Botulinum Toxin Injection Patterns, Complications, and Adjunctive Therapies

Alison Watson, MD
Philly Eye Plastics
Wills Eye Hospital, Oculoplastics and Orbital Surgery Service
Thomas Jefferson University Hospital, Ophthalmology Service

Overview

- Background
- Mechanism of Action
- Types of Botulinum Toxin
- Treatment
  - Pre-treatment
  - Pattern
  - Safety
- Causes of decreased efficacy
- Adjunctive Therapy

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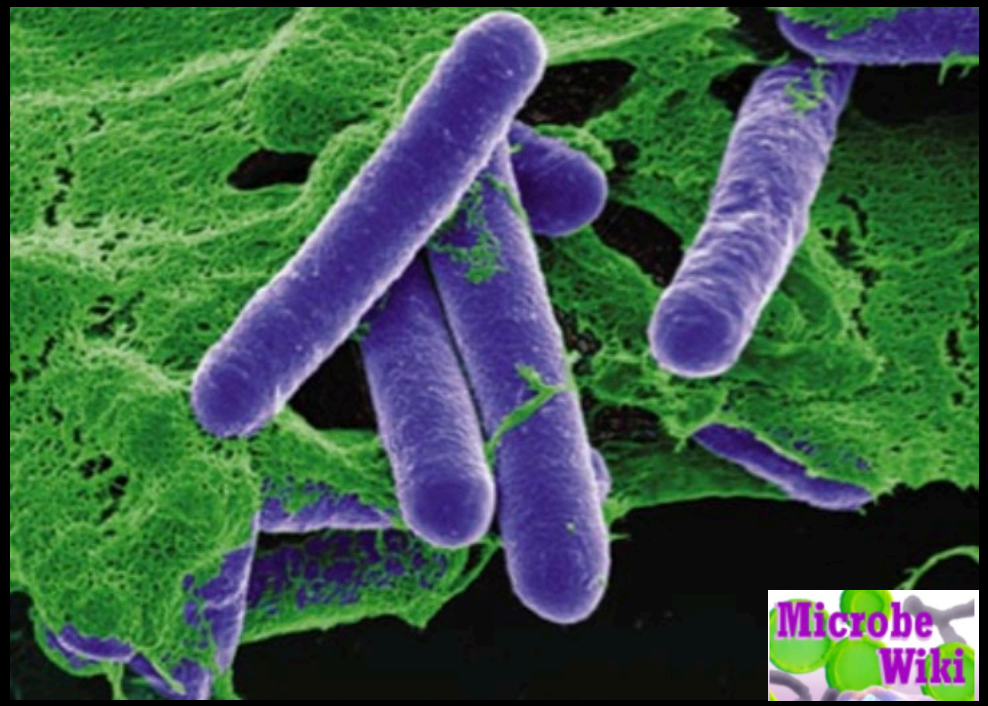
What is Botulinum Toxin?

- Clostridium botulinum is a type of bacteria which produces ubiquitous spores which release toxins that can impact the nervous system.
- In the early 1980s the first ophthalmic application of botulinum toxin was employed to treat eye movement issues.
- Late 1980s the purified toxin was approved by the FDA for the treatment of blepharospasm



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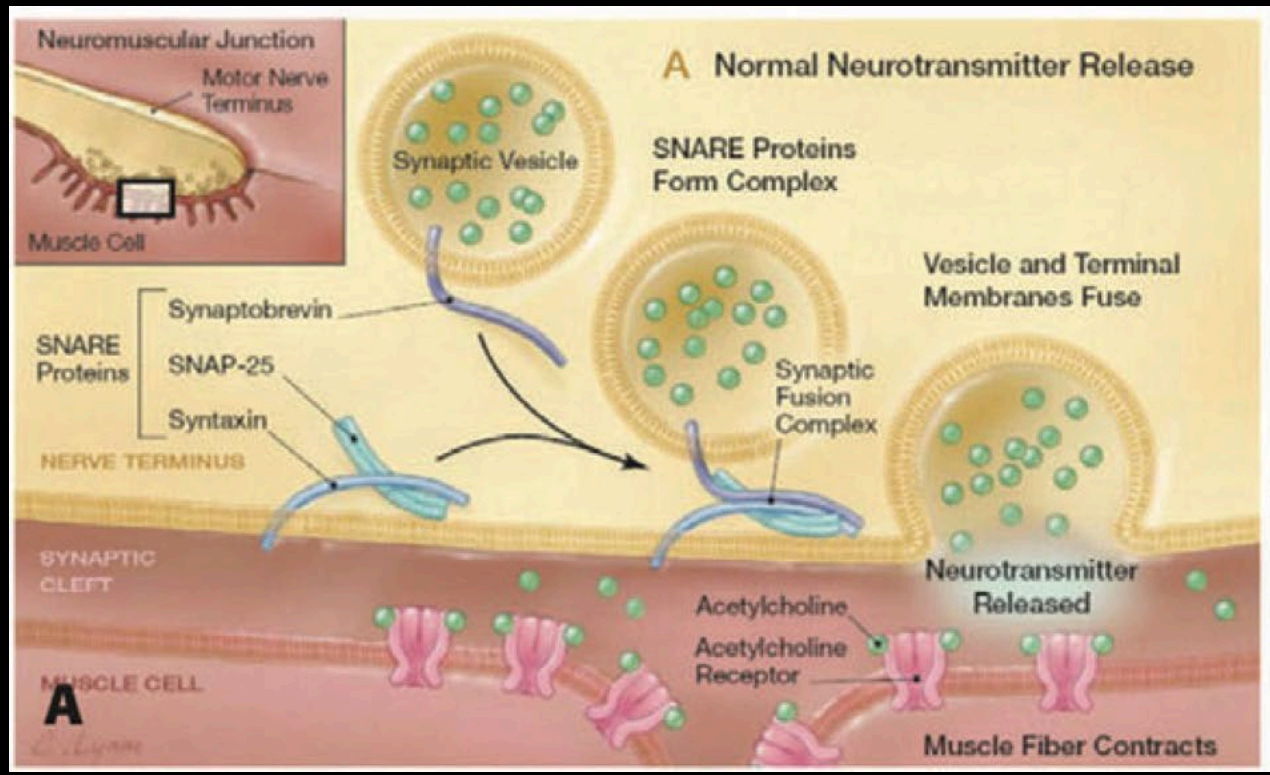
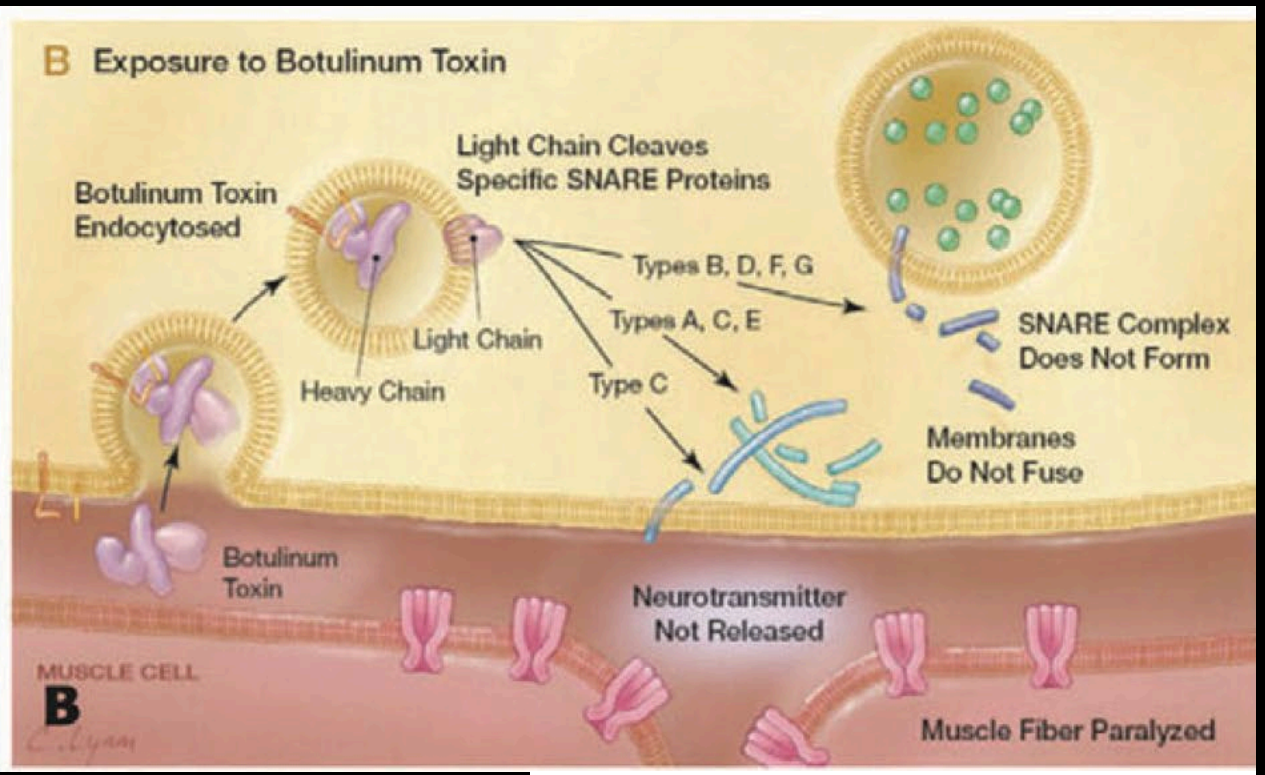
Mechanism of Action





Lorenc et al

Aesthetic Surgery Journal 33(1S)

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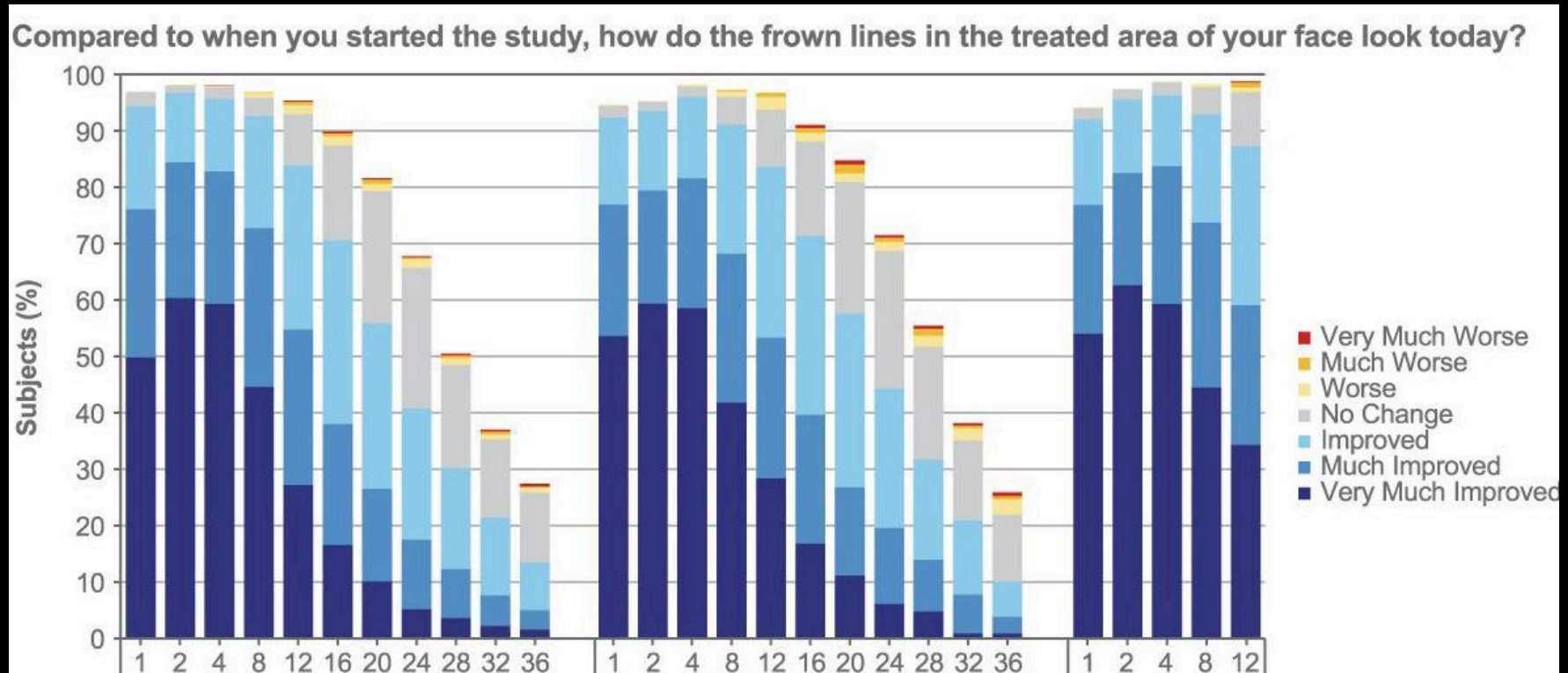
Types of Botulinum Toxin

