

## Ocular Pharm: A Conglomeration of New Ideas, New Uses, Old Drugs, & Old Topics

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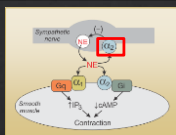
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- ◊ I have no disclosures to report.
- ◊ References/sources available if you want them...
- ◊ I'm not perfect...
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### Alphagan (Brimonidine) & Pupillary Miosis???

#### Brimonidine (Alphagan-P)

- A highly specific  $\alpha$ -2 adrenergic receptor agonist
  - Alpha-2 receptors at pre-synaptic nerve terminals
  - Binding sites for brimonidine localized on the iris
- Activation of Alpha-2 receptors inhibits the release of the neurotransmitter, norepinephrine
- Therefore, norepinephrine is not available for receptor activation & adrenergic Pupil Dilation  
→ **decreased by 1-2 mm**
- **Onset 30 mins; up to 4-6 hrs**



#### The Scotopic Miosis

- Speculated to be:
  - Due to a change in balance between the pupil sphincter and pupil dilator muscles.



- Tonus of the **cholinergic** driven sphincter remains intact/unaffected (PNS)
- Dilator (SNS controlled) is **relaxed** in the presence of the alpha-2 agonist
- Therefore, the sphincter has increased control over pupil size  
→ the balance has shifted to PNS → **Smaller pupil**

McDonald JE, et al. Effect of brimonidine tartrate ophthalmic solution 0.2% on pupil size in normal eyes under different luminance conditions. *J Cataract Surg.* 2001;27:560-4.

McDonald JE, et al. Effect of brimonidine tartrate ophthalmic solution 0.2% on pupil size in normal eyes under different luminance conditions. *J Cataract Surg.* 2001;27:560-4.

## Why less effect on pupil size in bright illumination?

### ◆ Brimonidine

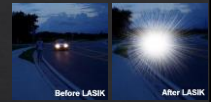
- ◆ Has no effect the cholinergic driven sphincter muscle in photopic conditions (PNS)
- ◆ There is a less obvious size difference with and without brimonidine



- ◆ Therefore, photopic pupil size is relatively normal

## When can we use this?

- ◆ Complaints of glare/halos/starbursts in dark/scotopic conditions
- ◆ Driving, movies, etc.
- ◆ McDonald et al. J Cataract Surg. 2001



- ◆ MOA: Pupil size is  $\geq$  treatment zone diameter
- ◆ General Tx Zone = **6.0 - 6.5 mm diameter**
- ◆ Ortho K Tx Zone = **6.0 - 6.5 mm diameter**

- ◆ LASIK/PRK
- ◆ OrthoK
- ◆ RGP's

## Scotopic Pupil Size & Age

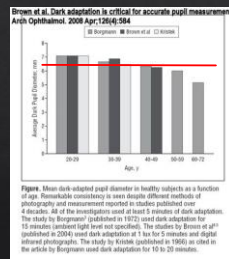
Bradley et al. Dark-adapted pupil diameter as a function of age. Invest Ophthalmol Vis Sci. 1993;34(1):154-158.

TABLE  
Dark-adapted Pupil Diameter Measured by the NeuroOptics Pupillometer as a Function of Age-decade

Age (y)	N	DAO (Mean $\pm$ SD) (Range) (mm)
10 to 19*	6	6.85 $\pm$ 0.72 (5.6 to 7.5)
20 to 29*	65	7.35 $\pm$ 0.81 (5.7 to 8.8)
30 to 39*	59	6.64 $\pm$ 0.78 (5.3 to 8.7)
40 to 49	51	6.25 $\pm$ 0.80 (4.5 to 8.2)
50 to 59	50	5.77 $\pm$ 0.74 (4.4 to 7.2)
60 to 69	30	5.58 $\pm$ 1.00 (3.5 to 7.5)
70 to 79	6	5.17 $\pm$ 0.60 (4.6 to 6.0)
80 to 89*	4	4.89 $\pm$ 0.54 (4.2 to 5.9)

DAO = dark-adapted pupil diameter (2 minutes at 7 lux white-green adaptation)  
\*10 study participants in the oldest groups were 28 to 43 years old; all study participants in the oldest groups were 80 years old.

Bradley et al. J Refract Surg. 2011;27:202-7.



Brown et al. Arch Ophthalmol. 2008;126:584.

## Wouldn't Pilocarpine work too?

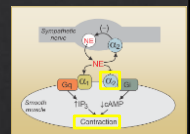
	Brimonidine	Pilocarpine
Ciliary spasm?	No	Yes
Effective in Photopic?	No	Yes
Effective in Scotopic?	Yes	Yes
Systemic side effects?	Limited	SLUDGE
Ocular side effects?	Allergy	RD

**Bottom Line** → consider Brimonidine in patients with scotopic vision complaints

## Alphagan (Brimonidine) & Redness Reliever

### Brimonidine tartrate 0.025%

- ◆ Diluted brimonidine solution → **vasoconstriction**
  - ◆ **Post-synaptic junction**
- ◆ Phase 3 trials completed (Bausch & Lomb)
  - ◆ Lumify® → (over-the-counter)
- ◆ No rebound hyperemia with discontinuation
- ◆ No tachyphylaxis noted
- ◆ Seems to work on smaller caliber conjunctival vessels without affecting larger vessels so blood flow is not affected
  - ◆ Venules > arterioles
  - ◆  $\alpha_2$  receptors predominantly in **veins**!
  - ◆  $\alpha_1$  receptors predominantly in **arteries**!

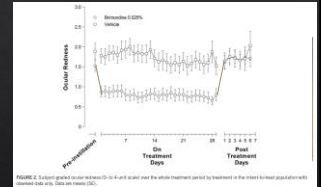


McLaurin E, et al. Brimonidine ophthalmic solution 0.025% for reduction of ocular redness: a randomized clinical trial. Optom Vis Sci. 2018;95:264-71.

## Lumify now available!

## McLaurin E, et al. *Optom Vis Sci.* 2018

- ◆ Phase III Clinical Trial (B&L)
- ◆ Brimonidine 0.025% QID x 30 days
- ◆ n=60
  - ◆ 40 brimonidine, 20 vehicle
- ◆ Onset: 1-5 minutes!
- ◆ Duration of action: 8 hours!
  - ◆ Largest effect within first 4 hrs
- ◆ No tachyphylaxis!
- ◆ Negligible rebound redness
- ◆ Note: IOP did not decrease!
- ◆ Only 4 subjects (10%) had SE's from brimonidine



McLaurin E, et al. Brimonidine ophthalmic solution 0.025% for reduction of ocular redness: a randomized clinical trial. *Optom Vis Sci.* 2018;95:264-71.

