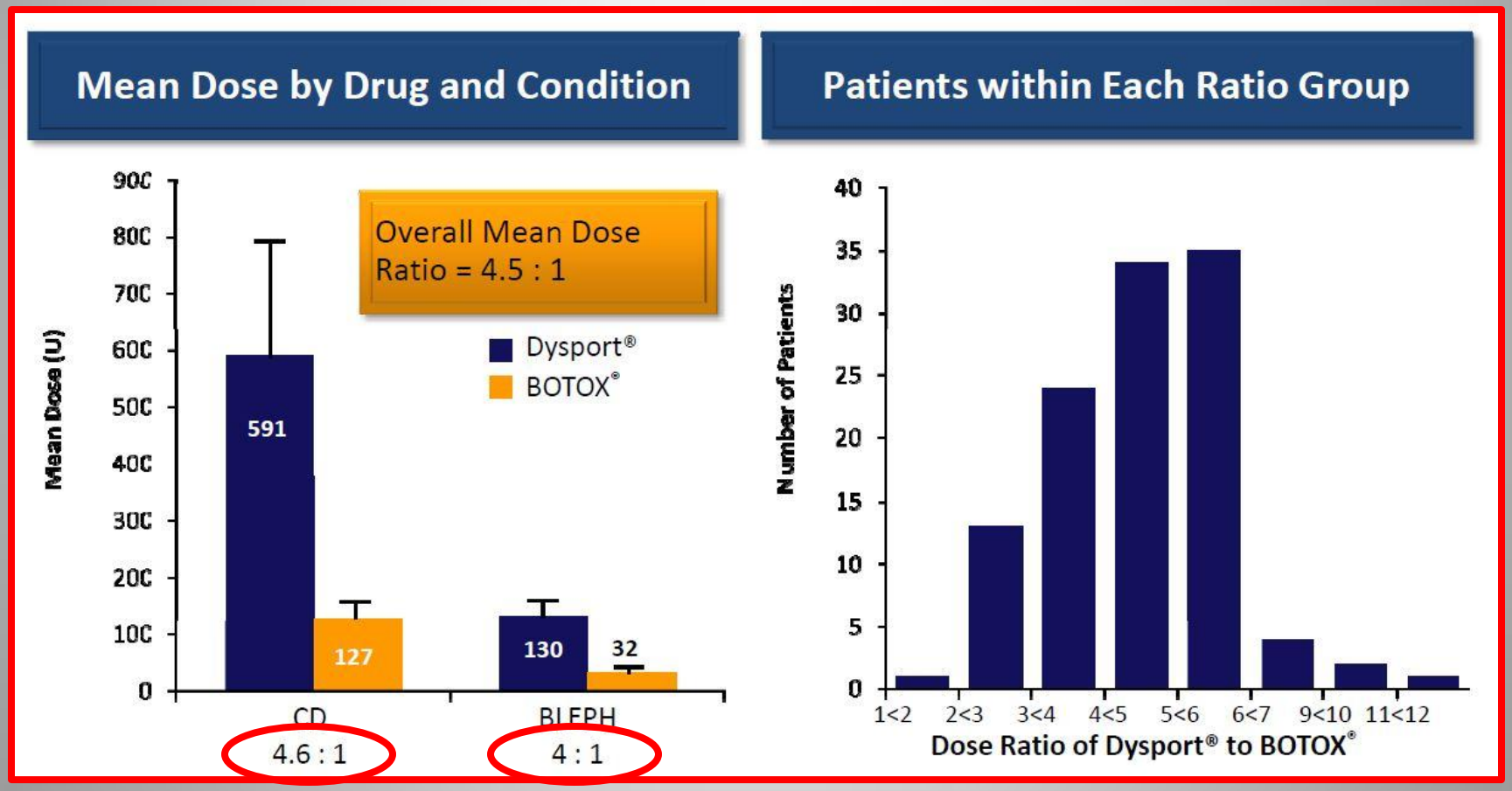
15% - 25% of patients maintain <u>2-Grade</u> improvement at 3 months