	OnabotulinumtoxinA	AbobotulinumtoxinA	IncobotulinumtoxinA	RimabotulinumtoxinB
US Tradename	Botox®	Dysport®	Xeomin®	Myobloc®
Company	Allergan, Inc.	Ipsen Inc./Medicis	Merz Pharmaceuticals	Solstice Neurosciences Inc./Eisai Co., Ltd.
Active substance	BoNT-A complex	BoNT-A complex	BoNT-A free from complexing proteins	BoNT-B complex
Molecular weight	900 kDa	500–900 kDa	150 kDa	700 kDa
Target protein	SNAP-25	SNAP-25	SNAP-25	VAMP
Units per vial	50 or 100	300 or 500	100	2500, 5000, or 10000
Pharmaceutical form	Powder	Powder	Powder	Solution
US FDA-approved indications	Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis, chronic migraine	Blepharospasm, cervical dystonia, glabellar lines	Blepharospasm, cervical dystonia, glabellar lines	Cervical dystonia
Storage temperature before and after reconstitution	2–8°C/2–8°C	2–8°C/2–8°C	<25°C/2–8°C	2–8°C/2–8°C

DaxibotulinumtoxinA for Injection for the Treatment of Glabellar Lines: Efficacy Results From SAKURA 3, a Large, Open-Label, Phase 3 Safety Study

Sabrina G. Fabi, MD,* Joel L. Cohen, MD,† Lawrence J. Green, MD,‡ Sunil Dhawan, MD,§ Theda C. Kontis, MD,‖ Leslie Baumann, MD,¶ Todd M. Gross, PHD,** Conor J. Gallagher, PHD,** Jessica Brown, PharmD,** and Roman G. Rubio, MD**



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Pre-treatment & Preparation

Impact on treatment

Efficacy of Botulinum Toxin Type A After Topical Anesthesia

Mirwat S. Sami, M.D.*, Charles N. S. Soparkar, M.D., Ph.D*, James R. Patrinely, M.D.*, Lisa M. Hollier, M.D, M.P.H.†, and Larry H. Hollier M.D.‡

Plastic Eye Surgery Associates, PLLC, Houston, Texas, U.S.A.; †University of Texas, Houston, Texas, U.S.A.; and ‡Baylor College of Medicine, Houston, Texas, U.S.A.

TABLE 2. *Patient-reported outcomes of botulinum toxin type A injection efficacy with topical anesthetic versus placebo cream*

	Anesthetic-treated side	Placebo-treated side	p value
Blepharospasm patients identifying a better effect from botulinum toxin type A on one side of the face (n = 48 trials)	6 (12.5%)	42 (87.5%)	<0.001
Cosmetic patients identifying a better effect from botulinum toxin type A on one side of the face (n = 46 trials)	4 (9%)	42 (91%)	<0.001

Ophthal Plast Reconstr Surg, Vol. 22, No. 6, 2006

Impact on treatment

Ophthalmic Plastic and Reconstructive Surgery
Vol. 24, No. 1, pp 10–12

Botox: Shaken, Not Stirred

Nadia A. Kazim, M.D., and Evan H. Black, M.D.

Department of Ophthalmology, Kresge Eye Institute, Wayne State University School of Medicine, Detroit, Michigan, U.S.A.

Purpose: To determine whether the effect of botulinum toxin type A is maintained and has the same duration when it is reconstituted vigorously.

Methods: A prospective, double-blinded, randomized study was performed on 7 consecutive patients who underwent botulinum toxin type A injections to the forehead by one oculoplastic surgeon. Half of each patient's forehead was injected with botulinum toxin type A that had been gently reconstituted according to the package insert and the other half of the forehead was injected with botulinum toxin type A that had been reconstituted vigorously. Eyebrow excursion was measured in millimeters before injection, 1 week after injection, and every month after injection up to a total of 6 months.

Results: Seven consecutive patients with an average age of 39.9 ± 2.8 years were evaluated. There was no statistically significant difference in eyebrow excursion between the side of the forehead that had been injected with gently reconstituted botulinum toxin type A and the side that had been injected with vigorously reconstituted botulinum toxin type A at every visit.

Conclusion: The effect of botulinum toxin type A is maintained and has the same duration when it is reconstituted vigorously compared with when it is reconstituted gently.

Pre-treatment & Preparation

Investigating the Efficacy of Vibration Anesthesia to Reduce Pain From Cosmetic Botulinum Toxin Injections

Aesthetic Surgery Journal
31(8) 966–971

DOI: 10.1177/1090820X11422809
www.aestheticsurgeryjournal.com
SAGE

Pooja Sharma, MD; Craig N. Czyz, DO, FACOS; and Allan E. Wulc, MD, FACS

Table 1. Patient-Reported Injection Pain With and Without Vibration Anesthesia

	With Vibration, No. (%)	Without Vibration, No. (%)
No pain	2 (4%)	0 (0%)
Mild pain	35 (70%)	6 (12%)
Moderate pain	11 (22%)	22 (44%)
Severe pain	2 (4%)	17 (35%)
Worst pain ever	0 (0%)	5 (10%)

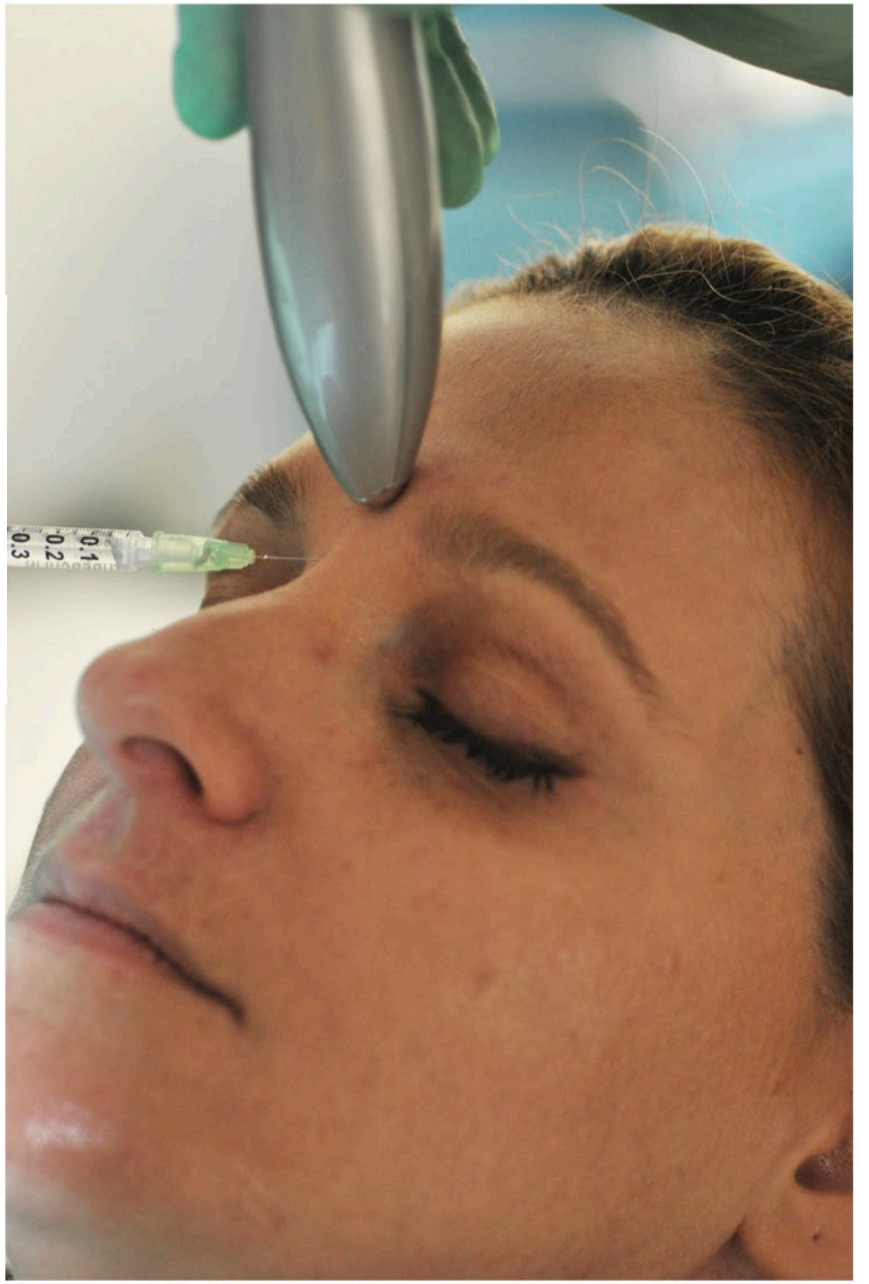

Figure 2. During treatment, the vibrating device was positioned on the patient's skin, approximately 1 to 2 cm from the injection site.