## Final thoughts on Brimonidine 0.025%...

- ◆ Dose: one drop q6-8h in affected eye(s); max of QID
- ◆ "In conclusion, the results from this trial suggest that brimonidine tartrate ophthalmic solution, 0.025% is safe and well tolerated and is effective in reducing ocular redness in adult subjects. Additionally, **use of brimonidine 0.025% does not appear to be limited by side effects associated with currently marketed ocular redness relief medications.**"
- ◆ Torkildsen GL, et al. 2018.

Torkildsen GL, et al. Evaluation of efficacy and safety of brimonidine tartrate ophthalmic solution, 0.025% for treatment of ocular redness. *Curr Eye Res.* 2018;43:43-51.d

## Recent question I received from CE attendee...

- ◆ Does Lumify (brimonidine 0.025%) have an effect on pupil size like the 0.1%, 0.15%, and 0.2% concentrations?
- ◆ n=56 eyes of healthy adults (avg age 39.7 years)
- ◆ Measured pupil size with pupillometer in scotopic conditions pre and post brimonidine 0.025% instillation after 1 hour
- ◆ Average pupil size pre-instillation: 7.28 mm
- ◆ Average pupil size post-instillation: 6.36 mm } 0.9 mm average pupil reduction overall
- ◆ Statistically significant!
- ◆ Clinically significant....???
- ◆ Light irides (1.55 mm) vs. dark irides (0.67 mm)

Negad M, et al. Effect of over-the-counter brimonidine tartrate 0.025% ophthalmic solution on pupil size in healthy adults. *Graves Arch Clin Exp Ophthalmol.* 2021;59:3333-8.

## Brimonidine Rosacea Gel

- Approved for rosacea redness/erythema
- Dosing: Apply to erythematous patches once daily
- MOA: post-synaptic alpha agonist → sympathomimetic
  - Causes vasoconstriction of facial blood vessels
- Onset 30 minutes; Duration up to 12 hours
- FDA category B
- Main SE's:
  - \*Flushing /redness (8-10%)\*
  - Worsening of rosacea (5%)
- 1 month study showed modest results only:
  - 28% saw reduction in redness with brimonidine
  - 10% saw reduction in redness with vehicle
- Other use: Immature scar redness reducer

## Rosacea Erythema Improvement with Brimonidine

Time post-application	Brimonidine gel	Placebo
30 minutes	28%	7%
15 days	56%	21%
29 days	58%	32%

Fowler J, et al. *J Drugs Dermatol.* 2013;12:650-6.

## Adverse Effects with Brimonidine

Time post-application	Brimonidine gel
1 day	6-14%
1 month	29-34%
1-3 months	42%
10-12 months	19.5%

"Adverse events were mild, transient, and limited to the skin. Irritation, flushing, worsened erythema, burning sensation, and pruritus were the most commonly reported side effects."

Fowler J, et al. *J Drugs Dermatol.* 2013;12:650-6.  
Moore A, et al. *J Drugs Dermatol.* 2014;13:56-61.

- ◆ We have to be ready for more brimonidine use other than with glaucoma!
- ◆ Remember, alpha-agonists are the most likely glaucoma drops to cause an allergic reaction/response!
- ◆ Get a *complete* medication list from your patients!

### Quick summary of brimonidine...

- ◆ IOP?
  - ◆ Yes, with 0.1%, 0.15%, 0.2% concentrations. No, with 0.025% concentration.
- ◆ Scotopic miosis?
  - ◆ Yes with 0.1%, 0.15%, 0.2%, and 0.025% concentrations.
- ◆ Conjunctival redness reliever?
  - ◆ Yes with all concentrations (unless allergy).
- ◆ Improved upper eyelid position?
  - ◆ No, not proven at this time.
- ◆ Rosacea erythema improvement?
  - ◆ Yes, with Mirvaso (brimonidine) 0.33% gel.

Tuncer I, et al. Effect of brimonidine tartrate 0.15% on scotopic pupil size and upper eyelid position: controlled trial. *Eye*. 2021;35:672-5.

## Topiramate (Topamax)

### PTC /IIH Treatment Options...

1. Weight loss (**5-10%** is sometimes curative!)
2. **Carbonic anhydrase inhibitors**
  - ◆ Acetazolamide (Diamox)
  - ◆ **No oral steroids → weight gain**
3. Ventriculoperitoneal Shunt / Lumboperitoneal Shunt
  - ◆ Headaches only ; vision stable
4. Optic Nerve Fenestration
  - ◆ Vision/Visual Field worsening ; no headaches
5. Venous Sinus Stenting
  - ◆ In venous sinus stenosis

### Topamax vs. Diamox?

- ◆ **Acetazolamide** = CAI inhibitor ; works on ciliary body and choroid plexuses
- ◆ **Topiramate** = novel anticonvulsant; epilepsy/migraines
  - ◆ Multiple MOA's
    1. Enhancement of GABA
    2. Na channel blockade
    3. Glutamate receptor blocker
- ◆ **Also has carbonic anhydrase inhibition component; and decreases appetite**
  - ◆ Weight loss of **5-10%** alone may be curative in some cases of IIH
  - ◆ **Average weight loss of 7.3%** was obtained in one year on topiramate
    - ◆ 11% weight loss in patients with BMI>30 in one year
- ◆ Sulfonamide drug...be careful of sulfa allergies (?)
- ◆ FDA Pregnancy Category D → Cleft palate risk

Alton PL, Jay WM, Mckinnon MP. Topiramate, paracetamol, acetos, weight loss and glaucoma: an ophthalmologic perspective. *Swiss Ophthalmol*. 2008;21:15-17.  
 Michogian M, et al. The ophthalmic side effects of topiramate: a review. *Cureus*. 2022;14:e28113.  
 Li H, Wu W, et al. Mitochondrial function, glucose metabolism and neuronal death in topiramate-induced retinopathy: a mouse model of glaucoma. *Int J Ophthalmol*. 2018;11:3039-48.

### Recent meta-analysis...

- ◆ 23.2% (937 million) of world population = overweight
- ◆ 9.8% (396 million) of world population = obese } **As of 2005**
- ◆ 1.35 billion = overweight
- ◆ 573 million = obese } **Projected for 2030**
- ◆ Phentermine/topiramate (Qsymia)
  - ◆ Average weight loss → 7.97% avg loss of body weight (17 lbs)
- ◆ "In conclusion, phentermine-topiramate and GLP-1 receptor agonists proved among the best for weight-lowering effects in adults with overweight and obesity as an adjunct to lifestyle modification." --- Shei, et al. *Lancet*. 2022

Lei XG, et al. Efficacy and safety of phentermine/topiramate in adults with overweight or obesity: a systematic review and meta-analysis. *Obesity*. 2021;29:985-994.  
 Shei O, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomized controlled trials. *Lancet*. 2022;399:794-804.



