Glaucoma Pharmacology: Old, New and What to Do?

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Despite all of the new knowledge in glaucoma pathophysiology and all of the new therapies under study, our only therapeutic option currently available is intraocular pressure reduction.

I. Prostaglandin Analogs (and Prostaglandin-like Medications)

- Mechanism of Action (MOA): Prostaglandin analogs (PGAs) are chemical mediators of inflammation which reduce IOP by increasing uveoscleral outflow (unconventional pathway as opposed to trabecular meshwork which is the conventional pathway)
  - Possibly a small component of increased trabecular outflow as well- controversial
- PGAs: revolutionary in glaucoma management- primary therapy
  - Advent of PGAs has caused reduction in glaucoma surgeries performed due to efficacy
- Latanoprost 0.005%; travoprost 0.004%; bimatoprost 0.01%; tafluprost 0.0015%; latanoprostene bunod 0.024%
- Dosing QD HS
- *Teal color caps*
- Excellent IOP reduction at night.
  - One of the few meds that have been shown to reduce IOP at night when IOP is typically highest
- Independent of episcleral venous pressure (drug of choice in glaucoma secondary to idiopathic elevated episcleral venous pressure, Sturge-Weber syndrome (which has elevated episcleral venous pressure due to AV malformations), and carotid cavernous fistula and dural arteriovenous shunt/malformation within the cavernous sinus).
- Ocular adverse and side effects: hyperemia, punctate keratopathy, increased eyelash and nose hair growth, blurred vision, dry eye, increased iris coloration, anterior chamber cells/flare (anecdotal evidence of uveitis). Unilateral usage should be used with caution due adverse effects
  - Periorbitopathy- may not be reversible with medication cessation
    - Periorbital skin darkening
      - Similar to increased iris coloration
      - Can possibly be avoided by immediately drying skin
    - Deepening of ocular sulcus
      - Gives pseudo-enophthalmos appearance
      - Likely due to periorbital fat atrophy
  - Anecdotal evidence of cystoid macular edema (CME) in aphakes and pseudophakes (with open/ broken posterior capsule). Prostaglandins been associated with pseudodendritic keratopathy as well as inducing recurrence of herpes simplex dendritic ulcers.
    - Anecdotal evidence at best (*however, I personally have caused CME, uveitis, and bilateral dendritic keratitis*)

- About 10-20% of population does not respond (probably overestimated). For those that do respond, IOP reduction can be dramatic.
  - Any patient not responding at all to PGAs should immediately be suspected of being non-compliant
- Systemic side effects: virtually none
- Systemic contraindications: none besides possibly pregnancy and being a child (pre-puberty-safe but no real effect)
- Prostaglandins are lesser choices in secondary inflammatory glaucoma or any clinical entity that has anterior segment inflammation as a primary component
  - PGAs have long been feared due to the potential to increase inflammation. In reality, they have not been shown to worsen inflammation and do lower IOP in eyes with inflammatory glaucoma. Thus, PGAs can be used in cases of inflammation, but perhaps as a lesser choice or used cautiously.
- Onset of action is generally considered too slow to use in acute situations.

Clinical Pearl: Prostaglandins are important in that they flatten the diurnal IOP curve as well as giving lingering IOP reduction even as much as 60 hours after dosing. Thus, they are more forgiving of patients that miss dosages.

Clinical Pearl: The most commonly encountered adverse effects from prostaglandin usage are hyperemia, eyelash growth, deepening of the ocular sulcus, and periorbital skin darkening. Hyperemia is reversible with medication cessation. Iris color changes appear to be irreversible. Periorbitopathy may be reversible if the medication is stopped soon enough but may indeed be permanent. Everything else likely is reversible.