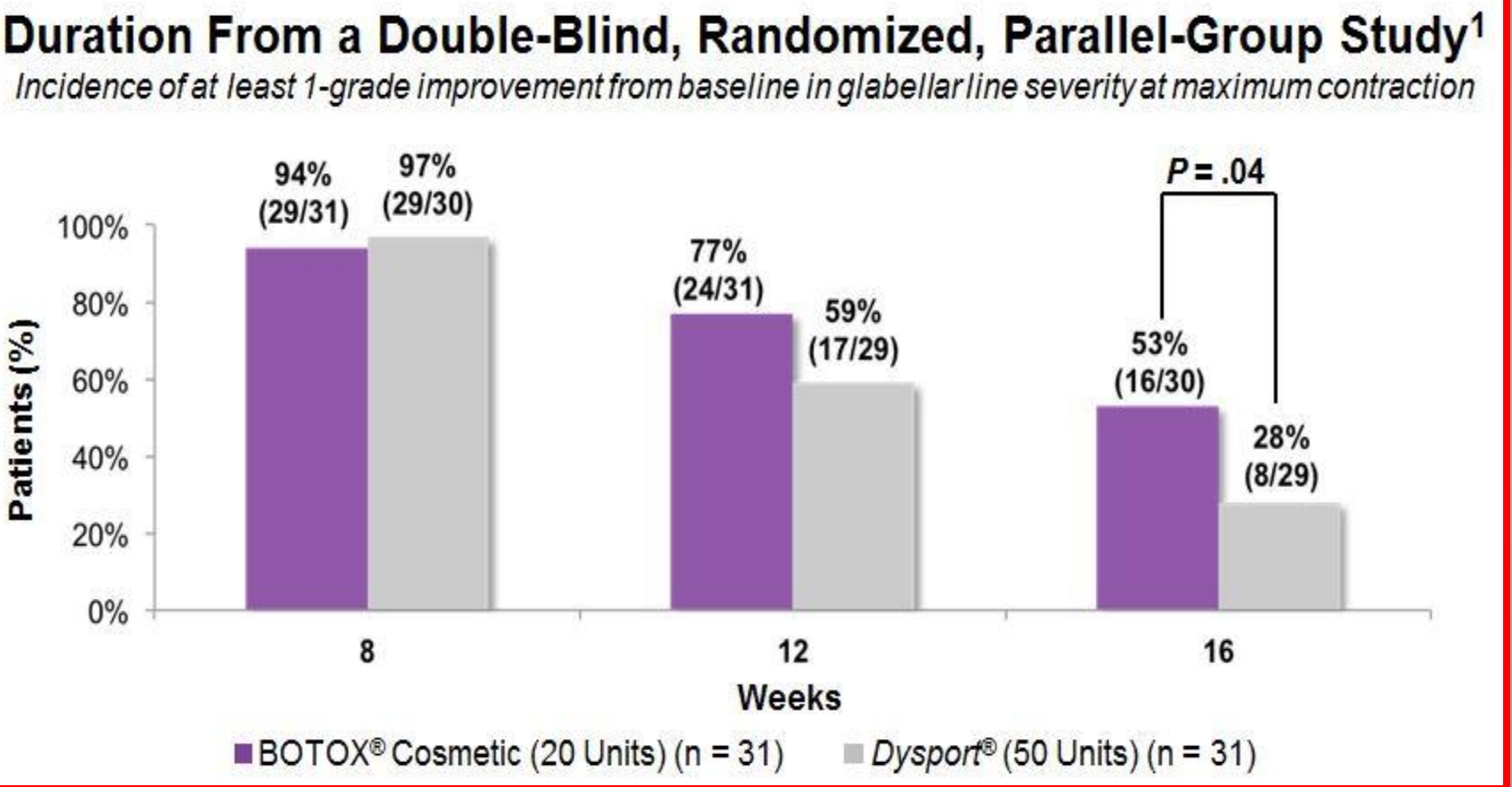


BOTOX vs DYSPORT Dose

For cervical dystonia and blepharospasm



BOTOX vs DYSPORT Duration



Lowe, J Am Acad Dermatol 2006

BOTOX vs XEOMIN Dose

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

JUNE 2012 | 731 | VOLUME 11 • ISSUE 6

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

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

Ravi Jandhyala MSc MBBS MRCS

Banbury Face Clinic, The Jandhyala Institute, Banbury, UK Consultant Pharmaceutical Physician, Medical Director, Latralis

ABSTRACT

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

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

Unique Characteristics

DYSPORT

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

XEOMIN

- Unreconstituted can store at room temperature

BoTN-A Resistance & Accessory Proteins

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

Personal Experience

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

* Depends on dose & rebates

Personal Experience

• Fastest time to onset	DYSPORT (1-3 days)
• Shortest duration	XEOMIN?
• **Cost***	**BOTOX ≥ DYSPORT > XEOMIN**
• Pain	Same (technique?)
• Spread	Same (dilution & technique?)
• **Dose**	**1BOTOX = 1XEOMIN = 2 or 3DYSPORT**

* Depends on dose & rebates

Personal Experience

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

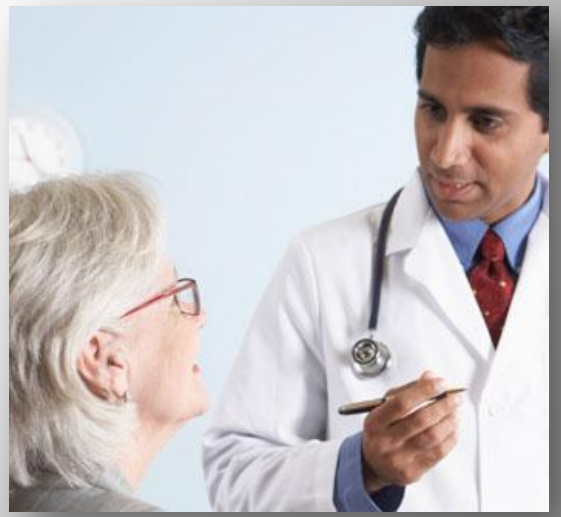
In Your Practice

- Consider your overall BoTN-A usage
  - Other product lines & rewards programs
  - Time to educate patients
  - High volume users may allow for 2 or 3 products
  - Low volume users may have more product waste
- What are patients demanding?
- Patient perceived superiority or inferiority of product
- Consider XEOMIN for touch-ups (cost & duration)
- New products = new marketing opportunities

Applications

Observe Patient During Conversation

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



Patient Education

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

New Patients

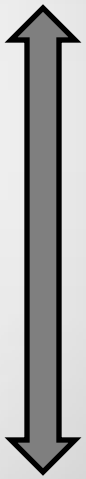
- Informed consent & “off-label” use
- Photo documentation
- Start with lowest doses needed
- Need for 2 week follow up visit

Product Dilutions

Assume vial with 100 units of BOTOX

- 1.0cc = 10u/0.1 cc
- 2.0 cc = 5u/0.1 cc
- 2.5 cc = 4u/0.1 cc
- 4.0 cc = 2.5u/0.1cc

Low injection volume limits diffusion (Glabella)
More product waste



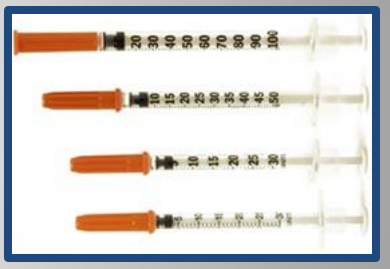
High injection volume increases diffusion (Forehead)
Less product waste

Injection

Assume vial with 100 units of BOTOX

- 1.0cc = 10u/0.1 cc
- 2.0 cc = 5u/0.1 cc
- 2.5 cc = 4u/0.1 cc
- 4.0 cc = 2.5u/0.1cc

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



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

Document the Treatment

Injectable Product Worksheet

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

Allergy & Medical Update: None

Results after Last Injection: Loved it!