## Topiramate Ocular Side Effects

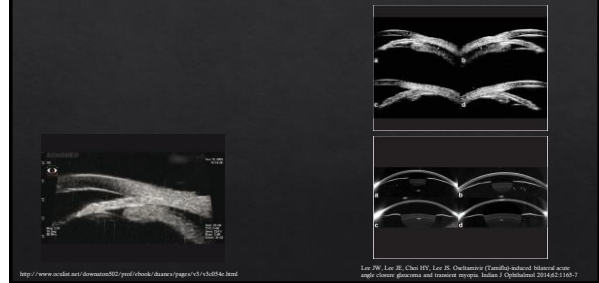
### ◆ **Angle closure glaucoma and myopic shift!!!**

- ◆ 85% of this happens within first 2 weeks of therapy
- ◆ MOA = lenticular/uveal effusion and ciliary edema causing forward displacement of the lens-iris diaphragm with resultant narrowing of the anterior chamber.
- ◆ \*\*\*Ciliochoroidal effusion occurs
  - ◆ Aka: suprachoroidal effusion, supraciliary effusion, ciliochoroidal detachment
  - ◆ Abnormal collection of fluid that expands suprachoroidal space, producing internal elevation of choroid
- ◆ Not related to dosage (86 reports):
  - ◆ Idiosyncratic response... no pattern

Dosage	Incidence of Angle Closure/Myopia
<50 mg/day	47% of cases
50-75 mg/day	33% of cases
100 mg/day	13% of cases
>100 mg/day	7% of cases

• Mocherzi M, et al. The ophthalmic side effects of topiramate: a review. *Clinics*. 2022;14(2861).  
 • Lee JW, et al. Bilateral acute angle closure glaucoma and myopia due to topiramate-induced ciliochoroidal effusion: case report and literature review. *Int Ophthalmol*. 2018;38:7630-40.

## Ciliochoroidal Effusion



Lee JW, Lee JE, Choi HY, Lee JB. Ocular toxicity (topiramate-induced bilateral acute angle closure glaucoma and transient myopia). *Indian J Ophthalmol*. 2014;62:1168-71.

## Topiramate MOA:

- ◆ All sulfa derived drugs can induce myopic shift & acute angle closure by increasing osmotic status of the tissues → H<sub>2</sub>O naturally follows gradient
  - ◆ HCTZ
  - ◆ Trimethoprim
  - ◆ Acetazolamide
- ◆ Ciliary body edema is final common pathway
  - ◆ Ciliary processes rotate forward, pushing iris/lens forward toward anterior chamber angle
  - ◆ Relaxation of the lens fibers causes lens thickening → increased myopia

Wu A, et al. A review of systemic medications that may modulate the risk of glaucoma. *Exp*. 2020;34:12-28.

## Topiramate-induced angle closure glaucoma??? Check list...

- ◆ Search medication list!
  - ◆ When was medication started? Increased dosage recently?
- ◆ Myopic Shift?
- ◆ Narrow anterior chamber on SLE?
- ◆ Elevated IOP?
- ◆ Detection of ciliochoroidal effusion?
  - ◆ Ant Seg Ultrasonography
  - ◆ B-scan for Post Seg
  - ◆ Ant Seg OCT
- ◆ Stop med!
  - ◆ Consult with prescribing physician first...
- ◆ Reduce IOP, cycloplege patient
  - ◆ Consider steroid

## Rechallenge with Topiramate???

- ◆ Controversial results....
- ◆ Fraunfelder et al. → 3 cases....(+)recurrence upon rechallenge
- ◆ Gubbay SS. → (-)recurrence upon rechallenge with lower dosage 5 days later
- ◆ Jurgens TP, et al. → 1 case....(+)recurrence with rechallenge

## Topiramate and EtOH-ism???

- ◆ MOA: suppression of ethanol-induced **nucleus accumbens** dopamine release → inhibition of EtOH reinforcing effects
- ◆ "...there is now solid clinical evidence to support the efficacy of topiramate for the treatment of alcohol dependence. Topiramate's therapeutic effects appear to be robust, with a medium effect size, thereby potentially ushering in a new era of a reliably efficacious medicine for the treatment of alcohol dependence."
- Johnson BA, et al. 2010

• Burnette EM, et al. Novel agents for the pharmacological treatment of alcohol use disorder. *Drugs*. 2022;82:251-274.  
 • Krasner LD, et al. Post-treatment effects of topiramate on alcohol-related outcomes: a combined analysis of two placebo-controlled trials. *Addict Biol*. 2022;27:e13130.

## Topiramate and Smoking Cessation???

- ◊ MOA: suppression of nicotine-induced **nucleus accumbens**  
-- dopamine release → inhibition of nicotine reinforcing effects
- ◊ "...topiramate (up to 300 mg/d) showed potential as a safe and promising medication for the treatment of cigarette smoking in alcohol-dependent individuals."  
--- Johnson BA, et al. 2005

• Johnson BA, et al. Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: a randomized controlled trial. *Arch Intern Med*. 2005;165:1600-5.  
• Manhapra A, et al. Topiramate pharmacotherapy for alcohol use disorder and other addictions: a narrative review. *J Addict Med*. 2019;13:7-22.

## Topiramate and other substance abuse???

- ◊ "There is now a growing body of literature examining the efficacy of topiramate in many different substance related disorders, including alcohol dependence and withdrawal, nicotine dependence, cocaine dependence, benzodiazepine dependence and withdrawal, and ecstasy abuse." -- Shinn AK, et al. 2010
- ◊ Gambling, binge eating, and smoking cessation also. -- Manhapra A, et al. 2019

• Shinn AK, Greenfield SF. Topiramate in the treatment of substance-related disorders: a review of the literature. *J Clin Psychiatry*. 2010;71:634-48.  
• Rounsaville BJ. The treatment of cocaine use disorder. *Sci Adv*. 2019;5:eaa11532.  
• Manhapra A, et al. Topiramate pharmacotherapy for alcohol use disorder and other addictions: a narrative review. *J Addict Med*. 2019;13:7-22.

## Quick Topiramate Summary:

- ◊ Might be beneficial for the following:
  - ◊ Weight loss
  - ◊ Alcohol use disorder
  - ◊ Smoking cessation
  - ◊ Cocaine use disorder
  - ◊ Benzodiazepine dependence
  - ◊ Ecstasy abuse
  - ◊ Gambling
  - ◊ Binge eating
  - ◊ More? Others in future?

