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

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SOUTHERN COLLEGE OF OPTOMETRY

Disclosures:

I have no disclosures to report.

Ground Rules…

- References/sources available if you want them…
- I'm not perfect…
- Please email me with questions:
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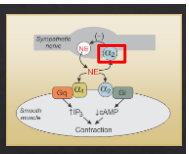
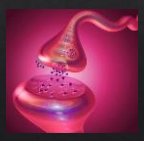
Alphagan (Brimonidine) & Pupillary Miosis???

Brimonidine (Alphagan-P)

- A highly specific α-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

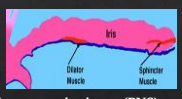




McDonald et al, J Cataract Surg 2001, 27:560-564

The Scotopic Miosis

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

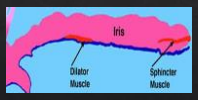


- Tonus of the cholinergic driven sphincter remains intact (PNS)
- Dilator (SNS controlled) is relaxed in the presence of the alpha-2 agonist
- Therefore, the sphincter has increased control over pupil size

→ the balance has shifted to PNS → Smaller pupil

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/haloes/starbursts in dark/scotopic conditions
  - Driving, movies, etc.
- MOA: Pupil size is ≥ 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

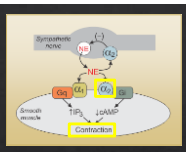
Wouldn't Pilocarpine work too?

	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
- Just completed Phase 3 trials (Bausch & Lomb)
- No rebound hyperemia with discontinuation
- No tachyphylaxis noted
- Onset within 5 minutes
- Seems to work on smaller caliber conjunctival vessels without affecting larger vessels so blood flow is not affected
- Duration of effect ~4 hrs

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 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

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. Ventricoloperitoneal 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

Alster PL, Jay WM, Macken MP. Topiramate, pseudotumor cerebri, weight-loss and glaucoma: an ophthalmologic perspective. Sem Ophthalmol. 2006;21:15-17.

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

Topiramate MOA:

- All sulfa derived drugs can induce myopic shift & acute angle closure by increasing osmotic status of the tissues → H2O 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

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

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

antagonist

Blurred Vision?

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

Borgman's Theoretical MOA???

- Studies show:
  - Increased levels of serotonin → increased sympathetic innervation → mydriasis!
  - SSRI's and/or MAOI's
- Abilify (aripiprazole) is a serotonin receptor blocker (5-HT2A receptor)
- Decreased levels of serotonin → decreased sympathetic innervation → miosis & accomm
- **Increased myopia!**

Topical Timolol & Superior Oblique Myokymia

Dx = Superior Oblique Myokymia

- First reported in 1906 by Duane "unilateral rotary nystagmus"
- In 1970, Hoyt coined term "superior oblique myokymia"
- Defn: monocular quivering/firing of superior oblique
- Sx: spontaneous monocular diplopia, quivering/jumping of vision, monocular oscillopsia, key is *monocular* nature
- Sn: low amplitude, high frequency intorsion of affected eye, intermittent/cyclic frequency, worse when looking down and in towards nose
- Most attacks last between 3-15 sec, rare cases of indefinite attacks

SOM Tx Options

- Observation
- Medical
  - Oral medications
- Surgical
  - EOM/Strab surgery
  - Microvascular decompression

New Tx? Topical Beta-blockers???

- Bibby et al. (1994) showed one case report of a patient's SOM Sx being relieved with betaxolol glaucoma drops
  - Based off of case reports which used oral propranolol
  - Weak membrane stabilizing abilities of beta blockers = MOA
- MOA: hypothesized that enough drug was absorbed ***systemically*** through conjunctival blood vessels to elicit its effect (systemic theory)

30 YO WF with SOM x 10 yrs

- Started topical timolol 0.5% drops BID OD!
- Patient reported 100% resolution of Sx after only **2 days** of use!!!!
- Phone call 4 months later, still 100% resolution of Sx but only using drops QAM OD
- 12+ month later….still Sx-free on drops!

Story doesn't end here…

- Given that numbers of SOM are low to begin with……cases reports of ***topical*** beta-blockers providing relief of Sx are even rarer
- Bibby et al……hypothesized "systemic theory"
- I developed my own theory……
- Chris Borgman's "Localized Theory"

CB's "Localized Theory"

- In SOM, when successfully treated with topical beta-blockers, the effect occurs *locally* at the trochlear nerve endings themselves and/or on the trochlear muscle itself, not systemically absorbed via the conjunctival blood vessels.
- I would argue *AGAINST* Bibby's *systemic* absorption theory.