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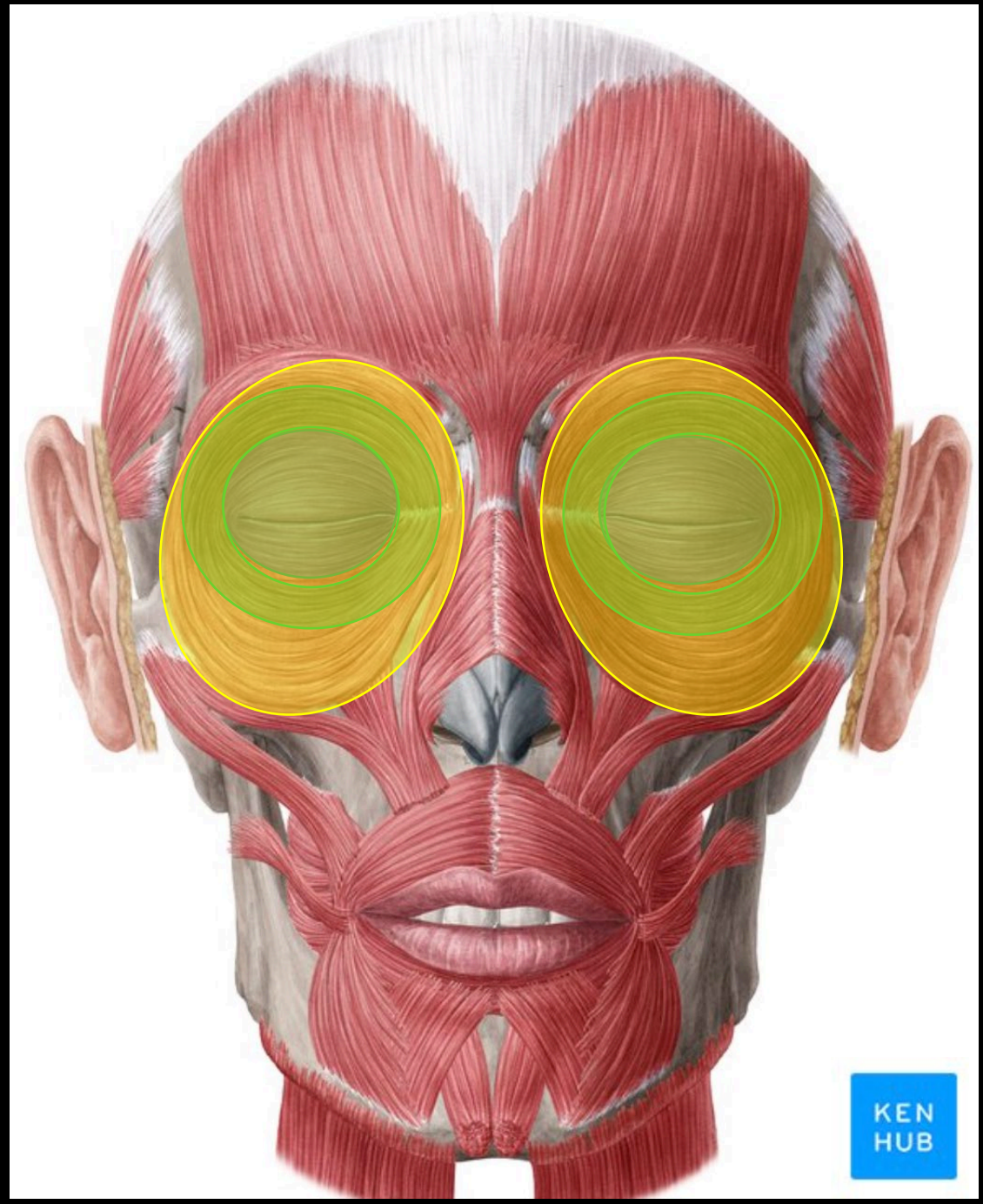
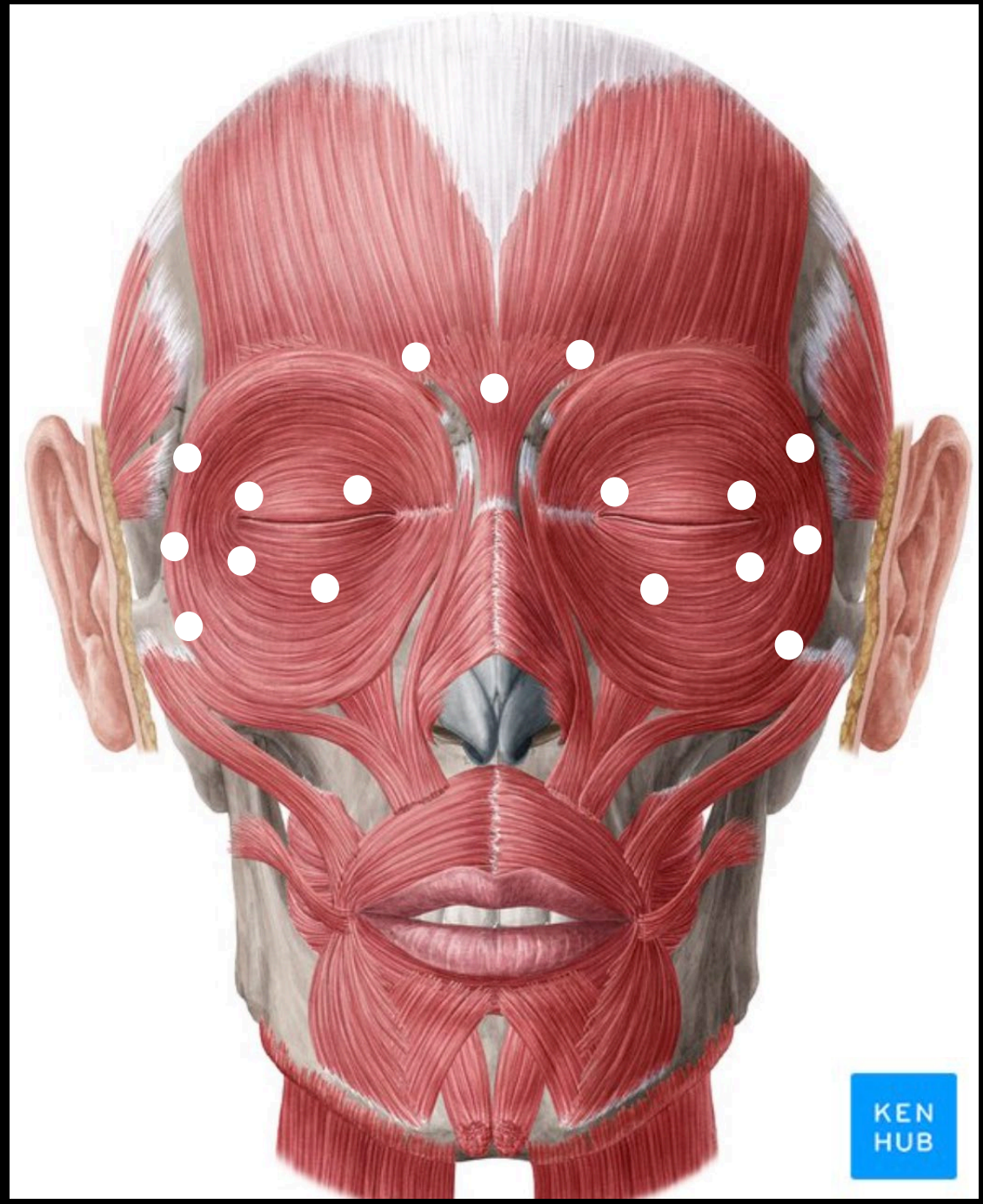
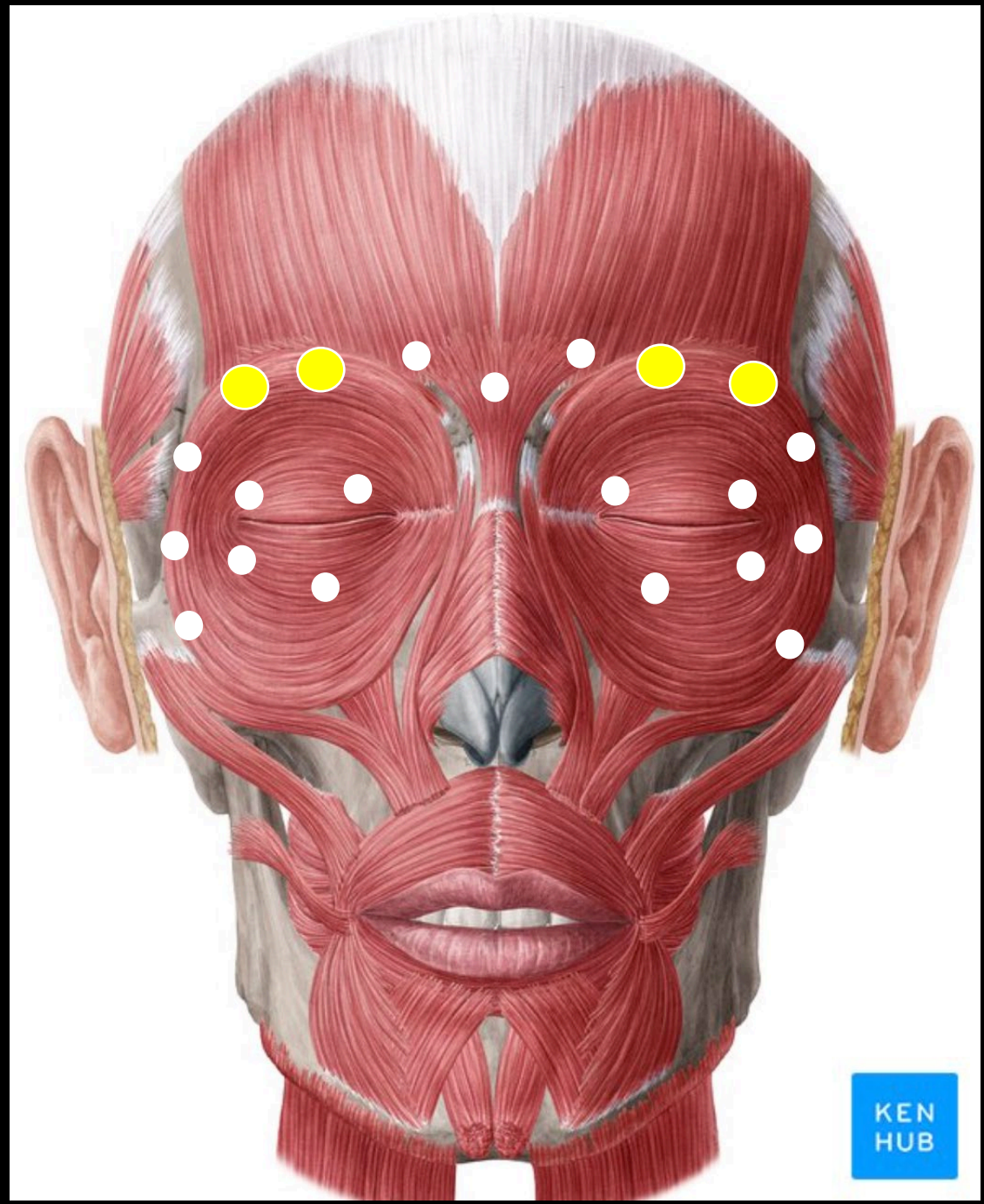
Treatment



Treatment

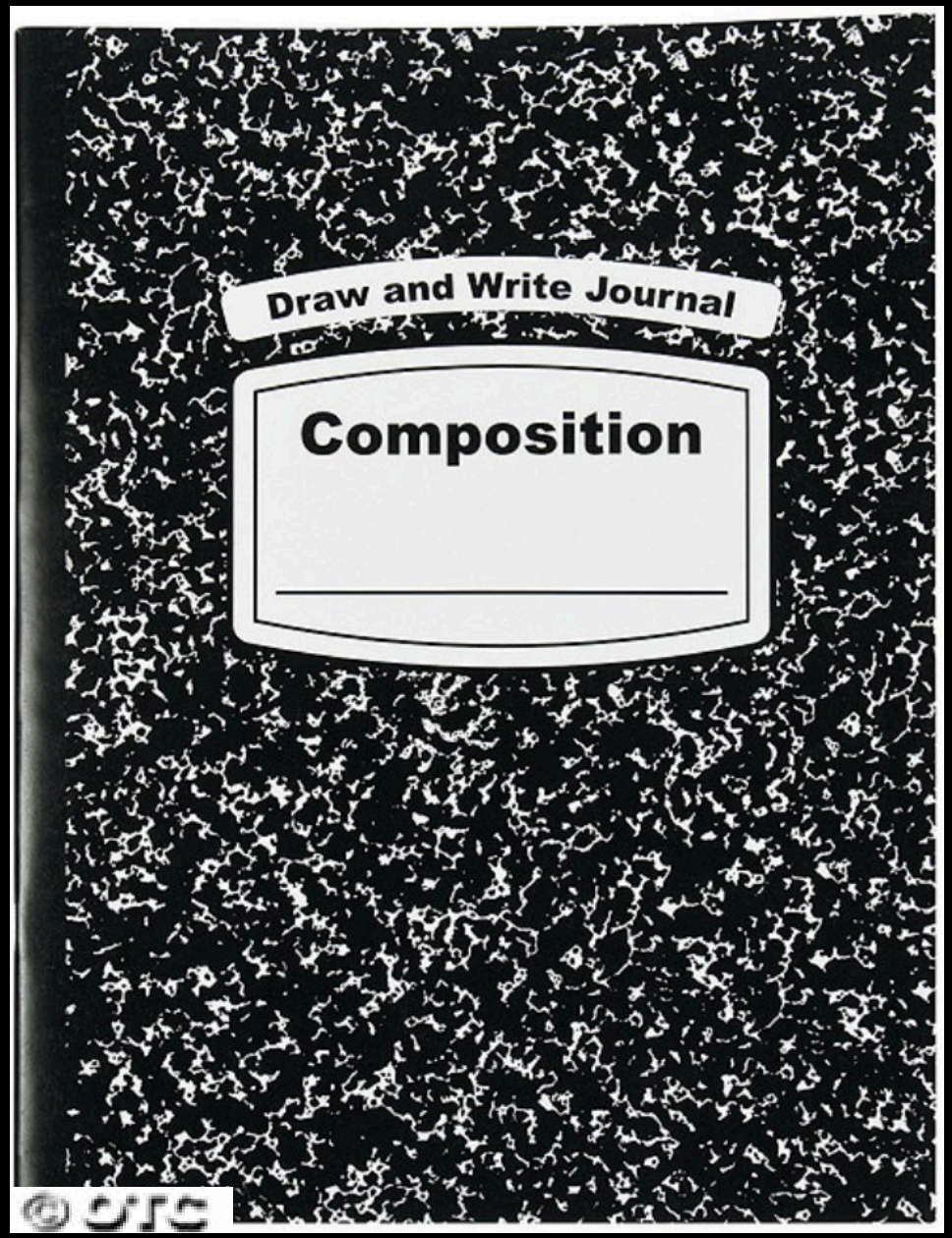


Treatment



Treatment

- Seeing a new provider? Previous Maps?
- Treatment onset?
- Duration of treatment efficacy?
- Which areas responded well to treatment?
- Any regions that did not respond well?
- Adverse effects?