Latanoprost 0.005%

- Trade name Xalatan- most popular generic
  - Preserved with benzalkonium chloride (BAK)
- Mean IOP reduction: 27-33.7%
  - Can sometimes exceed 50%, depending upon the initial IOP level
- Latanoprost is very oculoselective
- Peak action: 8-12 hours after instillation
- Should be refrigerated in storage, but for clinical usage, refrigeration may not be necessary. Shouldn't be exposed to high temperature or intense light
- Half-life is 17 minutes, thus rapid local absorption and very low degree of systemic effects
- Initial short-term response to latanoprost is likely due to PF-2 receptor stimulation. Later response may be due to latanoprost changing the ground substance in the cellular matrix of the ciliary meshwork- speculative.
- Long term IOP control is excellent with latanoprost and may be better than other meds, even if patients miss dosages.
  - Xalatan is as effective at 24 hours as at 4 hours.
- Xelpros (latanoprost ophthalmic emulsion) 0.005% is a formulation of latanoprost that does not contain the common preservative benzalkonium chloride (BAK). Potassium sorbate 0.47% is added as a preservative.

Clinical Pearl: Don't be confused about PGAs- their half-life is very short, but their duration of action is very long.

Travoprost 0.004%:

- Trade name: Travatan Z (preserved with SofZia- gentle ionic buffering system)
- New bottle design
  - No streaming
  - Smaller drop size
  - More drops/bottle
- Refrigeration not required
- Full FP agonist
- Sustained 30% IOP reduction at all times tested
- 7 – 8 mm Hg reduction over full diurnal
- No significant drift over time
- 56% have IOP reduction > 30% or IOP < 17 mm Hg
- QD dosing
- Peak activity 20 hrs post dose
- Excellent safety profile – well tolerated
- Original Travoprost 0.004 (BAK preserved) now available generically
    - Travatan Z is preserved with Sofzia, which is gentler to the ocular surface than BAK in previous iteration

Clinical Pearl: It takes about 2 weeks to see the full IOP lowering effect of Travatan.

Bimatoprost 0.01%:

- Trade name: Lumigan
- Technically a hypotensive lipid- Different receptors; still considered a PGA
  - Synthetic prostamide technically
  - Occurs naturally in ocular tissues
  - Regulates aqueous flow and IOP
- Strong IOP lowering activity
- Well tolerated by patients
- Lumigan QD PM most effective dosing
- Lumigan is the prostaglandin most likely to cause hyperemia, likely due to the FP receptors that it stimulates.
    - Again, somewhat anecdotal and is still very well tolerated
- Lumigan 0.01% has replaced original 0.03% concentration (which is still used and marketed as Latisse for eyelash growth).
    - Said to be as efficacious as Lumigan 0.03%, but with lesser hyperemia
    - Increased concentration of preservative (BAK)
        - 'Roughens up' the epithelium to enhance corneal penetration.
        - Generic bimatoprost 0.03% is now available- not commonly used

Clinical Pearl: IOP lowering effects of Lumigan are appreciated very fast, usually within a few days.

Clinical Pearl: Lumigan (bimatoprost 0.03%) is the exact same drug as Latisse for eye lash growth. Only difference is the label.

Tafluprost 0.0015%

- Trade name: Zioptan
- Hyperemia 4.4%
- 6-8 mm Hg IOP reduction/ 30% reduction
- Only preservative-free PGA
- Unit dose vials like artificial tears
    - 6-8 drops/vial- Done to account for spillage
    - Likely will result in patients re-using daily vial
    - Not recommended to do this because of no preservative, but patients will anyway
    - The vials re-seal, so it will be difficult to prevent patients from re-using vials

Vyzulta™ (latanoprostene bunod ophthalmic solution, 0.024%)