Proof of Localized Theory

- After successful Tx for 2+ months…
- Patient instructed to stop all drops
  - Sx returned to pre-treatment severity in 2-3 days
- Patient instructed to instill drops in contralateral eye
  - No effect, Sx still remained
- Patient told to re-start drops in original/affected eye
  - Sx disappeared in 1-2 days of use again
  - No recurrences since

What does this mean?

- Keep in mind…..this is only 1 case.
- Beta-blockers work locally on the ocular tissues themselves
  - Likely on superior oblique muscle itself or the trochlear nerve endings
- Perhaps not on a systemic level like Bibby et al. hypothesized…
- "Localized theory" holds water!
  - However, still unproven…needs more research

Interesting Potential Off-Label Uses of β-Blockers???

1. Superior Oblique Myokymia →

Borgman CJ. Topical timolol in the treatment of monocular oscillopsia secondary to superior oblique myokymia: a review. J Optom. 2014;7:68-74.

2. Eyelid Myokymia →

MOA: stabilization of membrane excitability/resting state of action potential (phase 4) →

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**

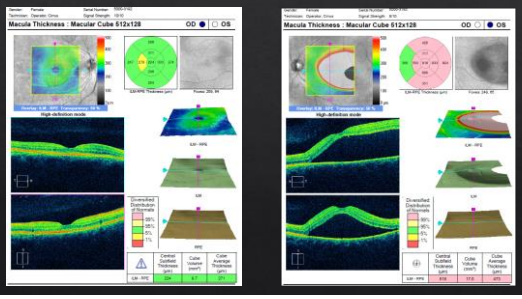
Mineralcorticoid Receptor

- 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

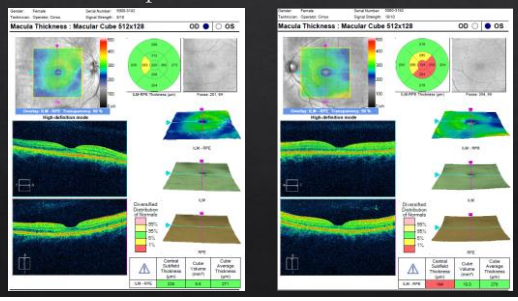
Eplerenone vs. Spironolactone

- Both are mineralcorticoid receptor blockers!
- Both are postassium-sparing diuretics!
  - Risk of hyperkalemia
- Eplenerone has 10-20x lower affinity for MR than spironolactone
- However, eplerenone has a much higher specificity for MR without antiandrogen SE's
- Eplenerone is best choice with the least probably SE's at this time between the two.

Case: 47 Year old HF w/ chronic CSR



Eplerenone: 6 weeks later



How effective is Eplerenone on CSCR?

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

- *"It's relatively limited adverse effect profile and high selectivity and specificity (to the mineralcorticoid & glucocorticoid receptors) make eplerenone an ideal treatment modality for CSCR."*
  - Salz DA, et al. 2015 Ophth Surg Lasers Imag Ret.

Bottom Line..

- **Consider Eplerenone in CSCR lasting >3-4 months**
- 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 monthly
  - 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 cheapest way to maximum meds for glaucoma?

- Latanoprost → $14.88
- Timolol 0.5% → $4.00
- Brimonidine 0.2% → $9.90

TOTAL: **$28.78/month**

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

- Latanoprost → $14.88
- Dorzolamide/Timolol (2%/0.5%) → $23.53

TOTAL: **$38.41/month**

What is cheapest way to get separate steroid and antibiotic?

- FML 0.1% → $34.06
- Pred Acetate 1% → $29.63
- Dexamethasone 0.1% → $23.00
- Tobramycin → $4.00
- Polymyxin/TMP → $4.00

} TOTAL: **$27.00/month**

What is cheapest option for steroid and antibiotic combo?

- Pred-G (brand) → $126.51
- Tobramycin/Dexamethasone → $55.54
- Tobramycin/Loteprednol (Zylet) → $210.28
- Neomycin/Polymyxin/Dexamethasone → $4.00 → TOTAL: **$4.00/month**

$4 List of Generics Available

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

Topical ABx	Glaucoma	Steroids	Combos
Gentamicin	Timolol	Triamcinolone	Maxitrol
Tobramycin	Levobunolol		
Polymyxin/TMP			

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

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
  - Neglible 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…

- 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**

Questions???

- Thank you!
- cborgman@sco.edu

SOUTHERN COLLEGE OF OPTOMETRY