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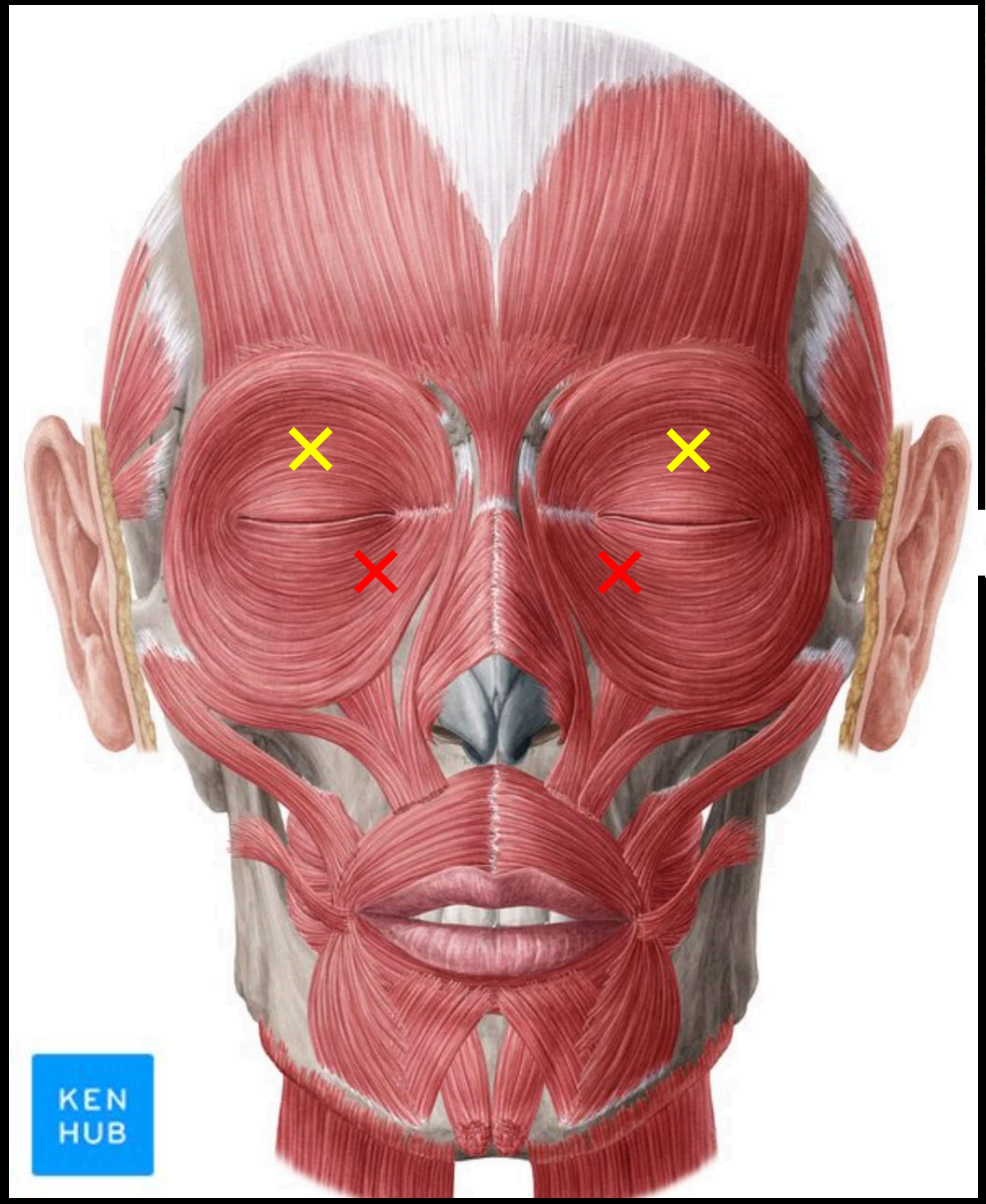
Safety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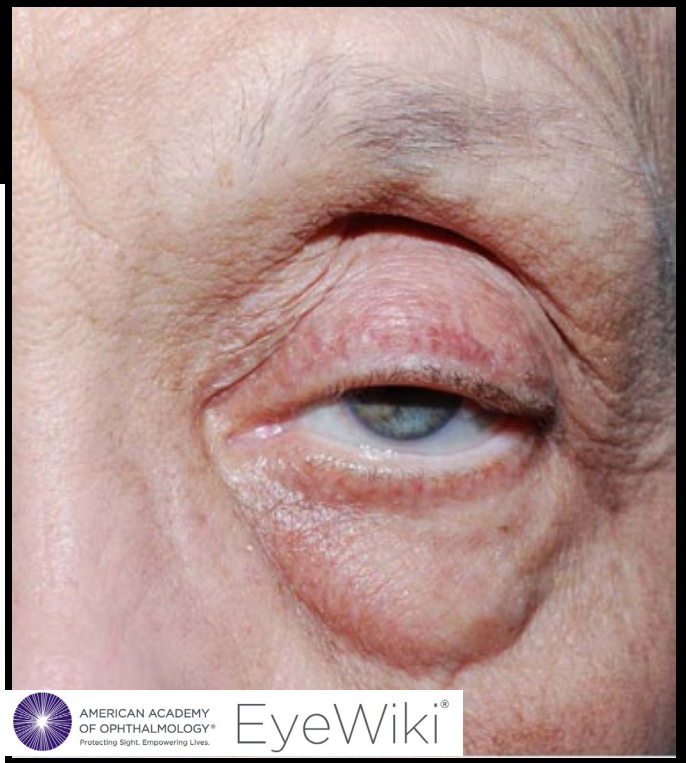
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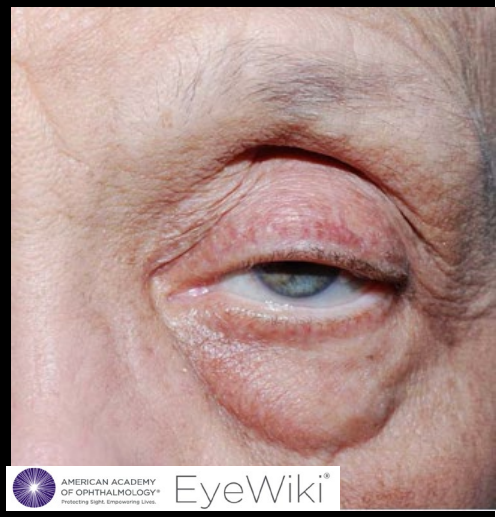
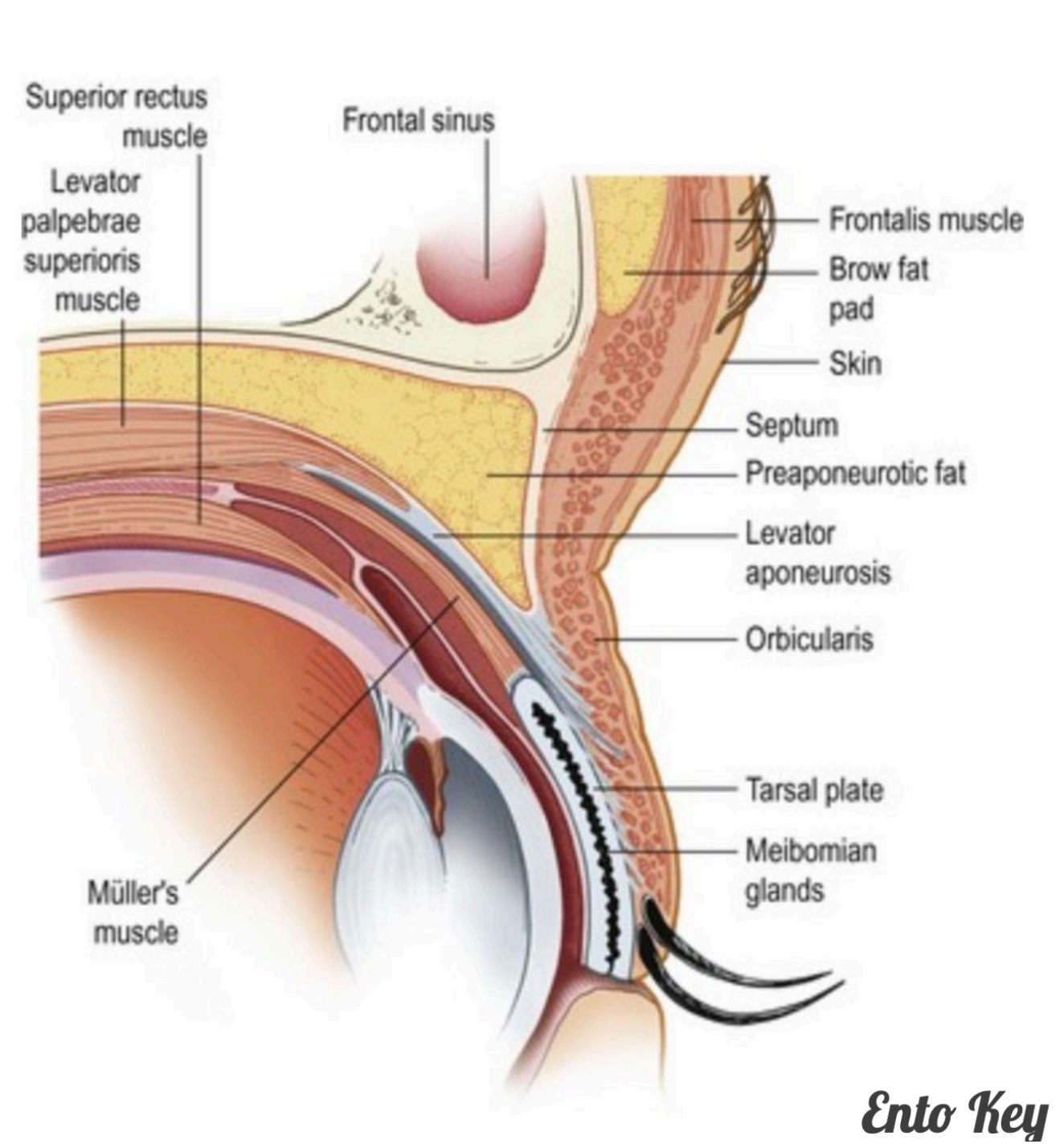

AMERICAN ACADEMY OF OPHTHALMOLOGY
EyeWiki


Superior rectus muscle
Levator palpebrae superioris muscle
Frontal sinus
Frontalis muscle
Brow fat pad
Skin
Septum
Preaponeurotic fat
Levator aponeurosis
Orbicularis
Tarsal plate
Meibomian glands
Müller's muscle
Ento Key

Safety


NDC 61314-143-05
Brimonidine Tartrate Ophthalmic Solution
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℞ only
5 mL
SANDOZ