**We should be ready for more topiramate use in our patients!**

**Look for:**

- Myopic shift
- Angle closure
- IOP elevation

## Iopidine (Apraclonidine) & Horner Syndrome

Any disruption along this oculosympathetic pathway has the potential to cause a Horner Syndrome

### Recommended Neuroimaging???

- Entire sympathetic chain using MRI of the brain and neck down to the T2 level
  - Margolin et al. *Pract Neurol*. 2020

## HS Diagnosis....

- ◊ 1) Cocaine 5-10%----- Is it a Horner's?
    - ◊ MOA: Indirect-acting sympathomimetic; increases norepinephrine (NE) availability
    - ◊ Horner's pupil = no dilation
    - ◊ Normal pupil = dilation
    - ◊ Maintenance of anisocoria = Horner's
    - ◊ Bilateral Dilation = physiologic anisocoria
  - ◊ 2) Hydroxyamphetamine 1%-----Where is the lesion causing the HS?
    - ◊ MOA: indirect sympathomimetic; forces NE out of presynaptic terminal
    - ◊ No dilation = post-ganglionic (3<sup>rd</sup> order neurons)
    - ◊ Dilation = pre-ganglionic or central (1<sup>st</sup> or 2<sup>nd</sup> order neurons)
- } Assess after **30-60** minutes
- ◊ Cocaine and Hydroxyamphetamine must be separated by **24-72 hours**; cocaine interferes with hydroxyamphetamine

## Diagnosis continued...

- ◆ 3) **Apraclonidine** 0.5% or 1.0%
  - ◆ Weak alpha-one receptor agonist affinity
  - ◆ Reversal of anisocoria after **30-60 minutes** if denervation hypersensitivity is present
  - ◆ Horner's pupil will dilate
  - ◆ Lid ptosis can also improve
  - ◆ Minimum **5-8 days** needed for denervation hypersensitivity
    - ◆ False negatives possible in early stages
- ◆ Apraclonidine effectively replaces cocaine to determine presence of HS
- ◆ Still need imaging and/or hydroxyamphetamine to determine location

## 5-8 days for denervation hypersensitivity is being challenged...

- ◆ Nguyen et al reported 2 cases of much faster positive apraclonidine test...
  - ◆ Case 1 -- positive in 72 hours
  - ◆ Case 2 -- positive in 48 hours
- ◆ Probably worth trying apraclonidine in any Horner syndrome regardless of onset...
- ◆ My opinion only ☺

Nguyen MTR, et al. Apraclonidine for the pharmacologic confirmation of acute Horner syndrome. *J Neurol Sci.* 2020;419:117190.

## Reversal of anisocoria with apraclonidine 0.5%

- Note the **improved ptosis** OD too

## Which drug (cocaine vs. apraclonidine) is better for diagnosing Horner syndrome?

- ◆ **Purpose:** compare cocaine 4% and apraclonidine 0.5% pupil responses in both normal and HS subjects after 40 minutes

- ◆ **Horner syndrome subjects (n=167):**

- ◆ Cocaine (n=95)
  - ◆ Increased pupil size 0.72 mm
  - ◆  $\geq 0.50$  mm  $\rightarrow$  40% sensitivity

- ◆ **Apraclonidine (n=72)**

- ◆ Increased pupil size 0.73 mm
- ◆  $\geq 0.10$  mm dilation in dark  $\rightarrow$  93% sensitivity

**TABLE 2** | Effect of drugs on the size of the pupil in normal eyes and in eyes with Horner syndrome.

		4% cocaine		0.5% apraclonidine	
		Normal	Horner	Normal	Horner
Drop effect	Mean	+2.06	+0.72	-0.44	+0.73
	SD	0.46	0.71	0.36	0.60
	Range	+0.95 to	+0.88 to	+1.3 to	+0.28 to
		+3.00	+2.64	+0.8	+2.26

Measurements (in mm) were made in the light for cocaine testing and in the dark for apraclonidine testing. "+" indicates an increase in pupil size. "-" indicates a decrease.

- ◆ "On that basis I recommend apraclonidine is now adopted as the 'gold standard' pharmacological test for diagnosing Horner syndrome (HS)." -- Bremner F, *Front Neurol* 2019

Bremner F. Apraclonidine is better than cocaine for detection of Horner syndrome. *Front Neurol* 2019;10:1-9.

## Naphazoline and Pheniramine & Mydriasis?

## Pupillary dilation?

- ◆ **Naphazoline (and Tetrahydrozoline)**
  - ◆ Decongestant in sympathomimetic class
  - ◆ Alpha-agonist  $\rightarrow$  **activates iris dilator muscle**
- ◆ **Pheniramine (and Antazoline)**
  - ◆ Antihistamine with secondary anticholinergic properties
  - ◆ Indirect/blocks acetylcholine binding (M receptor)  $\rightarrow$  **iris sphincter muscle**
- ◆ Both **synergistically** cause  $\uparrow$  sympathetic response...hence dilation!

## Why are they available in combination?

- ◆ **Naphazoline** great at reducing redness, but NOT itching
- ◆ **Pheniramine** great at reducing itching but NOT redness
- ◆ Onset ≈ 3 minutes!
- ◆ Duration = up to 2.5 hours; means multiple dosings needed daily
- ◆ No effect on: BP, HR, CNS, IOP, Visual acuity

## Upneeq

## Upneeq

- ◆ Oxymetazoline hydrochloride 0.1%
  - ◆ Preservative-free
- ◆ FDA-approved in July 2020
- ◆ Indication: acquired blepharoptosis in adults
- ◆ MOA: alpha-agonism (alpha-1) of Müller's muscle in upper eyelids
- ◆ Dose: one drop in eye(s) with ptosis daily
  - ◆ Supplied: 15 or 30 daily use carton
- ◆ n=360 subjects (over three Phase 3 trials)
  - ◆ 203 subjects for 6 weeks, 157 subjects for 12 weeks
- ◆ Results in approximately 1-2 mm of lid elevation (standard function of Müller's muscle)
  - ◆ Average of 1 mm improvement of MRD1 measurement in trials (per Upneeq™ website)
  - ◆ Some patients saw results 5 minutes after instillation
- ◆ Caution in those with HTN/blood pressure problems (alpha-1 = vasoconstriction)
- ◆ Side effects (incidence 1-5%):
  - ◆ Most common: SPK, hyperemia, dry eye, blurred vision, pain/irritation, headache

Package insert → <https://www.upneeq.com/what-upneeq-offers-your-patients/>

## Recent Upneeq article...

- ◆ n=29 subjects (58 eyes)
- ◆ Prospective cohort study
- ◆ Measured:
  - ◆ MRD1, MRD2, brow height, whiteness of sclera
- ◆ Outcomes:
  - ◆ MRD1 → 1.9 mm improvement in 2 hrs
  - ◆ MRD2 → 0.4 mm improvement in 2 hrs
  - ◆ Brow height → no change
  - ◆ Scleral whiteness → 57/58 eyes showed significant whitening at 2 hrs



No financial disclosures per article → independent study!

Ugural S, et al. Changes to eye whiteness and eyelid/brow position with topical oxymetazoline in anesthetic patients. *Anesth Surg J* 2022;42:582-9.

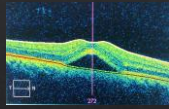
## My thoughts...