- First prostaglandin analog with one of its metabolites being nitric oxide (NO)
- QD dosing
- Nitric oxide donating PGA
    - Nitric oxide is a gas so in order to be given topically, it must be attached to another molecule
- Dual mechanism of action
    - Metabolizes into two moieties, latanoprost acid, which primarily works within the uveoscleral pathway to increase aqueous humor outflow, and butanediol mononitrate, which releases NO to increase outflow through the trabecular meshwork and Schlemm's canal.
- Nitric oxide (NO) was first discovered as a signaling mediator involved the cardiovascular system. Nitric-oxide synthase (iNOS, NOS-2) is present in astrocytes of optic nerve heads from glaucomatous eyes of humans and is increased in the trabecular meshwork (TM) with elevated perfusion pressure in vitro.
- NO induction increases outflow facility in nonhuman primates, with additional cellular targets in the TM and Schlemm’s canal; the process alters the cytoskeletal network and cell adhesion system of the cells of the conventional outflow pathway. This leads to relaxation of the TM and the inner wall of Schlemm canal.
- NO relaxes the TM by inhibiting the action of the enzyme Rho Kinase as well as suppressing calcium activation and influx.
- Schlemm’s canal releases nitric oxide to keep TM pliable and properly processing aqueous.
    - Pts with glaucoma have less nitric oxide being produced by Schlemm’s canal.
- Clinical trials have shown Vyzulta to have greater IOP reduction than latanoprost with similar side effect profile.
    - Well tolerated
    - About 1.2 mm more IOP lowering than latanoprost.

    - Has shown very impressive results when used in eyes with lower baseline IOP
- Approved 11/2/17

Clinical Pearl: Many drugs promote the fact that they increase ocular blood flow. This is nearly meaningless. Any medication that reduces IOP will increase perfusion by reducing blood flow impedance. Further, these studies are all in normal patients or animal models that likely have little bearing on glaucomatous patients.

Clinical Pearl: Every prostaglandin analog and prostaglandin-like drug have the same potential adverse effects and contraindications.

Clinical Pearl: Use prostaglandins cautiously in patients with known previous outbreaks of herpes simplex keratitis.

Clinical Pearl: Exercise care when using prostaglandins in cases of uveitis.

Clinical Pearl: Prostaglandins are the drug of choice in IOP rise secondary to carotid cavernous sinus fistula and other cases where the episcleral venous pressure is elevated.

Clinical Pearl: Hyperemia from prostaglandin use is not an allergic reaction, but a response to the prostaglandin, which mitigates inflammation.

Clinical Pearl: Due to chemical differences, each prostaglandin behaves differently. If a prostaglandin reduces IOP, but causes unacceptable redness, try another prostaglandin. Further, if the desired IOP reduction is not optimal with one prostaglandin, try another. Caveat- don't expect dramatic pressure reductions from switching prostaglandins. For example, if IOP is reduced to 18 mm Hg with a one prostaglandin and your target is 15 mm Hg, then switching prostaglandins may work. Don't expect much more.

Clinical Pearl: While uveitis and cystoid macular edema (CME) have occurred from prostaglandins usage (notably in patients who have had previous bouts of uveitis and CME), these side effects are unlikely to occur in a previously normal patient. PGAs are often temporarily stopped prior to and subsequent to cataract surgery to reduce risk of CME.

Clinical Pearl: Travoprost, bimatoprost, and latanoprost account for the vast majority of prescriptions for glaucoma written today, with generic latanoprost by far the most prescribed.

Clinical Pearl: PGAs are considered the medication class that best reduces IOP during the diurnal sleep cycle when patients are supine.

Clinical Pearl: It takes about 3-5 weeks to appreciate the full pressure lowering effects of PGAs. Don't check IOP too early after starting therapy.

II. Autonomic Glaucoma Medications
Effects are based upon actions on alpha and beta receptors

1. Sympathetic Agents

- Adrenergic agonists (beta and alpha agonists)
  - Sympathomimetic
    - Norepinephrine based
- Adrenergic antagonist (beta blockers)
  - Sympatholytic