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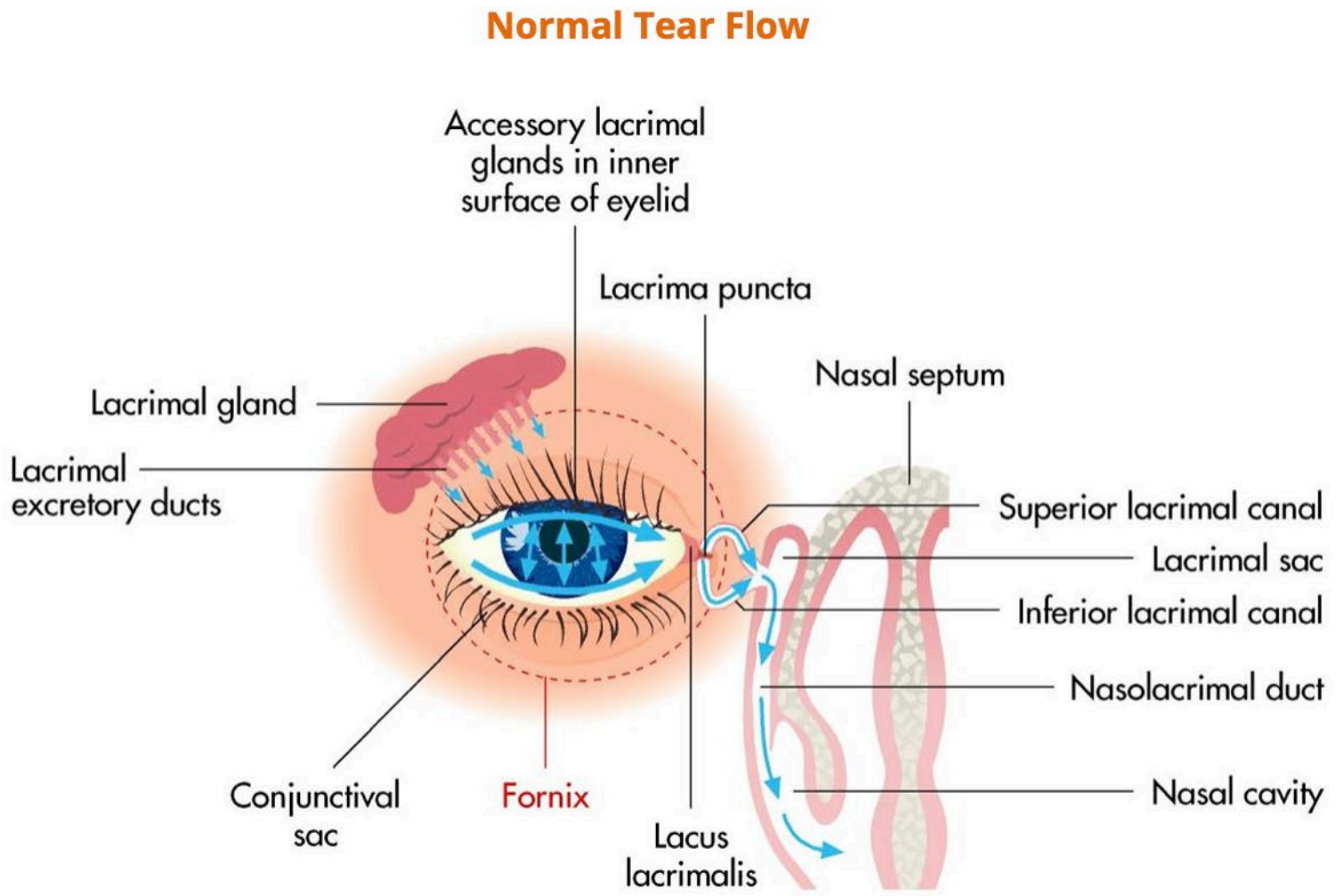
Safety



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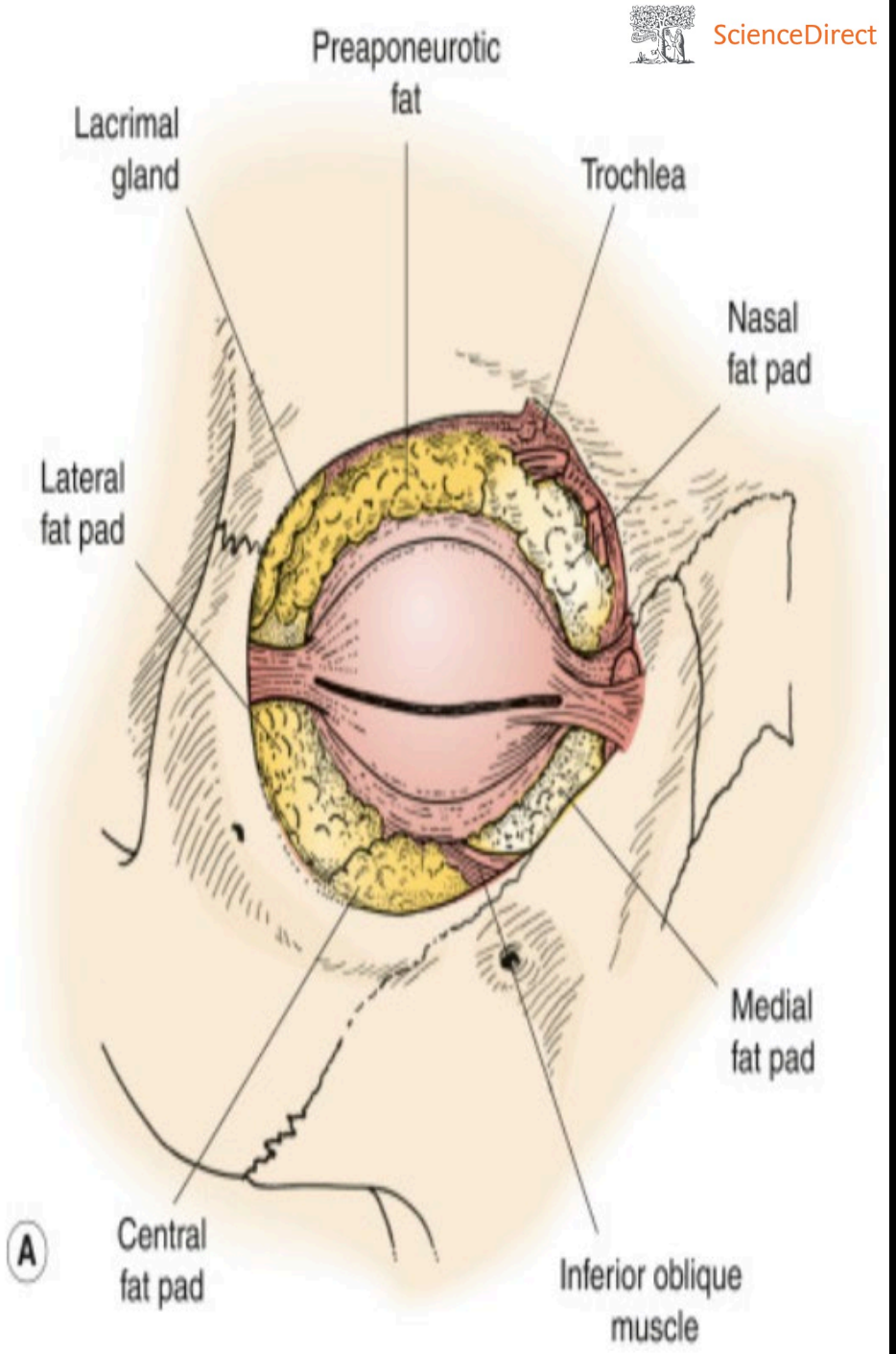
ScienceDirect
Preaponeurotic fat
Lacrimal gland
Trochlea
Nasal fat pad
Lateral fat pad
Medial fat pad
A
Central fat pad
Inferior oblique muscle

Safety

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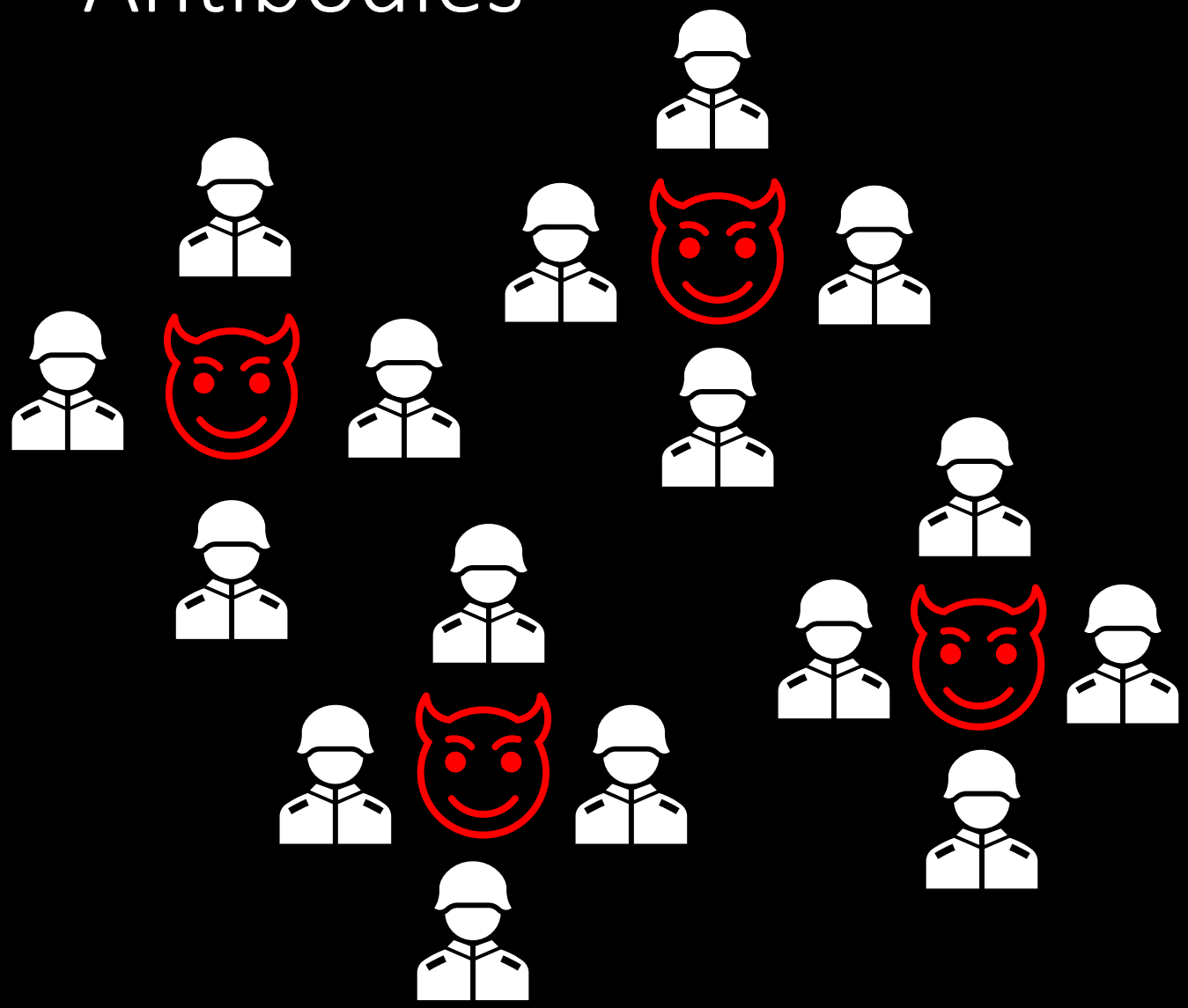
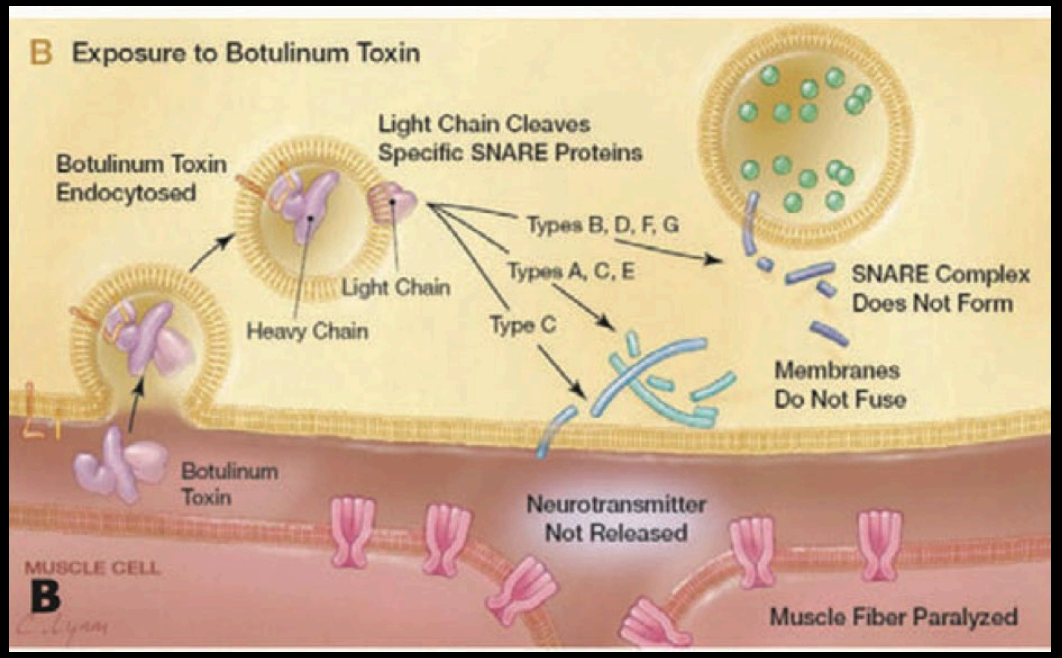
Antibodies