- ◆ Again, I have NO financial disclosures to report of any kind!
- ◆ I have used Upneeq on only one patient...price was too high per patient
- ◆ Have to order through one pharmacy (RVL pharmacy)
  - ◆ RVL does not take insurance (per Upneeq website)
- ◆ Price seems steep to me...
  - ◆ Cost: \$105 for 30-day supply???
- ◆ Other alpha-agonists are available too....would these work also?
  - ◆ Phenylephrine
  - ◆ Apraclonidine
  - ◆ Naphazoline
  - ◆ Tetrahydrozoline
- ◆ But do these other alpha-agonists last as long during the day? Multiple times per day required?
- ◆ Borgman Thought Of The Day?: consider the following...
  - ◆ In-office trial of 2.5% phenylephrine
  - ◆ Measure pre- and post- instillation.....if good effect, then consider prescribing Upneeq

## Mineralcorticoid Receptor Antagonists & CSR

## Central Serous Chorioretinopathy

- ◊ Circumscribed serous RD; usually macular region
  - ◊ Pathophysiology = unknown
- ◊ M>F (72-88% of time); 30-50 YO age range normally
- ◊ Bilateral in 40%
- ◊ Most acute episodes resolve in 2-3 months on own
- ◊ Recurrences common (up to 50%) → chronic CSCR in 5-10% of cases
  - ◊ Chronic CSR = >3-4 mo duration in most studies
- ◊ Historically, corticosteroids can aggravate CSCR; unknown MOA
- ◊ Exogenous/endogenous cortisol, Cushing's syndrome, psychological stress, Type A, pregnancy = risk factors
  - ◊ Males, HTN, collagen vascular diseases, H. Pylori infection
- ◊ PDT, anti-VEGF, CAI's, beta-blockers have been tried with varied success



## OCT Evidence of MOA?

- ◊ New evidence: diffuse choroidal thickening in CSCR eyes (and contralateral eyes)
  - ◊ **Choroidal vascular hyperpermeability!**
- ◊ How does this hyperpermeability occur?
  - ◊ Unknown still...
  - ◊ Corticosteroid related?

## Corticosteroids

- ◊ Produced by adrenal cortex:
  1. **Mineralcorticoid** = aldosterone
    - ◊ Bind to both mineralcorticoid (MR) and glucocorticoid receptors (GR)!
  2. **Glucocorticoid** = cortisol
    - ◊ Bind to both mineralcorticoid and glucocorticoid receptors too!
- ◊ **Cross binding to each receptor! Equal affinity for both!**
- ◊ MOA: Excess cortisol spills over to activate MR receptors as well
- ◊ Choroid has both MR and GR; **retina does not!**
- ◊ Glucocorticoids & Mineralcorticoids both induce choroidal enlargement/thickening and cause vessel dilation and leakage which can overcome RPE's defenses → neurosensory detachment

## Eplerenone (Inspra)

- ◊ FDA-approved in 2002 for HTN; 2003 for CHF
- ◊ **Oral mineralcorticoid/aldosterone receptor antagonist**
  - ◊ Competitive antagonist with high selectivity of MR; potassium sparing diuretic
- ◊ Reverses "endothelial vasodilatory potassium channel (KCa2.3)" activation in choroid
  - ◊ Stops/reverses choroidal thickening/leakage; down regulates KCa2.3
  - ◊ KCa2.3 only is expressed in choroid, not retina!
  - ◊ This is why MCR antagonists do not induce retinal vessel vasodilation!
- ◊ Side effects: **hyperkalemia**
- ◊ Contraindications: liver or renal disease, pregnancy
- ◊ Standard dose for CSCR: **25 mg/day PO x 1 week, then 50 mg/day x 3 months**

## Mineralcorticoid Receptor

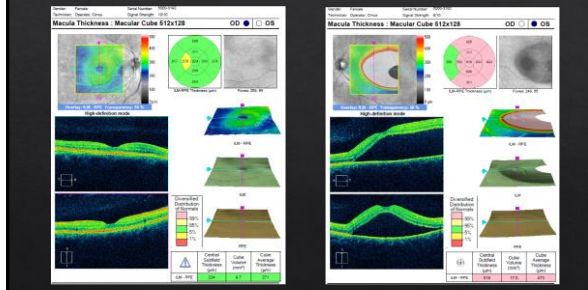
- ◊ MR **agonists** → upregulate KCa2.3 channels → choroidal vasodilation/leakage → SRF accumulation
- ◊ MR **antagonists** → down-regulate KCa2.3 channels → choroidal vasoconstriction → SRF reduction
- ◊ Remember, MR is **NOT** found in retinal tissues, therefore retina is unaffected by both mineralcorticoids and glucocorticoids

## Eplerenone vs. Spironolactone...

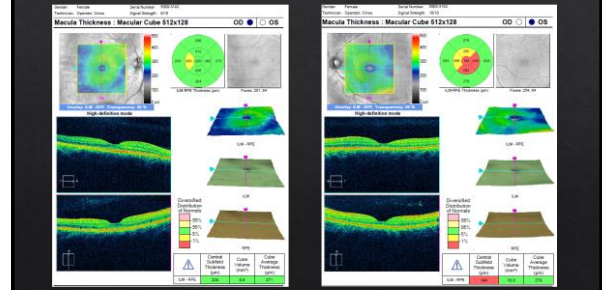
- ◊ Both are mineralcorticoid receptor blockers!
- ◊ Both are potassium-sparing diuretics!
  - ◊ Risk of hyperkalemia! = Biggest Risk!
- ◊ Eplerenone = **1-3% risk** @ 50-200 mg/day
- ◊ Spironolactone = **3-6% risk** @ 12.5-400 mg/day
- ◊ Standard Eplerenone dose for CSCR:
  - 25 mg/day PO x 1 week, then 50 mg/day x 3 months**
- ◊ Eplerenone has 10-20x lower affinity for MR than spironolactone
- ◊ However, Eplerenone has a much higher **selectivity** for MR without antiandrogen SE's
- ◊ **Bottom Line:** Eplerenone is best choice with the least probable SE's at this time



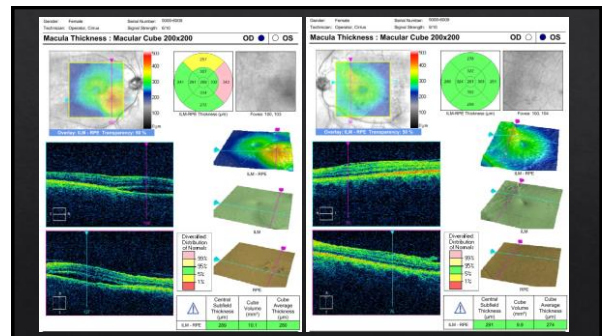
## Resident's Case: 47 Year old HF w/ chronic CSR (6+ mo)