Neuromodulator

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

For first time injections

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

Filler or Stimulator

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

Injection

32 G Needle
27 G Microcannula

Anesthetic

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

Treatment outcomes: ____

Complications: None

Place Product Stickers Here

C 32 1578

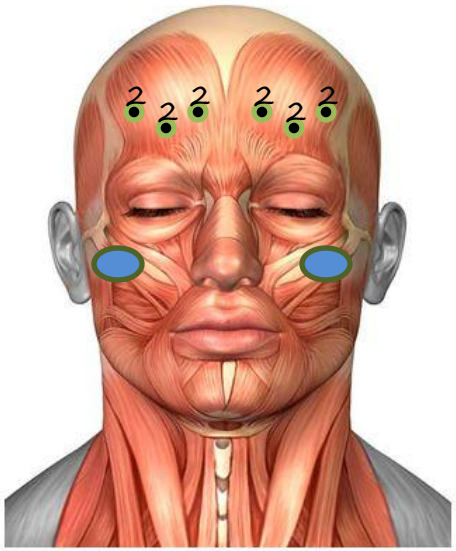
Voluma 13-578

Additional Notes

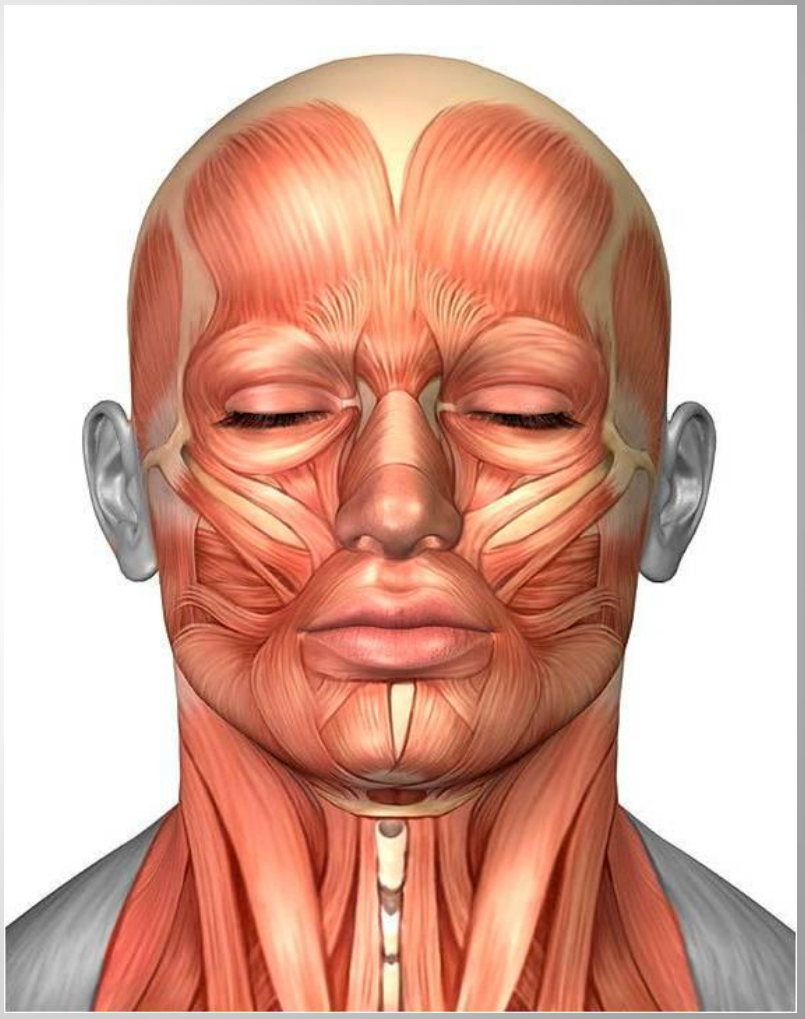
F= 2u x6 = 12u

Malar = 0.5cc per side

May need more in 2 weeks

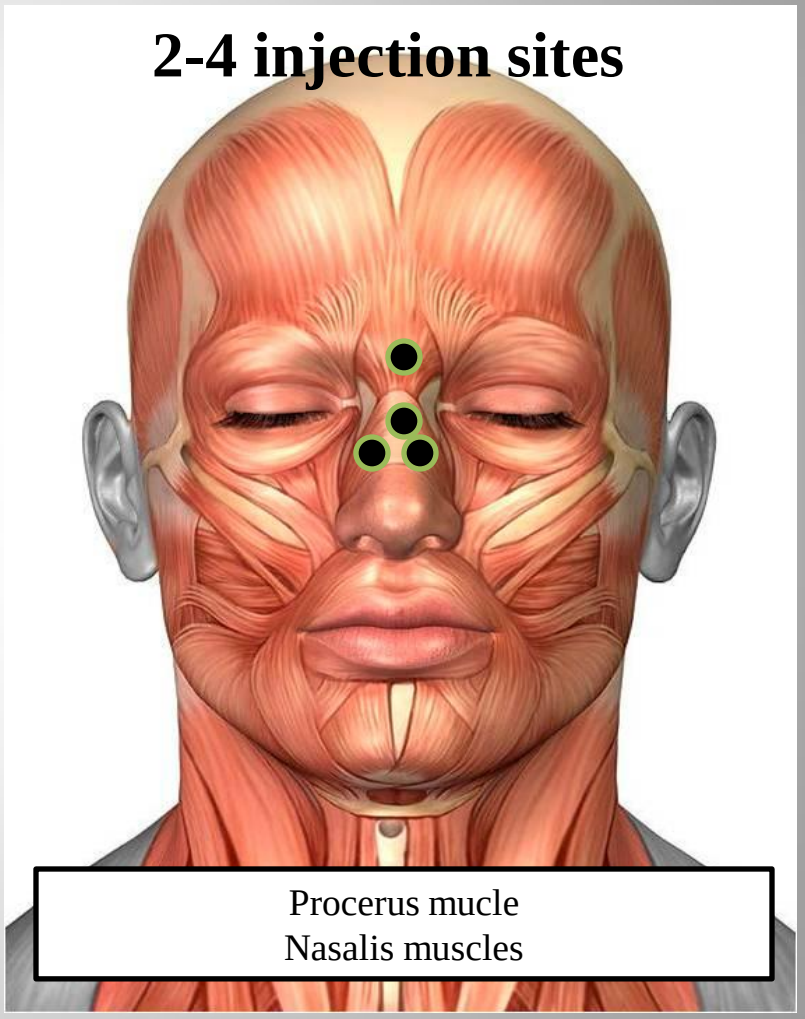


Injection Sites
Assume Botox Units & First Treatment



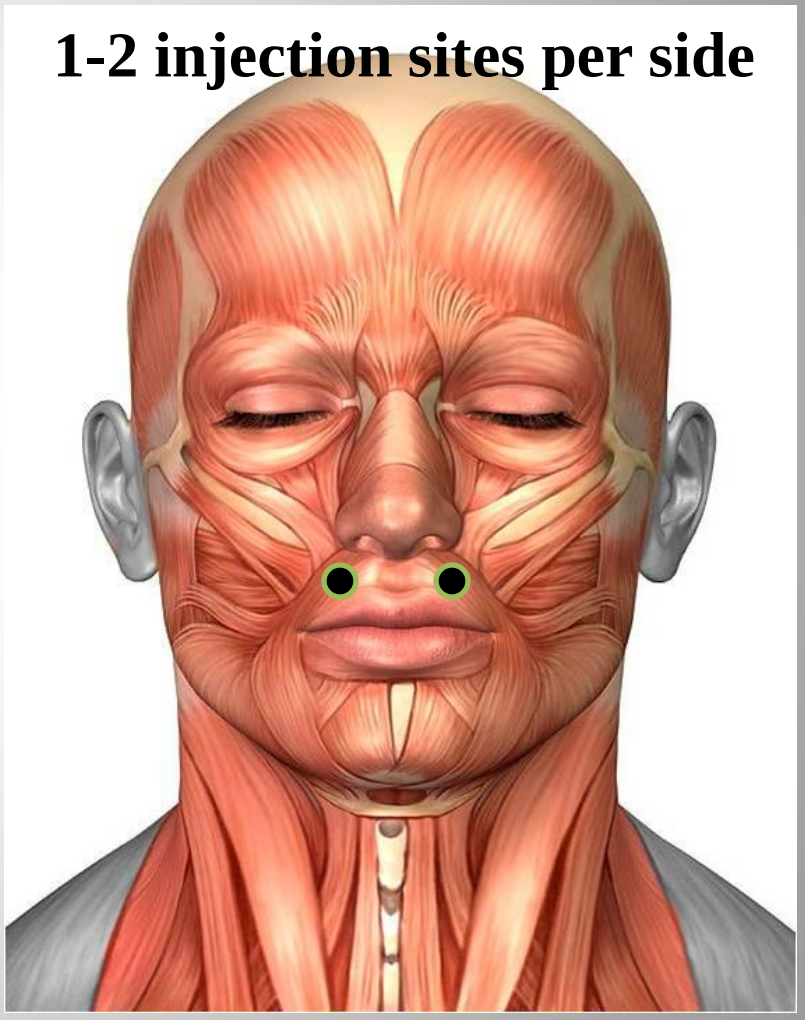