2. Parasympathetic Agents

- Parasympathomimetics
- Cholinergic agonists
- Acetylcholine based

Sympathetic System

- Alpha 1
  - Blood vessels of ciliary body: vasoconstriction, which reduces blood flow and subsequently aqueous production.
    - Epinephrine-like drugs (propine)- not used any longer
- Alpha 2
  - Nerve terminal
    - Stimulation results in diminished release of norepinephrine
      - Stimulation here result in *decrease* in norepinephrine release, thus a reduction in sympathetic tone and reduction in aqueous production
      - Alpha-2 adrenergic agonist (apraclonidine and brimonidine)
- Beta 1
  - Receptors on heart: increased activity
- Beta 2
  - Receptors on lungs: relaxed- increased breathing ability
- Beta 1 & 2 on ciliary body
  - Stimulation increases aqueous production
    - Blocking B1 & 2 receptors reduces aqueous production- Beta blockers

Ocular Parasympathetic receptors

- Iris: miosis
- Ciliary body: accommodation and trabecular meshwork opening
- Trabecular meshwork: aqueous outflow increase- main mechanism of action
- Ciliary meshwork (uveal meshwork-uveoscleral pathway)- aqueous outflow decrease

Systemic Parasympathetics

- Glands: increased activity
- Heart: reduced activity
- Blood vessels: vasodilation
- Lung: bronchiole constriction
  - Because these organs are more controlled by the sympathetic system, there is less systemic affects by parasympathomimetic drugs than would be expected.
- Gastrointestinal tract: increased motility
- Urinary tract: increased motility
- Stimulation of parasympathetic system often results in increased sweating, bradycardia and syncope, vomiting, and incontinence. You will likely see these reactions when a patient undergoes vasovagal syncope from over stimulation of the vagus nerve. This can result from everting an eyelid or instilling medications into an eye. True anaphylaxis is extremely rare with ocular medications. If a patient has a medical situation following diagnostic medication instillation, consider vasovagal syncope as the cause.

Adrenergic Agonists:

Adrenergic Agonists: Apraclonidine 1% & 0.5%

- MOA: Alpha-2 agonist: acts presynaptically to inhibit release of norepinephrine and reduces adrenergic receptor stimulation. The reduced sympathetic activity in ciliary body reduces aqueous production. Inflow reduction/ aqueous suppressant. There is also a small component of increased uveoscleral outflow as identified through fluorometry studies.
- Iopidine 0.5% (ophthalmic bottle), 1% (single use containers designed for laser procedures)
  - 1% approved and used during laser surgery (trabeculoplasty, iridoplasty, capsulotomy) to prevent IOP spike
    - Has been used for acute angle closure (off label)
  - 0.5% concentration- used for POAG management
    - TID dosing
    - Initially was not viewed for long-term treatment (beyond 3 mos) due to tachyphylaxis.
    - 20-30% incidence of allergic ocular reactions requiring discontinuation.
    - Best use today is to confirm a diagnosis of Horner's syndrome (due to weak alpha 1 agonism).

Clinical Pearl: Apraclonidine is virtually never used in modern glaucoma chronic therapy but has use in acute situations and testing for Horner's syndrome.

Adrenergic Agonists: Brimonidine tartrate (Alphagan)

- MOA: Alpha-2 agonist: acts presynaptically to inhibit release of norepinephrine and reduces adrenergic receptor stimulation. The reduced sympathetic activity in ciliary body reduces aqueous production. Inflow reduction/ aqueous suppressant. There is also a small component of increased uveoscleral outflow as identified through fluorometry studies.
- Alphagan 0.2% (available only generically now)