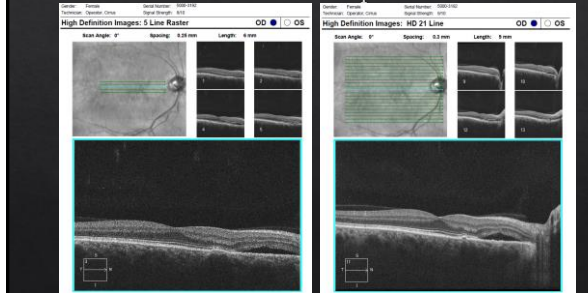
## Eplerenone: 6 weeks later



## Feb 2017: My first experience with CSR &amp; Eplerenone...



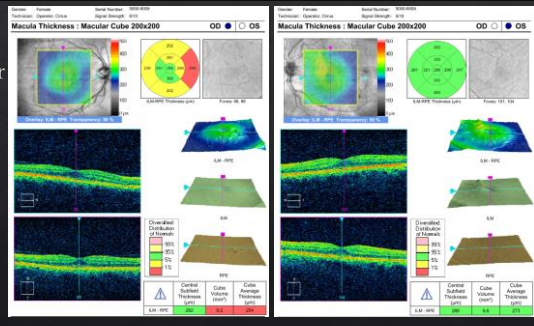
## 2 months later---no improvement



## BMP: baseline

Test Requested: VENT, BMP	result	reference range	site
test			
chemistry			(1)
SODIUM	145 mEq/L	135-145 mEq/L	
POTASSIUM	4.7 mEq/L	3.5-5.4 mEq/L	
CREATININE	1.02 mg/dL	0.6-1.05 mg/dL	
CARBON DIOXIDE	33 mmHg (High)	21-31 mmHg	
UREA NITROGEN	14 mg/dL	6-20 mg/dL	
GLUCOSE	105 mg/dL	65-100 mg/dL	
CALCIUM TOTAL	10.3 mg/dL	8.5-10.5 mg/dL	



2.5  
mo  
later

## BMP: post-eplerenone Tx

Test Requested: BMP, VENT	result	reference range	site
test			(1)
CHEMISTRY	142 mg/L	135-145 mg/L	
CODIUM	5.0 mg/L	3.5-5.4 mg/L	
POTASSIUM	101 mg/L	96-106 mg/L	
CHLORIDE	32 mg/L	21-31 mg/L	
CARBON DIOXIDE	15 mg/dL	6-20 mg/dL	
UREA NITROGEN	0.74 mg/dL	0.6-1.3 mg/dL	
CREATININE	118 mg/dL	65-108 mg/dL	
GLUCOSE	9.8 mg/dL	6.5-10.5 mg/dL	
CALCIUM TOTAL			

Stable!!!

## How effective is Eplerenone on CSCR?

- Reduced SRF within 1 month = 25-71%
- Reduced SRF within 3 months = 93%
- Complete resolution within 3 months = 64-67%

“It's relatively limited adverse effect profile and high selectivity and specificity (to the mineralocorticoid & glucocorticoid receptors) make eplerenone an ideal treatment modality for CSCR.”

Salz DA, et al. 2015 Opth Surg Lasers Imag Ret.

## New articles on eplerenone for CSCR!

	Total (n)	Full Resolution of SRF	Total Improvement?
Leisser et al. Eur J Ophthalmol. 2015	11	36.4%	73%
Singh et al. Int J Ophthalmol. 2015	17	35%	47%
Salz et al. Ophthalmic Surg Lasers. 2015	14	64%	93%
Cakir et al. Graefes Arch Oph. 2016	24	29%	62%
Kapoor et al. Ophthalmic Res. 2016	12	58.3%	83.4%
Schwartz et al. Acta Ophthalmol. 2017	13	23%	46.2%
Gergely et al. Retina. 2017	28	~30%	~55%
Rahimy et al. Retina. 2017	15	33%	73%
Zucchiattiet al. Opth Ther. 2018	15	80%	100%
Petkovsek et al. Br J Ophthalmol. 2020	100	31%	63%

Total (n)	Avg Full Resolution of SRF	Average Total Improvement
249	~42%	~70%

## Most recent meta-analysis I could find...

- Could only find 5 RCT's to use for analysis
- n=145 eyes
- Mineralocorticoid receptor antagonists (MRA) showed positive improvement in BCVA at 1 month and 2 months
- MRA also showed positive reduction in SRF at 1 month (~81 µm) and 2 months (~59 µm)
- No patient withdrew due to side effects
- Final thoughts: “Our findings suggest a modest benefit with MR antagonist therapy for CSCR patients in improving BCVA. We anticipate that MR antagonists will be well tolerated by most CSCR patients and that barriers to starting a trial of these medications in nonresolving CSCR should be low.”

Wang SK, et al. Mineralocorticoid receptor antagonists in central serous chorioretinopathy: a meta-analysis of randomized controlled trials. *Ophthalmol Retina*. 2019;3:154-169.

## Bottom Line..

- Consider Eplerenone in CSCR lasting >3-4 months
- Maybe in first line Tx???
- 25mg daily x 1 week then 50 mg PO daily for up to 3 months
- Tx lasted until resolution of fluid or 3 months of treatment
- Monitor serum potassium levels; co-manage with PCP
- Measure serum potassium levels q1-3 months
- Discontinue med if:
  - Kalemia increase of >5 mmol/L
  - Creatinine clearance rate decrease of <60 mL/minute
- Likely best avoided in patients with renal problems
- Monitor q4-6 weeks while on medication with OCT's

## New Direction...

### What is the cheapest prostaglandin?

- ✧ Latanoprost
- ✧ Travoprost
- ✧ Bimatoprost 0.03%
- ✧ Zioptan
- ✧ Lumigan 0.01%
- ✧ Travatan Z
- ✧ Vyzulta
- ✧ Rhopressa

### What is cheapest way to maximum meds for glaucoma?

- ✧ Latanoprost 0.005%
- ✧ Timolol 0.5%
- ✧ Dorzolamide 2%
- ✧ Levobunolol 0.5%
- ✧ Brinzolamide 1%
- ✧ Brimonidine 0.2%
- ✧ Pilocarpine 1%

### What is cheapest way to maximum meds for glaucoma with the least amount of drops?

- ✧ Latanoprost
- ✧ Dorzolamide/timolol
- ✧ Brimonidine/timolol
- ✧ Brimonidine/brinzolamide

### What is cheapest way to get separate steroid and antibiotic?

- ✧ FML 0.1%
- ✧ Dexamethasone 0.1%
- ✧ Pred Acetate 1%
- ✧ Polymyxin/TMP
- ✧ Tobramycin
- ✧ Ciprofloxacin
- ✧ Loteprednol 0.5%
- ✧ Gatifloxacin 0.5%
- ✧ Moxifloxacin 0.3%
- ✧ Besifloxacin 0.6%
- ✧ Ofloxacin 0.3%