Bunny Lines

2 Units per Injection Site



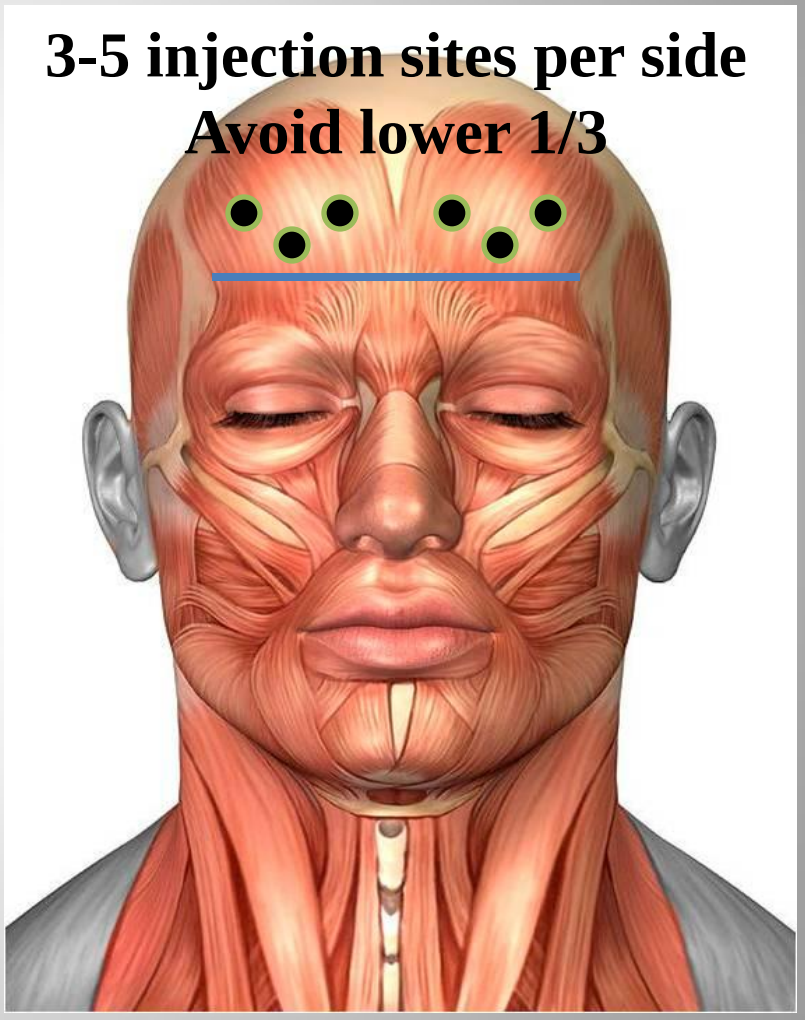
Upper Lip Lines

2 Units per Injection Site



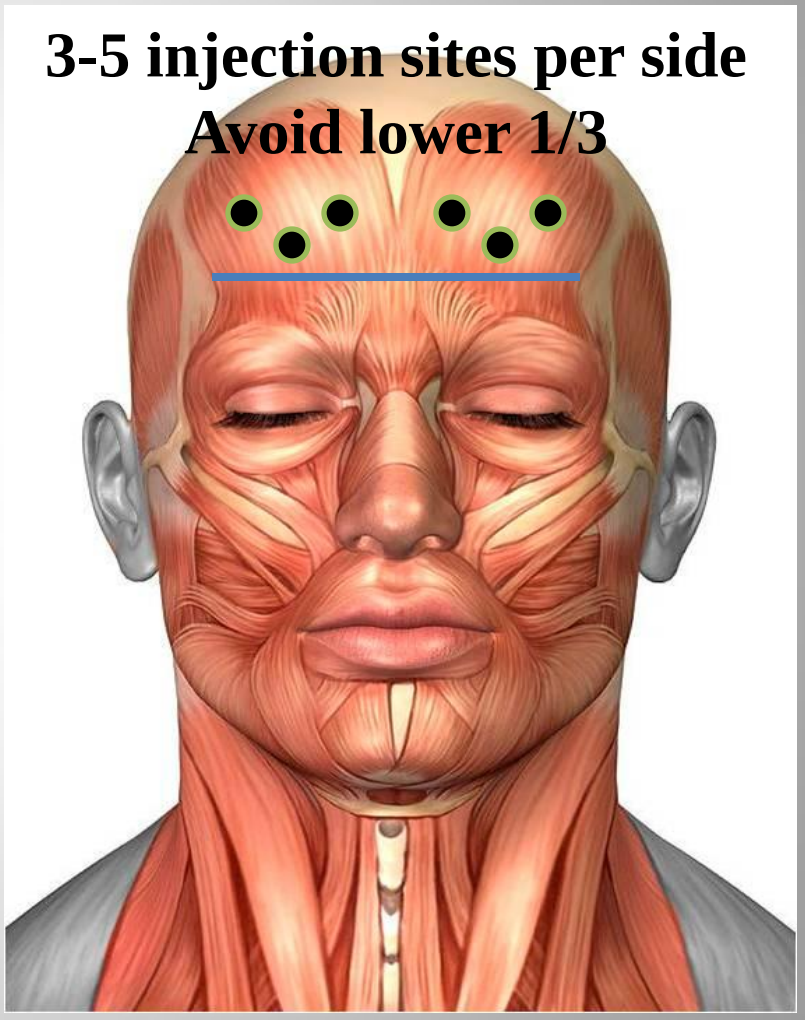
Forehead

2 Units per Injection Site



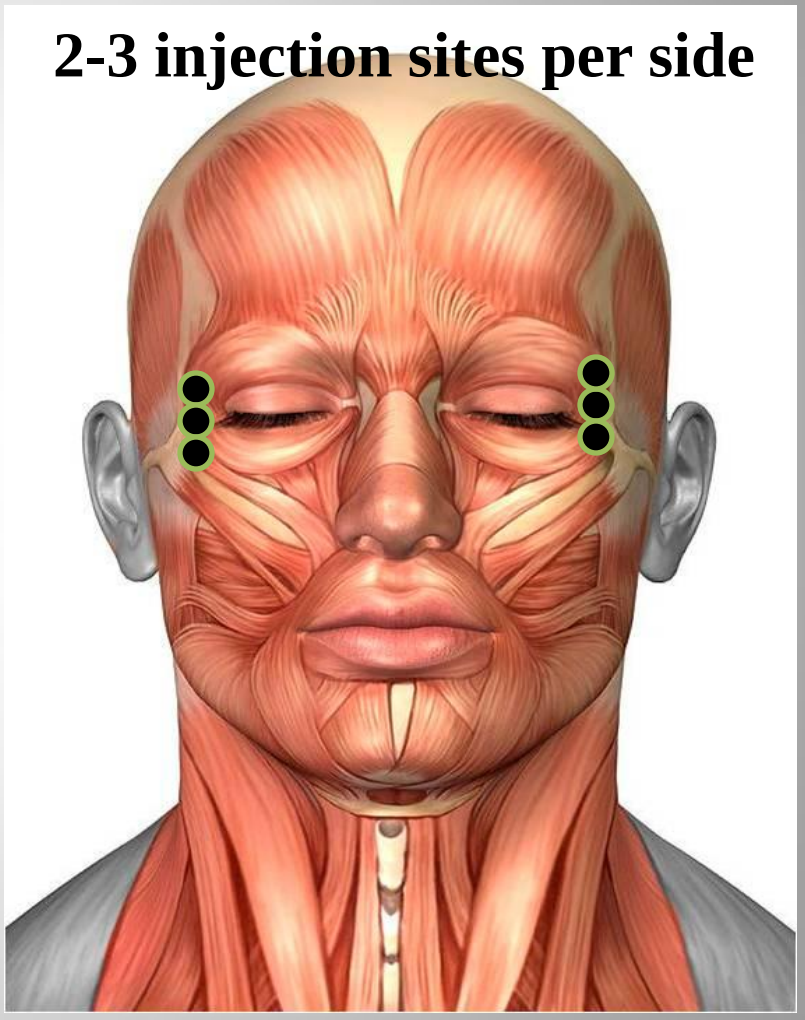
Forehead

2 Units per Injection Site



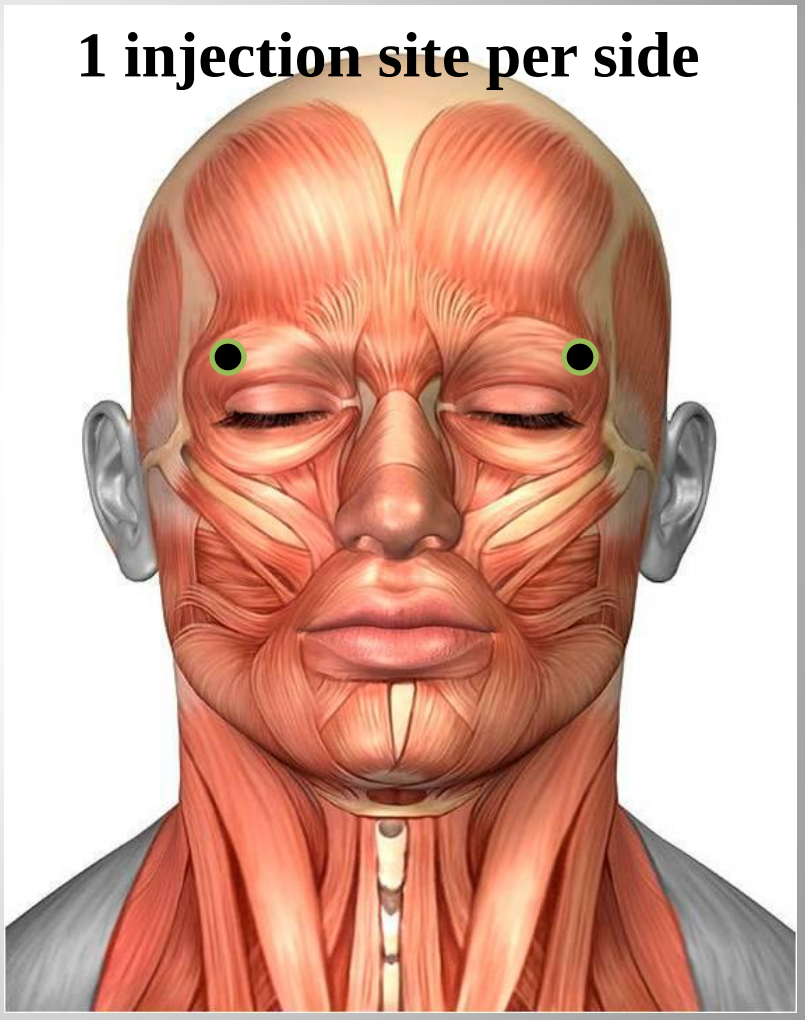
Crow's Feet & Laugh Lines

2 Units per Injection Site