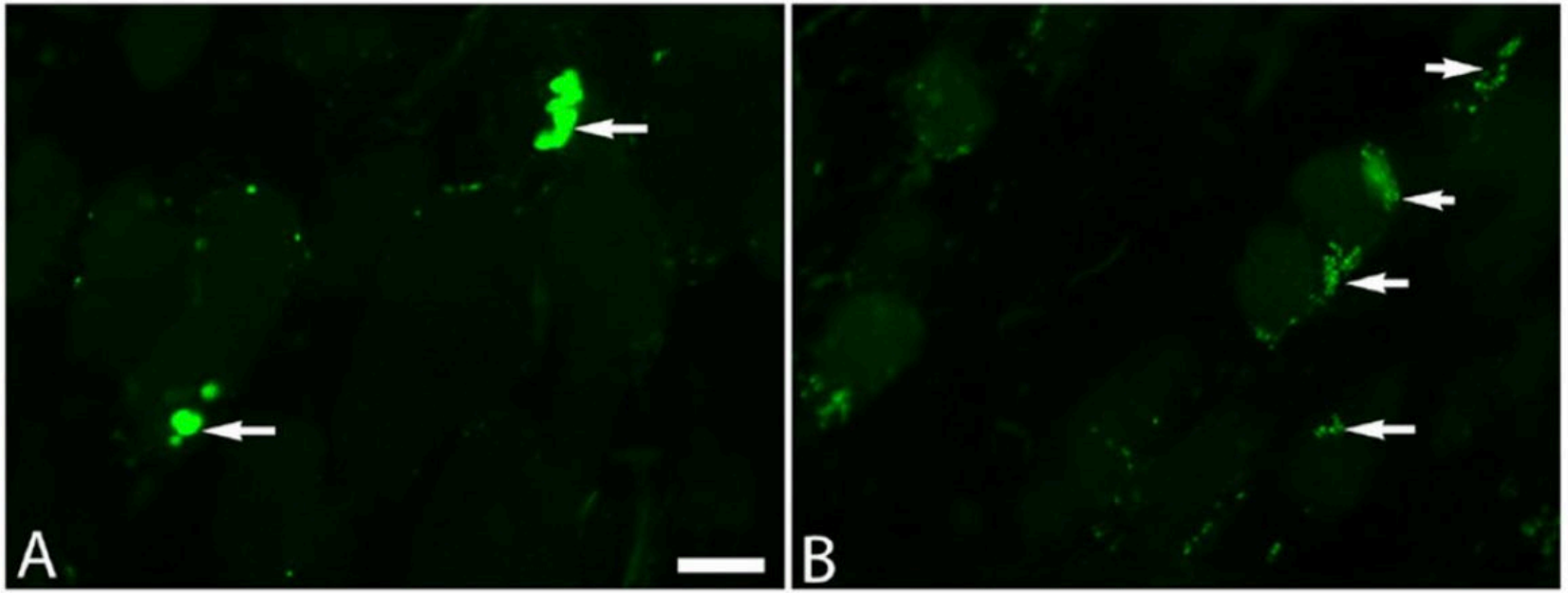

B Exposure to Botulinum Toxin
Botulinum Toxin Endocytosed
Light Chain Cleaves Specific SNARE Proteins
Types B, D, F, G
Types A, C, E
Type C
Light Chain
Heavy Chain
SNARE Complex Does Not Form
Membranes Do Not Fuse
Botulinum Toxin
Neurotransmitter Not Released
MUSCLE CELL
B
Muscle Fiber Paralyzed

Impact of Botulinum Toxin Injections

Effects of Repeated Eyelid Injections with Botulinum Toxin A on Innervation of Treated Muscles in Patients with Blepharospasm

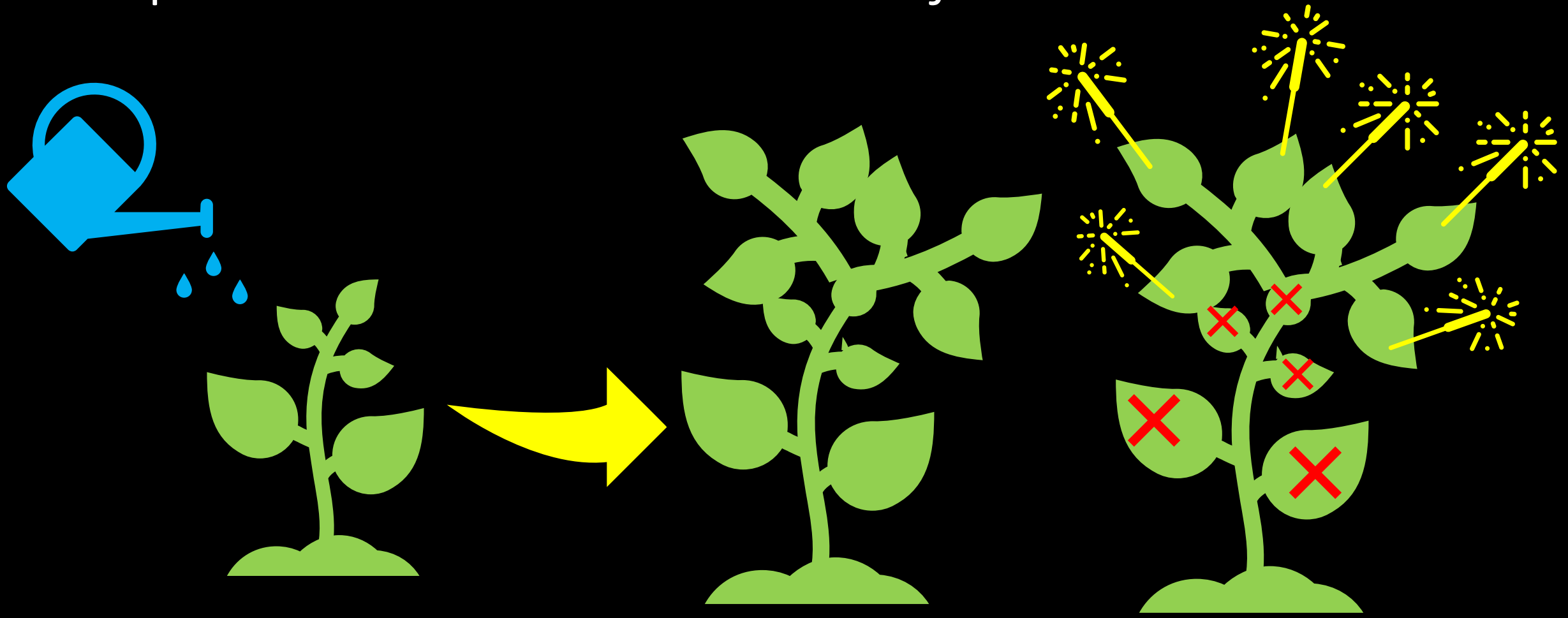
Curr Eye Res. 2019 March ; 44(3): 257–263. doi:10.1080/02713683.2018.1543707.

Rose M. Olson, B.S.[1], **Ali Mokhtarzadeh, M.D.**[1], **Linda K. McLoon, Ph.D.**[1,2], and **Andrew R. Harrison, M.D.**[1,3]



Neuromuscular Junction Density

Impact of Botulinum Toxin Injections

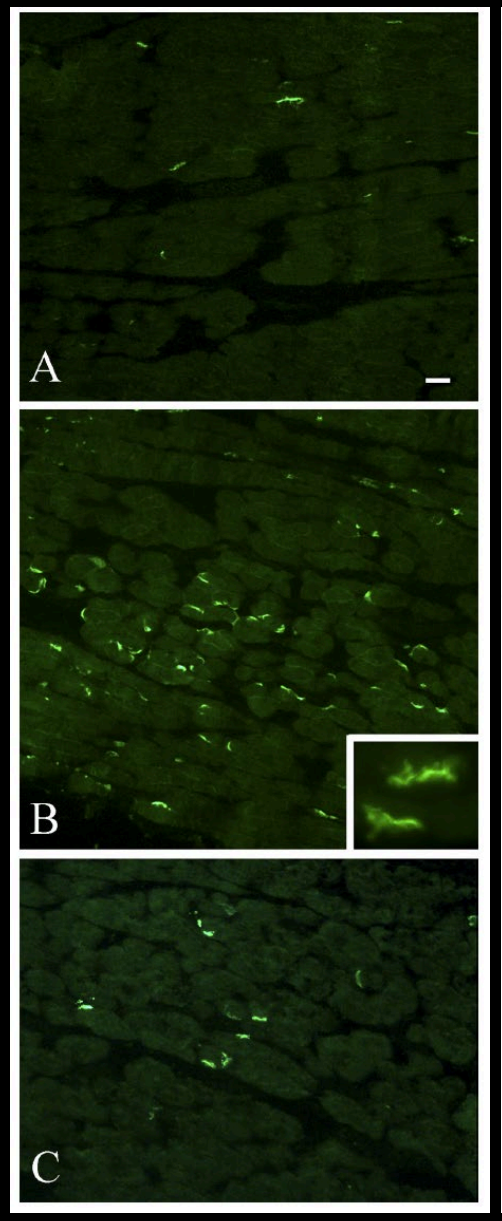


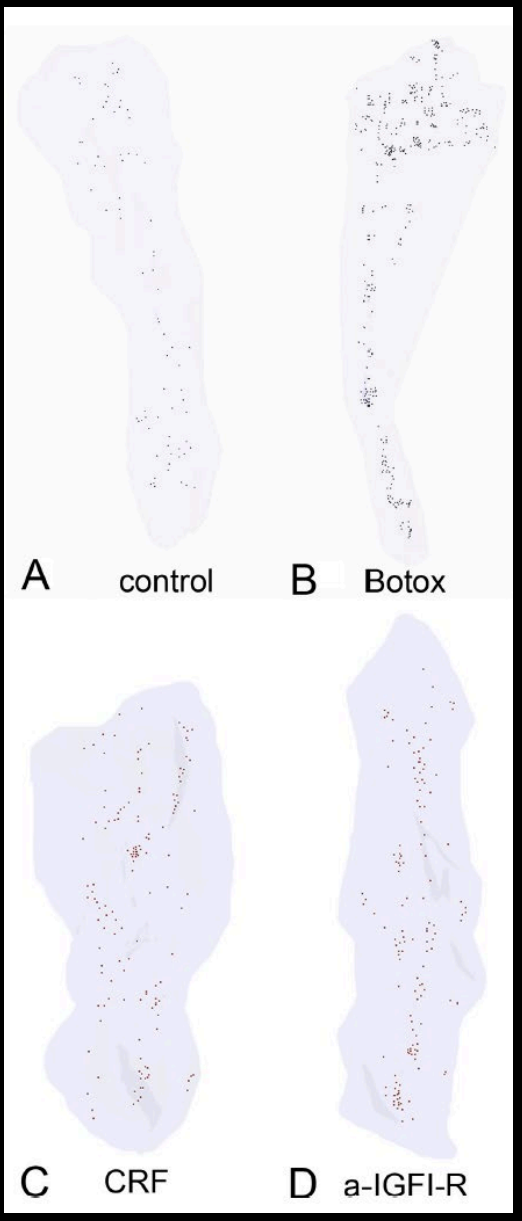
Impact of Botulinum Toxin Injections

Modulating Neuromuscular Junction Density Changes in Botulinum Toxin–Treated Orbicularis Oculi Muscle