### What is cheapest option for steroid and antibiotic combo?

Pred-G (brand)  
 Tobramycin/Dexamethasone  
 Tobramycin/Loteprednol (Zylet)  
 Neomycin/Polymyxin/Dexamethasone

### How about antiviral meds?

- ◊ Antivirals
  - ◊ Trifluridine
  - ◊ Zirgan
  - ◊ Acyclovir 400 mg
  - ◊ Valacyclovir 500 mg
  - ◊ Famciclovir 250 mg

### What about oral antibiotics?

- ◊ Oral Antibiotics
  - ◊ Amoxicillin/Clavulanic Acid 500/125 mg
  - ◊ Cephalexin 500 mg
  - ◊ Sulfamethoxazole/trimethoprim DS
  - ◊ Ciprofloxacin 500mg
  - ◊ Azithromycin (Z-pak)
  - ◊ Azithromycin 1000mg (single dose)
  - ◊ Doxycycline 100 mg

### Cheap Generics Available

Antihistamine	NSAID's	Oral ABs	Antiviral	Steroids
Loratadine	Naproxen	Cephalexin	Acyclovir	Prednisone
	Indomethacin	Amoxicillin	Valacyclovir	Dexamethasone
	Ibuprofen	Ciprofloxacin	Famciclovir	
	Meloxicam	SMZ/TMP		

Topical ABs	Glaucoma	Steroids	Combos
Gentamicin	Timolol	Triamcinolone	Maxitrol
Tobramycin	Levobunolol		
Polymyxin/TMP	Brimonidine		
	Dorzolamide		

**Additional Resource for Cheap Meds:**  
Borgman CJ. Many common conditions respond to inexpensive treatment options. *Primary Care Optometry News*. January 2015.

### Quick Side Note: OTC Allergy Drops

### OTC Anti-Allergy Drop Medication Options

Brand	Generic	Size	Cost	Cost/mL	Dosing	Duration
Zaditor	Ketotifen 0.035%	5 mL	\$11.96	\$2.39/mL	BID	~25 days
Alaway	Ketotifen 0.035%	10 mL	\$13.99	\$1.40/mL	BID	~50 days
Patanol	Olopatadine 0.1%	5 mL	\$15.99	\$3.20/mL	BID	~25 days
Pataday	Olopatadine 0.2%	2.5 mL	\$18.99	\$7.60/mL	QD	~25 days
Pazeo	Olopatadine 0.7%	2.5 mL	\$23.99	\$9.60/mL	QD	~25 days
Lastacast	Akafadine 0.25%	5 mL	\$23.99	\$4.80/mL	QD	~50 days

### My Approach: The Borgman Ranking Scale for OTC Allergy Eye Drops

1. Alaway → cheapest, lasts 50 days, BID dosing
2. Lastacast → next cheapest, lasts 50 days, QD dosing
3. Zaditor → next cheapest, lasts 25 days, BID dosing
4. Patanol → next cheapest, lasts 25 days, BID dosing
5. Pataday → next cheapest, lasts 25 days, QD dosing
6. Pazeo → most expensive, lasts 25 days, QD dosing

- Bottom Line:
- If cost is biggest barrier → Alaway!
- If once daily dosing is most important → Lastacast!

GoodRx  
Single Care  
Cost Plus Drug Company  
Amazon Pharmacy  
  
Others???

As mentioned before, I do not have any financial disclosures for anything mentioned in this lecture!

## Abilify & Blurry Vision?

### Aripiprazole (Abilify)

- ◆ Atypical antipsychotic medication
  - ◊ Schizophrenia
  - ◊ Schizoaffective disorder
  - ◊ Resistant depression
  - ◊ Bipolar disorder
  - ◊ OCD
- ◆ MOA's:
- ◆ Dopamine receptors (D2 & D3) → partial agonist
- ◆ Serotonin receptors (1A) → partial agonist
- ◆ Serotonin receptor (2A) → antagonist

aripiprazole

### Blurred Vision?

- ◆ 3 of 926 subjects (0.32% cases)
- ◆ **Transient increase in myopia**
- ◆ 8 cases reported in the literature
- ◆ How?
- ◆ The various mechanisms of drug-induced myopia reported in literature are:
  1. accommodation spasm
  2. ciliary spasm
  3. increase in thickness of the lens and peripheral uveal effusion
  4. ciliary body rotation and edema resulting in forward movement of iris lens diaphragm → acute myopia

• Nair AG, et al. Aripiprazole induced transient myopia: a case report and review of the literature. *Optom Vis Sci*. 2012;31:74-76.  
 • Karadag H, et al. Aripiprazole-induced acute transient bilateral myopia: a case report. *Russian Med J*. 2015;32:230-232.  
 • Kumar KVP, et al. Aripiprazole-induced transient myopia: a rare entity. *Indian J Ophthalmol*. 2018;66:130-1.  
 • Bulgin V, et al. Aripiprazole-induced acute transient bilateral myopia: a case report. *Bozga Eya J*. 2020;5:57-58.  
 • Cimmetci T, et al. Aripiprazole-induced transient myopia. *Merit Clin Invest*. 2020;7:516-518.

\* Sharif NA, et al. Serotonin-2 (5-HT2) receptor-mediated signal transduction in human ciliary muscle cells: role in ocular hypotension. *J Ocul Pharmacol Ther*. 2006;22:389-401.  
 \* Sharif NA. Serotonin-2 receptor agonists as novel ocular hypotensive agents and their cellular and molecular mechanisms of action. *Cell Physiol Toxicol*. 2010;11:978-993.

### Classic Case:

Kumar KVP, et al. *Indian J Ophthalmol*. 2018;66:130-1.

- ◆ Only 5 cases in the literature!
- ◆ 22 YO schizophrenic patient
- ◆ CC: "blurry distance vision"
- ◆ HPI: OD=OS, onset 3 days post Abilify initiation
- ◆ VA: 20/200 OD, 20/200 OS
- ◆ IOP: 14 OD, 16 OS
- ◆ Previous Rx: plano OU → 20/20 OU
- ◆ Post-Abilify Rx: -3.50 sph OU → 20/20 OU
- ◆ Tx → d/c Abilify, vision completely normal at 2 week followup



Kumar KVP, et al. Aripiprazole-induced transient myopia: a rare entity. *Indian J Ophthalmol*. 2018;66:130-1.