- Alphagan P
  - Brimonidine tartrate 0.15% (generic) and 0.1% (Trade) preserved with Purite®
  - Comparable effectiveness to Alphagan 0.2%
  - Reduced (by 40%) incidence of local toxic adverse effects (but does not obviate the alphagan allergy which is a component of the base product and not the preservatives).
  - Does not affect headache, somnolence or other problems associated with the medication, not the vehicle
- 30-fold more selective for alpha 2 receptors than apraclonidine
- Decreases aqueous production (and *possibly* increasing uveoscleral outflow- not a big component of action and this should be considered an aqueous suppressant)
  - Selective alpha-2 agonist
    - Seems to work via inhibition, thus lesser effects on heart and blood pressure as seen with sympathomimetics
- IOP reduction of approximately 4-6 mm hg (25-30%)
- TID dosing by FDA approval
  - Often used initially BID.
    - BID dosing can leave the patient with uncontrolled IOP at certain times of the day.
      - This is significant for monotherapy
      - Patients on polytherapy may be able to get away with BID dosing
- *Purple cap*
- Approximately 7% of patients have toxic allergic responses that require discontinuation of the drug
  - Allergic response can come after weeks, months or years
- The most significant side effects are drowsiness and fatigue, headache, and dry mouth
  - Crosses blood-brain barrier
  - These effects are most significant in smaller patients and children
  - This medication has induced fatigue, drowsiness and even coma in children
- Other side effects: conjunctivitis, blurring, burning
- There are some vasoconstriction effects in 20% of patients
- No effect on blood pressure, pulse, or pulmonary function
- Minimal cardiovascular and pulmonary responses- not frankly contraindicated in patients with cardiovascular disease, but use caution in patients with ischemic heart disease or prior MI
- Concurrent use of MAO inhibitors (anti-depressants) are a strict contraindication to the use of Alphagan
- Has been said to have a neuro-protective effect. Totally speculative and unproven.
  - At this point, Alphagan is not proven to be nor is considered to be neuroprotective. It is irresponsible to use this medication for any perceived neuroprotective effects
- This is currently a popular and important medication (both as primary and adjunctive therapy)
- Does not appear to have IOP lowering effects at night/during sleep

Clinical Pearl: Alphagan is a more popular alpha 2 agonist than Iopidine and is one of the most popular glaucoma medications in use.

Clinical Pearl: Do not use Alphagan in children (especially under age 8 years). It is unsafe

Clinical Pearl: No currently approved medication has been proven to be neuroprotective. You should not use any medication for this reason.

Clinical Pearl: Patients can have a late-onset Alphagan allergy months or years after starting therapy.

Clinical Pearl: It has been shown that patients using brimonidine are four-times more likely to not leave their homes.

Beta Antagonists (Blockers):

- All forms block norepinephrine and thus blocks aqueous formation- considered aqueous suppressants
- May be selective
  - Beta 1 specific (blocks only beta 1 receptors)
  - Most are non-specific and block both beta 1 and beta 2
- Reduced sympathetic activity
- Aqueous suppressant
- *Yellow cap (0.5%) or light blue cap (0.25%)*
- Bilateral effects when using in only one eye due to systemic absorption
- Does not appear to have IOP lowering effects at night/ during sleep
- Short term escape
  - After an initial decrease in IOP from several days to weeks, a rise in IOP will occur. After an additional 2-4 weeks, the IOP will stabilize, often below pre-treatment levels.
- Long term drift
  - A slow steady rise in IOP after months to years of treatment.
  - Medications become ineffective
    - Common problem with beta blockers

Beta Blockers: Adverse Effects

- Ocular allergic reactions (generally insignificant magnitude, but may necessitate discontinuation of the medication)
  - Burning/stinging
  - Hyperemia
  - Punctate keratitis
  - Corneal hypoesthesia
- BP decrease (beta 1)
- Bradycardia (beta 1)
- Pulmonary bronchiole contraction (beta 2)

- Depression
- Confusion
- Anxiety
- Fatigue
- Malaise
- Irritability
- Somnolence
- Confusion
- Death
  - Deaths from topical beta blocker use have been reported in the literature
- Syncope
- Palpitations
- Impotence
  - Though accepted as fact by many practitioners, there is scant evidence from placebo-controlled trials to link systemic beta blocker therapy with sexual dysfunction. There appears to be no reason to withhold topical beta blocker therapy in patients for fear of inducing sexual dysfunction, even if they have a pre-existing history.
- Diarrhea, nausea, cramps
- Altered lipid profiles
  - Decreased high density lipoproteins
  - Increased triglyceride levels
- Depression has been reported, but there is no reason to expect that topical beta blocker therapy will induce depression in an otherwise normal individual. However, the impact of beta blockers in patients that already suffer from depression is presently unknown.
- Most of the above-mentioned effects are anecdotal cases or case series. Very few controlled studies have been performed to identify true adverse reactions and contraindications.