Andrew R. Harrison,[1,2] *Zachary Berbos,*[1] *Renzo A. Zaldivar,*[1] *Brian C. Anderson,*[1] *Mollie Semmer,*[1] *Michael S. Lee,*[1,3,4] *and Linda K. McLoon*[1,5]

Investigative Ophthalmology & Visual Science, February 2011, Vol. 52, No. 2





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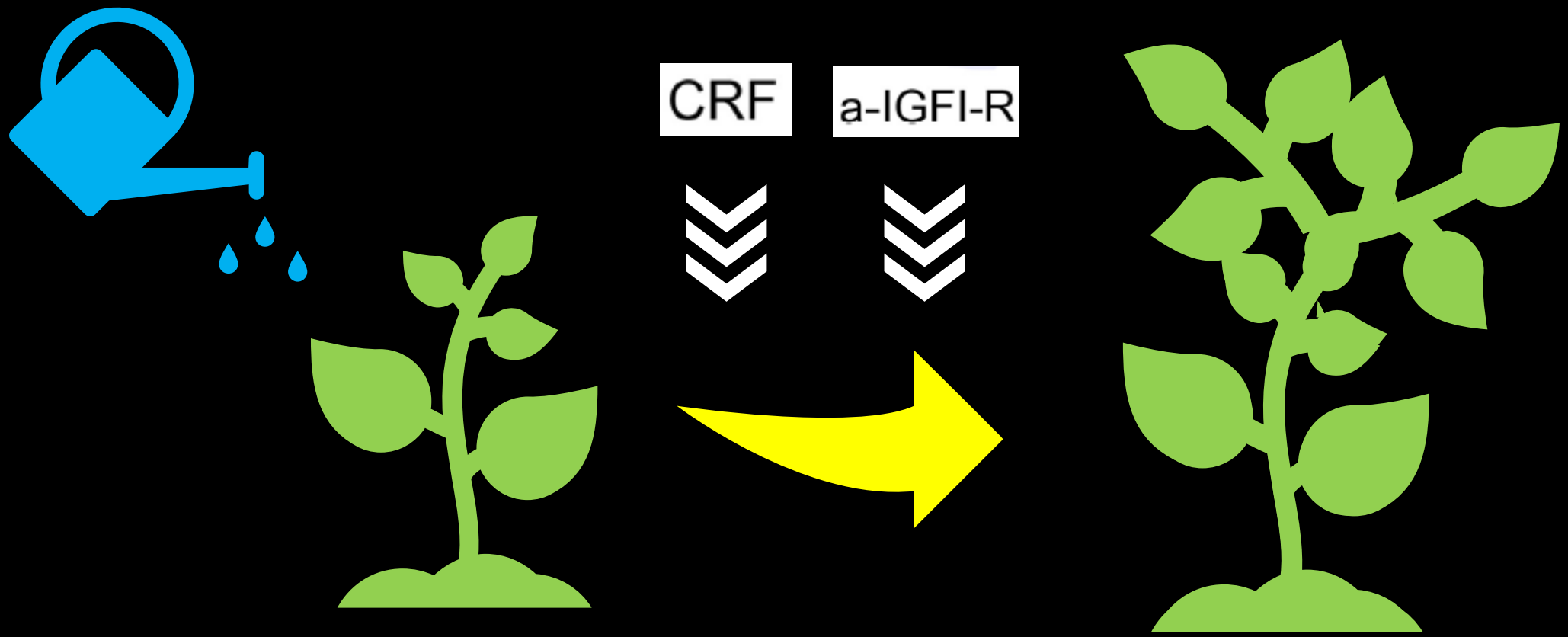

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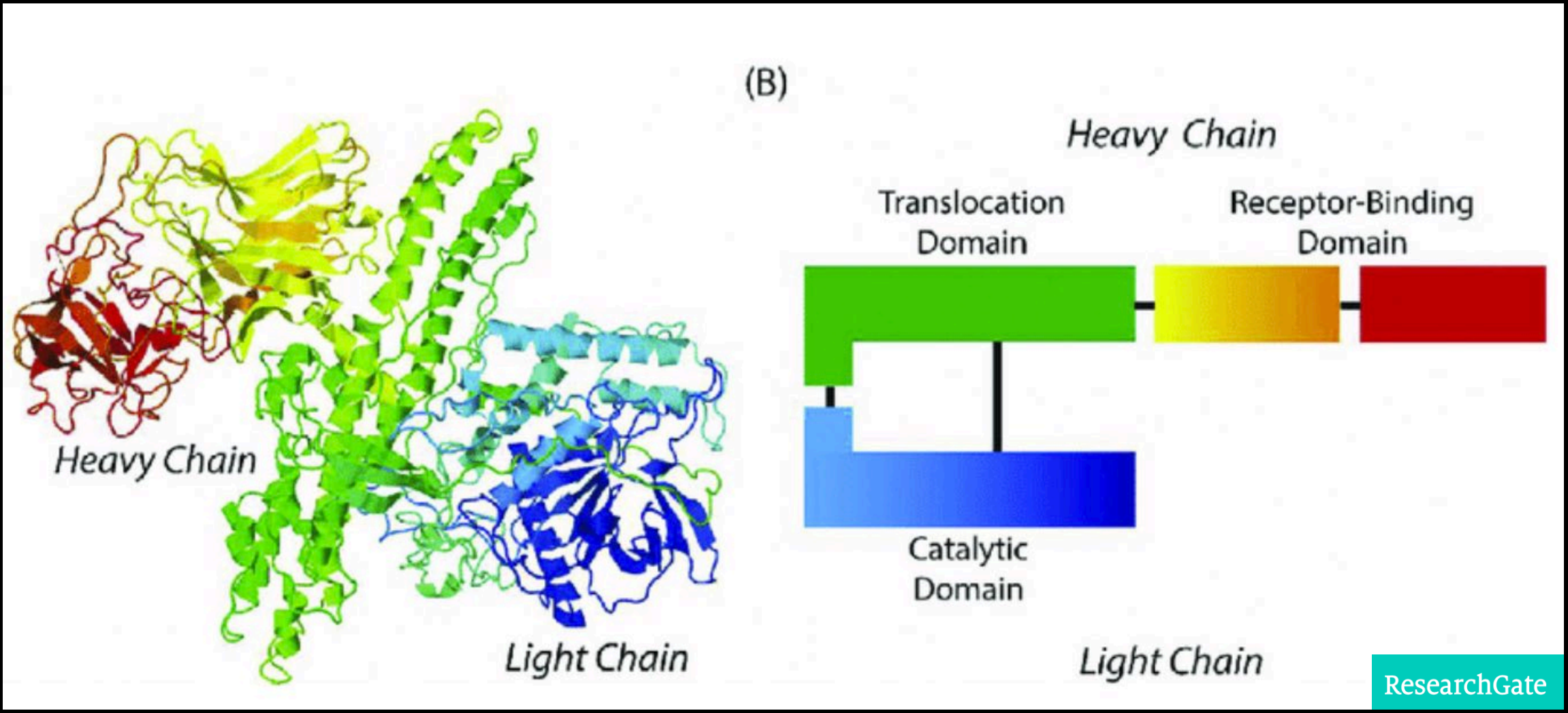
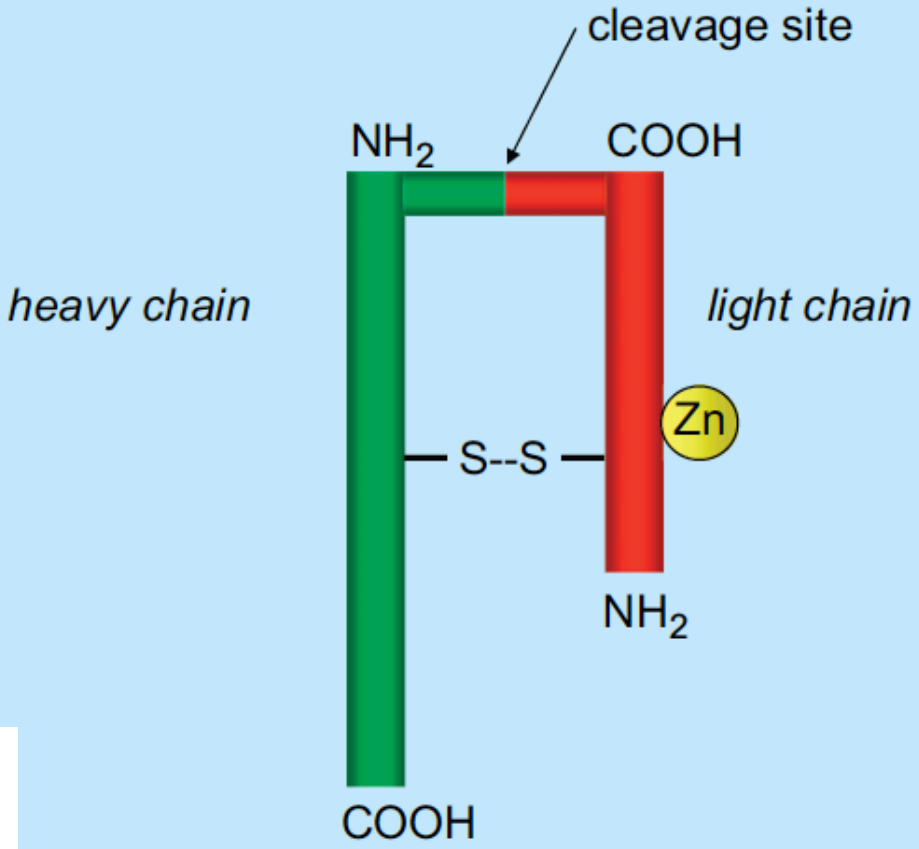
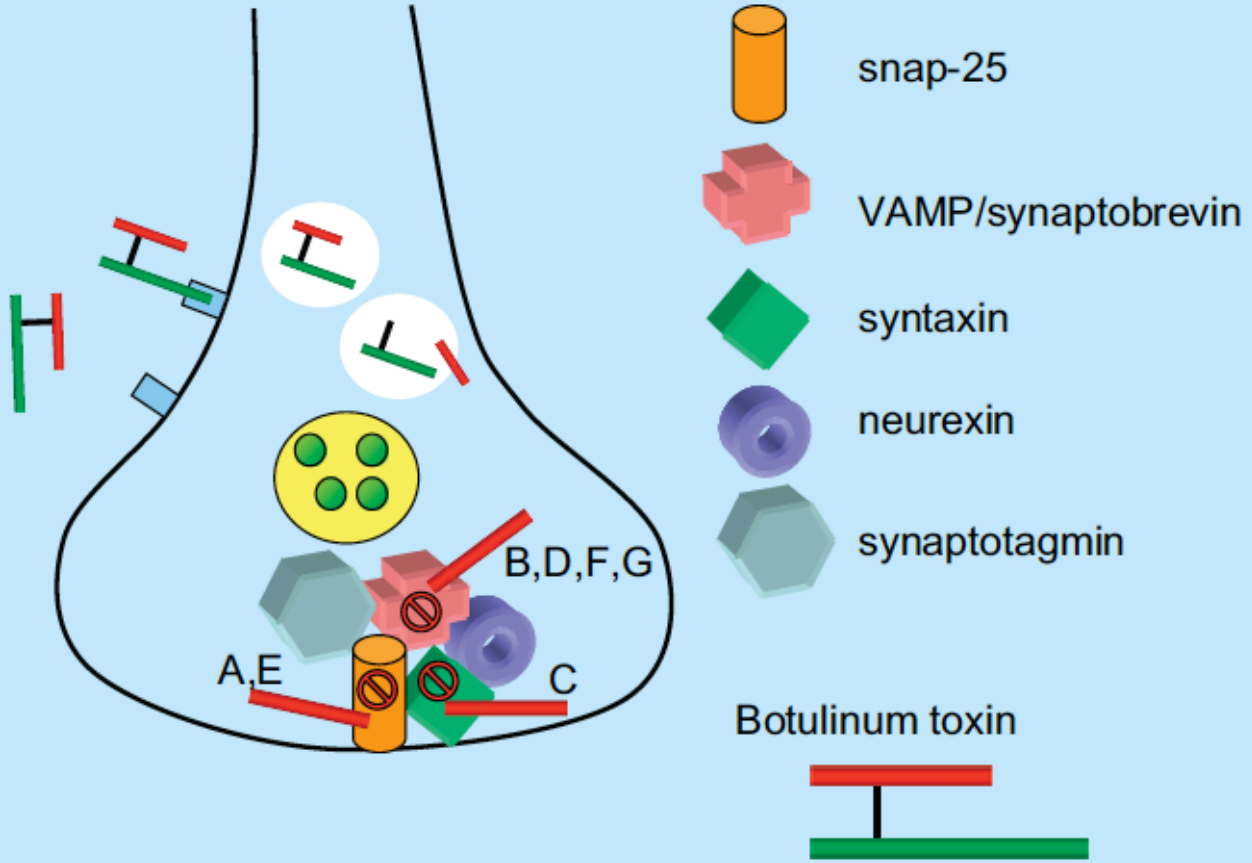
Role of Zinc