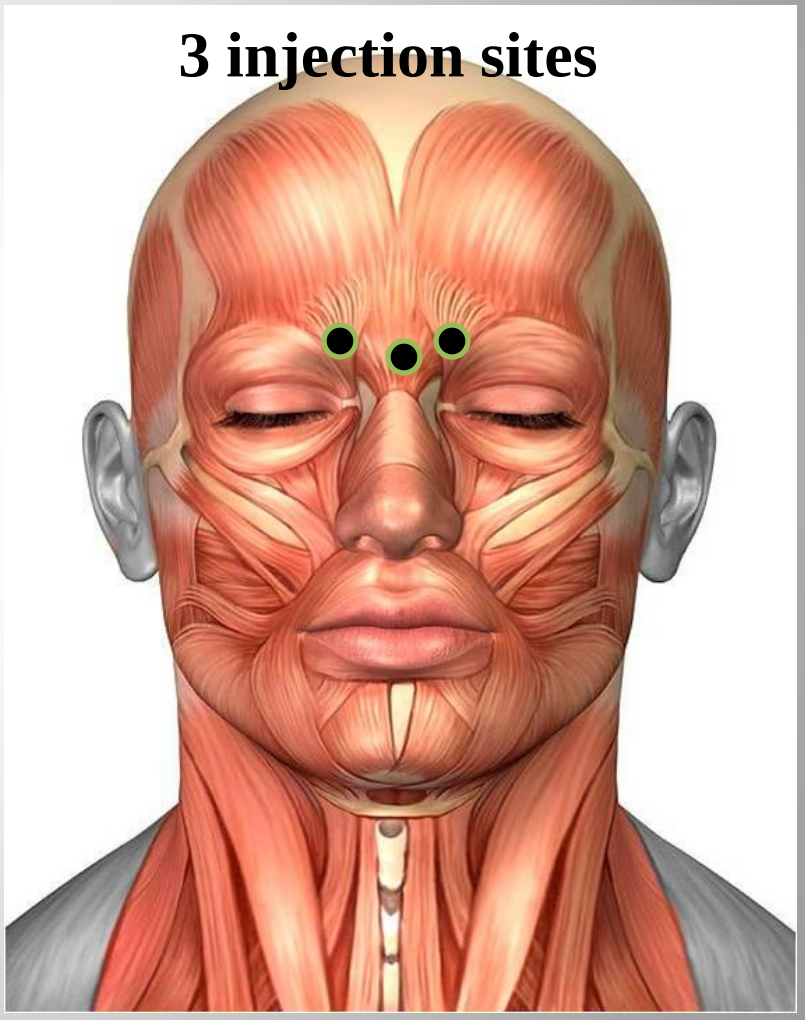
Lateral Brow Lift

2 Units per Injection Site



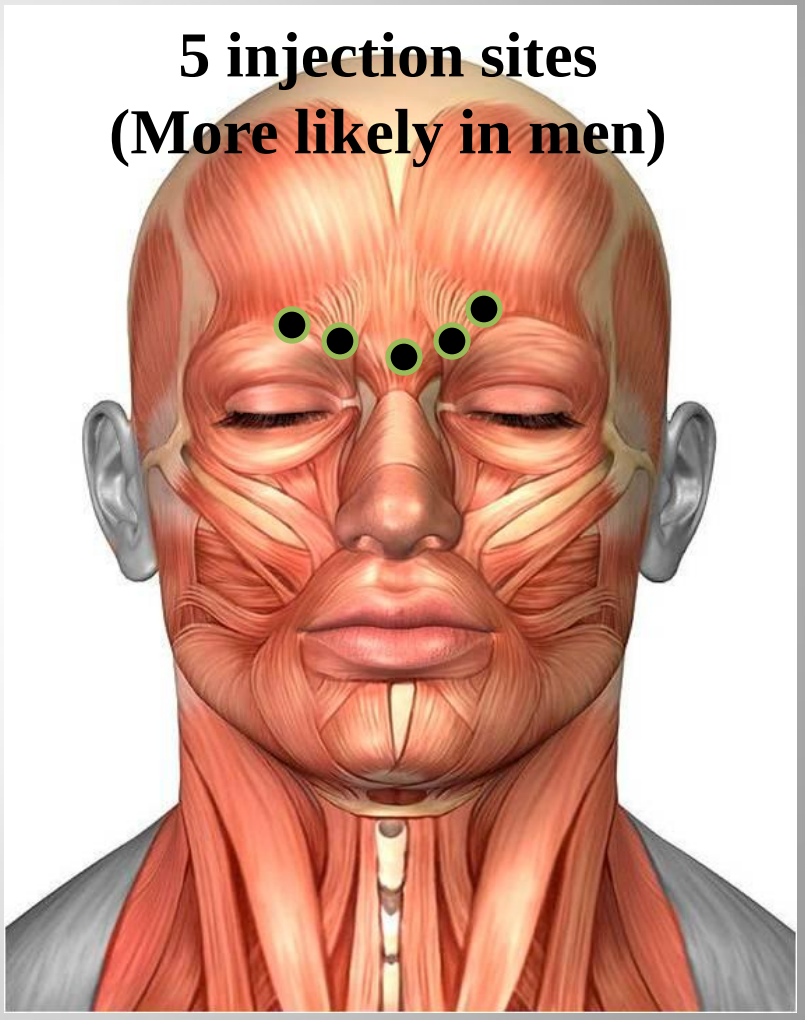
Glabella

4-5 Units per Injection Site



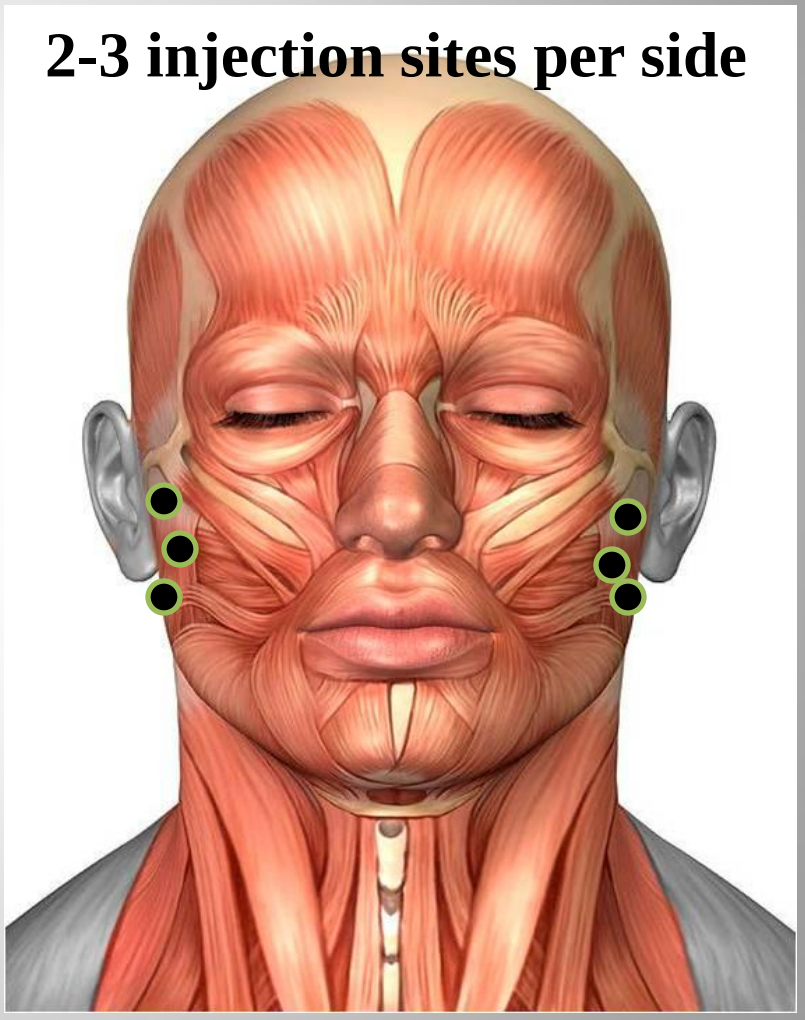
Glabella

4-5 Units per Injection Site



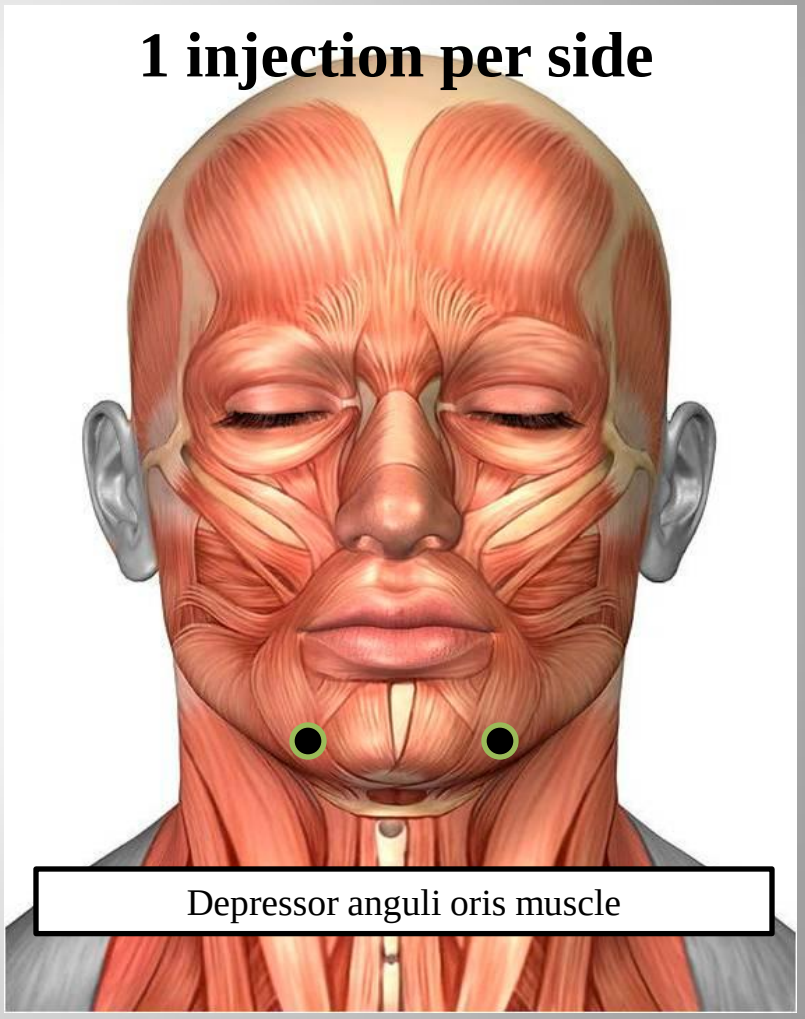
Masseter Hypertrophy

5-10 Units per Injection Site