Beta Blockers: Contraindications

- Bradycardia: Beta blockade can result in slowing of sinus nodal discharge with resultant dose-dependent bradycardia. In most cases, the degree of bradycardia is asymptomatic and does not impact a patient's life.
  - Patients using topical beta blockers who develop symptomatic bradycardia -- as manifested by diminished capacity for physical activity or undiagnosed syncope -- likely have coexistent pathology of the sinus AV node or conduction pathways and should be referred to a cardiologist.
  - Beta blocker therapy can be implemented in a patient with an implanted pacemaker following approval from the treating cardiologist.
  - Topical beta blocker therapy should be avoided in patients with asymptomatic bradycardia and heart block. Patients with symptomatic bradycardia often present with syncope and dizziness and are identified prior to ophthalmic examination.
  - Asymptomatic patients without aerobic conditioning (i.e., athletes) with resting pulse rate under 55 beats per minute should be evaluated by a cardiologist. However, patients with normal resting pulse rates and with no history of syncope or dizziness are unlikely to experience any serious bradycardia effects from topical beta blockers.

- COPD
- Asthma
- Emphysema
- Myasthenia gravis
  - Can worsen myasthenia gravis
- Cerebrovascular insufficiency
- Greater than 1st degree heart block
- Hypotension (<100/60)
- Beta blockers are bad for athletes as it prevents heart rate from exceeding 135 BPM. Athletes cannot train through this block.
- Every patient considered for a topical beta blocker needs baseline blood pressure and resting pulse measurement in addition to review of medical history.
- Can be used even if the patient is on systemic beta blockers for hypertension
  - However, systemic beta blockers reduce effectivity of topical beta blockers
  - Those on both forms experienced a greater degree of bradycardia
  - Physician approval should be obtained before prescribing topical form with oral form

Beta Blocker Controversies: Congestive Heart Failure and Diabetes

- Congestive heart failure (CHF) has long been a contraindication to the use of topical and systemic beta blockers. Possibly, this warning came from the theoretical potential for beta blockers to reduce cardiac contractility and therefore worsen cardiac output.
  - Currently, it is accepted that beta blockade benefits patients with CHF and reduces mortality. Reduced resistance to ejection improves cardiac output.
  - Beta blockers also function as anti-arrhythmics, likely by inhibiting cardiac sympathetic stimulation, thus reducing sudden death from arrhythmia.
  - In contrast to early concerns, beta blockade is now a well-accepted therapy for patients with stable class II-III CHF
- There is at present no conclusive evidence-based information regarding the effects of topical beta blocker therapy on the intrinsic recovery of plasma glucose levels in patients with diabetes. It may be that patients requiring insulin in an advanced stage of diabetic disease may be at greater risk from beta blocker-induced prolongation of hypoglycemia. However, topical beta blockers are quite safe for the vast majority of diabetic patients.

Clinical Pearl: Beta blocker contraindications are somewhat controvertible. The most significant contraindications are COPD, asthma, emphysema, symptomatic bradycardia, and asymptomatic bradycardia with heart block. Beta blockers can be considered in patients with CHF pending approval by the patient's PCP. All other contraindications can be considered 'relative' and beta blockers can be used in many of these situations on a case-by-case basis. However, if a 'contraindication' is present, it doesn't mean that beta blockers (or any medication for that matter) cannot be used, but should be a lesser choice.