Heavy Chain
Light Chain
(B)
Heavy Chain
Translocation Domain
Receptor-Binding Domain
Catalytic Domain
Light Chain
ResearchGate

Role of Zinc


cleavage site
NH2
COOH
heavy chain
light chain
Zn
S--S
NH2
COOH


snap-25
VAMP/synaptobrevin
syntaxin
neurexin
synaptotagmin
B,D,F,G
A,E
C
Botulinum toxin

Role of Zinc

Effect of dietary zinc and phytase supplementation on botulinum toxin treatments.

Koshy JC[1], Sharabi SE, Feldman EM, Hollier LH Jr, Patrinely JR, Soparkar CN

Purpose

To determine whether oral zinc supplementation might affect the efficacy and duration of botulinum toxin treatments.

Methods

In a double-blind, placebo-controlled, crossover pilot study, we examined the efficacy of three botulinum toxin preparations (onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB) following oral supplementation with zinc citrate 50 mg and phytase 3,000 PU, zinc gluconate 10 mg, or lactulose placebo in individuals treated for

Journal of Drugs in Dermatology : JDD, 01 Apr 2012, 11(4):507-512

Results

In seventy-seven patients, 92% of subjects supplemented with zinc 50 mg and phytas experienced an average increase in toxin effect duration of nearly 30%, and 84% of participants reported a subjective increase in toxin effect, whereas no significant increase in duration or effect was reported by patients following supplementation with lactulose placebo or 10 mg of zinc gluconate. The dramatic impact of the zinc/phytase supplementation on some patients' lives clinically unmasked the study and prompted an early termination.

Conclusions

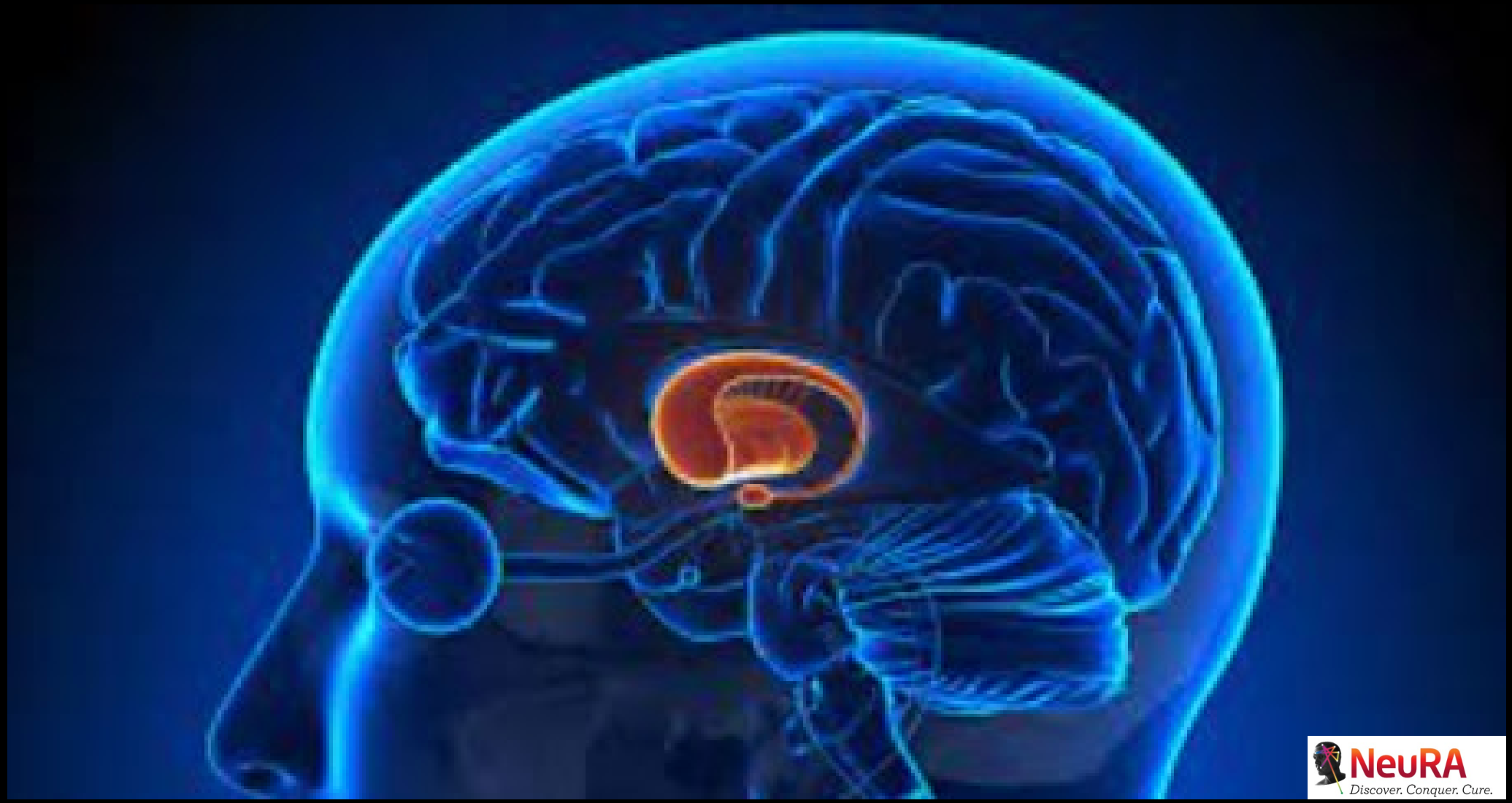
This study suggests a potentially meaningful role for zinc and/or phytase supplementation in increasing the degree and duration of botulinum toxin effect in the treatment of cosmetic facial rhytids, benign essential blepharospasm, and hemifacial spasm.

Non-Pharmacologic Treatments

- Light Filter Lenses
- Eyelid Crutches
- External Magnetic Eyelid Device
- Transcrainial Magnetic Stimulation
- Deep Brain Stimulation

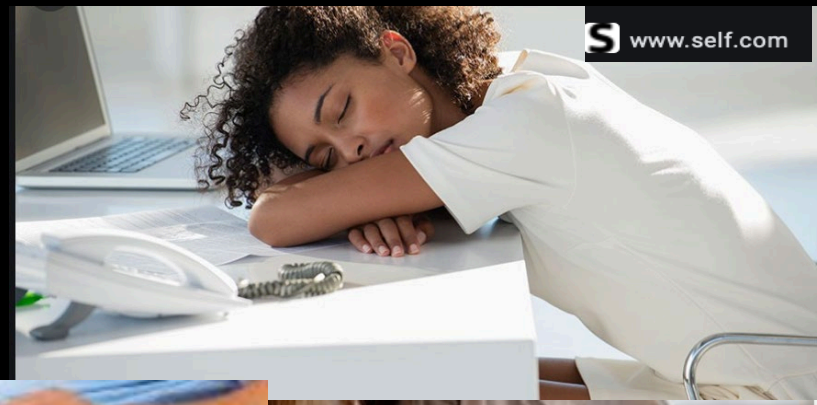
EXPERT REVIEW OF OPHTHALMOLOGY
https://doi.org/10.1080/17469899.2018.1503535

Systemic Pharmacologic Treatments



Systemic Pharmacologic Treatment

- Dopamine Agonists
- Dopamine Inhibitors/Depleter
- Anticholinergics
- GABAergic
- Neural Membrane Stabilizing Agents



Medical treatment of blepharospasm

Dhanya Vijayakumar[a] and Joseph Jankovic[b]

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EXPERT REVIEW OF OPHTHALMOLOGY
https://doi.org/10.1080/17469899.2018.1503535

Table 1. Pharmacotherapies in the treatment of blepharospasm.

Pharmacological class	Mechanism of action	Pharmacological agent	Pertinent clinical use	Selected adverse effects
Dopaminergic agents	Dopamine precursor	Levodopa	• PD patients with blepharospasm as part of dystonic dyskinesia or wearing off dystonia	Nausea, drowsiness, orthostatic hypotension
	Dopamine receptor agonist	Apomorphine	• Patients with blepharospasm as a symptom of atypical parkinsonian conditions • Dopa-responsive dystonia	Nausea, drowsiness, sleep attacks, impulse control disorder, hallucination, injection-site reactions
Dopamine transporter blocker	Blocks dopaminergic reuptake into presynaptic terminals	Methylphenidate	• Patients with blepharospasm and increased daytime somnolence or fatigue secondary to use of other medications • Patients with comorbid Attention deficit hyperactivity disorder (ADHD) (often co-existent in patients with Tourette syndrome)	Cardiac clearance needed due to risk of cardiac arrhythmia
Anticholinergics		Trihexyphenidyl	• Younger patients with blepharospasm	Cognitive impairment in elderly
GABA agonists	GABA-A agonist	Clonazepam	• Patients with multiple sites of dystonia like in generalized dystonic conditions • Most commonly used oral agent in blepharospasm patients	Drowsiness
	GABA-B agonist	Baclofen	• Generalized dystonia/multiple dystonic sites	Drowsiness

Medical treatment of blepharospasm

Dhanya Vijayakumar[a] and Joseph Jankovic[b]

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Neural membrane stabilizing agents	Blocks voltage-gated sodium and calcium channels	Carbamazepine	• Use in conjunction with BoNT in patients with concomitant neuropathic pain symptoms as well	Hyponatremia, drowsiness
	Nonselective calcium channel blocker	Mexiletine	• Consider in patients with eyelid myotonia, or impaired eyelid relaxation	Sedation, ataxia, nausea
		Lithium	• Potential use in patients with comorbid mood symptoms that may benefit as well	Tremor, parkinsonism
	Antihistamine	Cyproheptadine	• Potential consideration in patients with comorbid seasonal allergies	Drowsiness, fatigue
		Zolpidem	• Consider in patients with insomnia	Sedation
Local eyelid constrictors	Alpha 2 adrenergic receptor agonist	Apraclonidine	• Short duration use in patients with premature wearing off of BoNT injection benefits	Local eye allergic reactions
Topical muscle relaxant	Competitive SNAP-25 inhibitor	Topical acetyl hexapeptide-8	• Concomitant use with BoNT with a trend to extend duration of benefit	Local skin allergic reactions
Anti-androgenic drug	5 alpha-reductase inhibitor	Finasteride	• Single case report, insufficient data • Potential use in male patients with comorbid Benign prostatic hyperplasia (BPH)	Orthostatic hypotension

EXPERT REVIEW OF OPHTHALMOLOGY
https://doi.org/10.1080/17469899.2018.1503535

THANK YOU!

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Alison Watson, MD