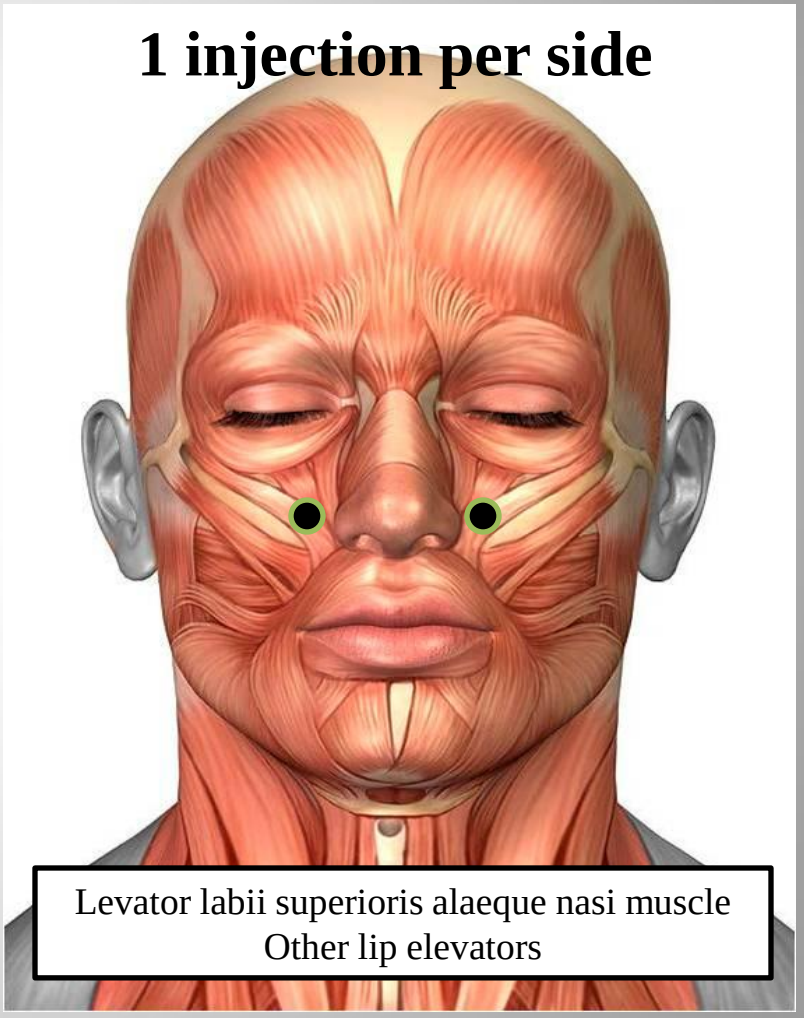
Lip Corner Elevation

3 to 5 Units per Injection Site



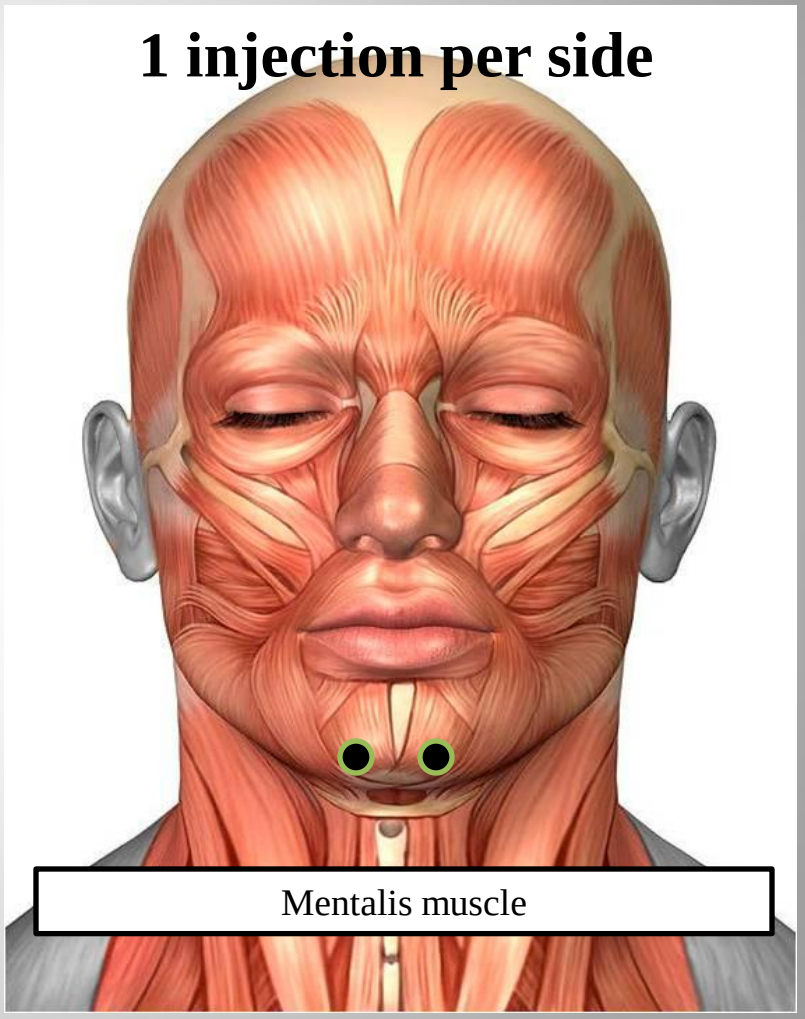
Gummy Smile

4-5 Units per Injection Site



Chin Dimples

4-5 Units per Injection Site



Platysmal Bands

4 Units per Injection Site

Eyelid Ptosis Reversal

- Alpha-adrenergic agonist ophthalmic eye drops
  - Apraclonidine 0.5% (Iopidine)
  - Naphazoline (Naphcon)
  - Phenylephrine 2.5% (Myfrin)
- Stimulate Mueller's muscle → elevate ptotic eyelid
  - Typical 2 mm of lid elevation

Botulinum Neuromodulators: Clinical Data & Applications

Karol A Gutowski, MD, FACS

ENDLESS POSSIBILITIES.
CHICAGO
OCTOBER 10-14 2014
AMERICAN SOCIETY OF PLASTIC SURGEONS
THE PLASTIC SURGERY FOUNDATION
ASMS
plastic surgery
THE MEETING