### Borgman's Theoretical MOA???

	Relative Abundance of 5HT Receptor Subtype mRNA Signals						
	5HT <sub>2A</sub>	5HT <sub>2B</sub>	5HT <sub>2C</sub>	5HT <sub>3</sub>	5HT <sub>4</sub>	5HT <sub>5</sub>	5HT <sub>6</sub>
Iris	+++	+++	--	+	+	++	+
Ciliary body	+++	+++	++	++	++	++	+++
b-TM cells	+++	+++	+	--	--	+	--

- ◆ Studies show:
  - ◆ Increased levels of serotonin → increased sympathetic innervation → mydriasis!
  - ◆ SSRI's and/or MAOI's
- ◆ Abilify (aripiprazole) is a serotonin receptor **blocker** (5-HT<sub>2A</sub> receptor)
- ◆ Decreased levels of serotonin → decreased sympathetic innervation → miosis & accomm
- ◆ **Increased myopia!**

Sharif NA, et al. RT-PCR mapping of serotonin receptor subtype mRNAs in human ciliary body and trabecular meshwork. *IOVS*. 2005 May;46:3688.

## Proof! I was correct!

- ◆ N=32
- ◆ Purpose: Does aripiprazole cause pupil size changes?
- ◆ Single dose of 10 mg aripiprazole
- ◆ **Pupils constrict with aripiprazole!**
  - ◆ Modest effect; 0.5-1.0 mm on average
- ◆ Pupil sizes effect coincided with maximum systemic/serum ARI concentration
  - ◆ 2-4 hours post-dose
- ◆ Refractive error & accommodation were not measured in this study
- ◆ MOA: unknown; believed to be secondary to serotonin receptor antagonism

Koller D, et al. Effects of aripiprazole on pupillometric parameters related to pharmacokinetics and pharmacogenetics after single oral administration to healthy subjects. *J Psychopharmacol*. 2018;32:1212-22.

## Phenylephrine & Risk of Increased Blood Pressure

*Is the fear justified???*

## Phenylephrine Review...

- ◆ Developed in 1933 from EPI
- ◆ **Potent vasoconstrictor → alpha-1 agonist**
  - ◆ No beta receptor activity at all
  - ◆ Dilation of pupil without cycloplegia
  - ◆ Negligible effect on IOP
- ◆ Maximum dilation = 15-90 minutes
- ◆ Maximum duration of action = 6-7 hrs
- ◆ Peripheral vasoconstriction can lead to rapidly elevated BP in some patients
  - ◆ Systolic and diastolic are affected

## Can PHE cause increased BP? How likely is this to happen if it does?

- ◆ First episodes of elevated BP from topical PHE were in 1956
- ◆ Some authors say: PHE has no effect on BP
- ◆ Some authors say: Mixed PHE-induced HTN responses
- ◆ Others yet say: definite increases in BP with topical PHE
- ◆ Mass confusion across the board...

## Phenylephrine-Induced HTN

- ◆ Widespread use; actual risk is likely lower than reported
  - ◆ Likely idiosyncratic responses
- ◆ Majority of cases are within **10-30 minutes** of instillation
- ◆ HTN effect is **transient**; 20-60 minutes duration
- ◆ HTN effects coincide with peak tissue and plasma levels
- ◆ 2.5% PHE ≈ 10% PHE with dilation
- ◆ Orthostatic hypotension pts at highest risk?
  - ◆ Denervation hypersensitivity?
- ◆ **Sn/Sx:**
  - HA
  - Tachycardia
  - Chest pain
  - Palpitations
  - Perspiration
  - Nausea/vomiting
  - SOB
  - Reflex bradycardia/hypotension
- ◆ **End-Organ Damage:**
  - SAH
  - Aneurysm rupture
  - \*Papilledema
  - Pulmonary edema
  - MI
  - CVA

## Worst Cases Reported In Literature...

- ◆ Cotton pledget soaked in 10% PHE and left on surgical eye
- ◆ More than one drop of 10% PHE
- ◆ PHE used in conjunction with Atropine
- ◆ Multiple rounds of PHE in peds/children

## 10% PHE Total Risk of Adverse Events

	Total (n)	10% PHE Severe	10% PHE Increased BP
Adults	1864	7.56% (n=141/1864)	14.70% (n=274/1864)
Pediatrics	44	11.36% (n=5/44)	84.09% (n=37/44)

## 2.5% PHE Total Risk of Adverse Events

	Total (n)	2.5% PHE Severe	2.5% PHE Increased BP
Adults	2210	0.18% (n=4/2210)	0.70% (n=15/2155)
Pediatrics	363	0.28% (n=1/363)	4.98% (n=12/241)

Note: numbers based on 80+ articles on HTN & PHE risk

What about # of drops and risk in **ADULTS**???

	Total (n)	Risk of causing increased blood pressure in adult patients
10% PHE---1 gtt OU	460	2.17% (n=10/460)
10% PHE---2 gtts OU	181	11.05% (n=20/181)
10% PHE---3+ gtts OU	761	26.81% (n=204/761)

	Total (n)	Risk of causing increased blood pressure in adult patients
2.5% PHE---1 gtt OU	767	0.65% (n=5/767)
2.5% PHE---2+ gtts OU	414	1.93% (n=8/414)

What about # of drops and risk in **PEDS**???

	Total (n)	Risk of causing increased blood pressure in pediatric patients
10% PHE---1 gtt OU	4	100% (n=4/4)
10% PHE---2 gtts OU	20	100% (n=20/20)
10% PHE---3+ gtts OU	20	65% (n=13/20)

	Total (n)	Risk of causing increased blood pressure in pediatric patients
2.5% PHE---1 gtt OU	31	0% (n=0/31)
2.5% PHE---2 gtts OU	0	Unable to quantify with available studies
2.5% PHE---3+gtts OU	211	7.11% (n=15/211)

## PHE Guidelines

- ✦ One drop of 2.5% PHE OU should be used without hesitation
  - ✦ <1% risk of elevated BP with one round of 2.5%
- ✦ 5-10% PHE is best reserved for stubborn posterior synechiae cases
  - ✦ If used, no more than one drop in each eye, or two drops total in single eye
- ✦ Do **NOT** use 5-10% in infants
  - ✦ Only use one drop of 2.5% PHE OU in select cases in peds
- ✦ **Borgman's Rule:** no more than 2 rounds of 2.5% PHE OU should be used at any one visit in adults regardless of BP

Original Investigation

## Cardiovascular Adverse Effects of Phenylephrine Eyedrops A Systematic Review and Meta-analysis

Bethany Stavert, BSc; Myra B. McGuinness, MSc; C. Alex Harper, MBBS; Robyn H. Guymer, PhD;  
Robert P. Finger, PhD

JAMA Ophthalmol. 2015;133:647-52.

- ✦ **Conclusion:** Phenylephrine, 2.5% leads to no clinically relevant change in BP or HR and can be considered safe to use in clinical routine. The changes in BP and HR seen with phenylephrine, 10% are short lived and of uncertain clinical relevance.

So.....is the fear justified???



Thanks!

- ◆ Questions? Accolades?
- ◆ [cborgman@sco.edu](mailto:cborgman@sco.edu)



SOUTHERN  
COLLEGE OF  
OPTOMETRY

- Complaints?
- [wmcgriff@sco.edu](mailto:wmcgriff@sco.edu)