Timolol maleate

- Timoptic (Trade- original name)
  0.25% (light blue cap)

0.50% (yellow cap)
    - Ocudose- non-preserved in unit dose vials
        - Only non-preserved beta blocker, but at $475/month, not widely accepted for clinical use
- BID dosing
- Beta 1 & 2 blocker (non-selective)
- 25-30% decrease in IOP
- Timoptic XE (GFS- gel-forming solution): forms a gel for better contact and penetration. Same concentrations, but is designed to be used QD. However, new understanding of diurnal pressure variations make QD AM dosing suspect
    - 0.25%, 0.5% concentration in gelrite
    - Longer corneal contact time
    - AM dosing preferred
    - Can cause transiently blurred vision
    - Same cap colors as solution
    - Reduced systemic absorption with reduced systemic adverse effects
    - Generic
    - Does not give any IOP reduction overnight
- Istalol: timolol maleate 0.5%: brand only- QD FDA dosing approval- no better than generic and costs $170/month

Clinical Pearl: Beta blockers are still popular glaucoma medications and timolol is the most popular beta blocker.

Other Beta Blockers
- Timolol hemihydrates (Betimol 0.25% and 0.5%) - generic. BID
- Levobunolol (Betagan). Only available as generic 0.25% (blue cap) and 0.5% (yellow cap); BID

Betaxolol
- Betoptic S (Original name) 0.25% suspension – light *blue cap*
- Beta 1 selective- partial beta blocker
- Pulmonary friendly (but not perfect)
    - May still exacerbate asthma- caution required
- Affects heart as does previous beta blockers
- Weaker than previous beta blockers
- BID dosing
- May have action to increase optic nerve perfusion and is favored by many practitioners for this reason- controversial
    - May exhibit calcium channel blocking activity through a secondary receptor stimulus and thus may be neuroprotective. Absolutely unproven

Carteolol 1%

- Ocupress (original name)- Generic only
- Has intrinsic sympathomimetic activity (ISA) and transient agonist activity and is the beta blocker least likely to cause bradycardia even though it is non-selective. There remains some agonal tone, which allows for more normal cardiac rhythm. There appears to be incomplete beta 2 receptor blockages. Less likely (of non-selective beta blockers) to cause bronchospasm and bradycardia.
- Less dyslipidemia
- BID dosing
- *Yellow cap*

Clinical Pearl: Beta blockers work well and are generally safe in children. Beta blockers tend not to work well in cases of uveitic glaucoma.

Clinical Pearl: Beta-blockers should not be dosed at bedtime for two reasons. Some patients have nocturnal hypotension and this may lower blood pressure further. Also, aqueous formation decreases in the evening during sleep and topical beta-blockers have less effect. Beta blockers appear to have no IOP lowering effect at night/ during sleep.

Clinical Pearl: A month supply of generic timolol is about $7.00. It's hard to argue with that.

Parasympathetic Agents (Miotics): Pilocarpine

- MOA: Increases outflow of aqueous through trabecular meshwork (conventional pathway). Tends to decrease outflow through uveoscleral pathway (unconventional pathway).
- Direct acting cholinergic agonist
- Miotic
- Ciliary body contraction
- Accommodation- myopic shift
- Cholinesterase independent
- 4-8 hrs IOP effect
  - QID dosing
  - Very unfriendly dosing schedule
  - Possibly can be done BID if part of poly-therapy
- Oldest anti-glaucoma medication
- Generic and inexpensive
- Effects on IOP at night are unknown
- 1%, 2%, 4% are only concentrations available today commonly used
- *Dark green cap*
- 4% Pilopine Gel HS: side effects occur during sleep and may be better tolerated

Pilocarpine: Ocular Adverse Effects

- Miosis
- Brow ache: ciliary body (CB) contraction

- Globe and orbital pain
- Allergic reactions
- Increased myopia due to accommodative spasm
- Vision reduction: especially with cataracts
- Posterior synechiae in some cases
- Retinal detachment: Ciliary body contraction- not common, but be aware of the potential
- Angle closure: Due to pupil block with a changing cataractous lens
- Field constriction

Miotics: Relative Contraindications

- Uveitic glaucoma
  - Any significant ocular inflammation
- Neovascular glaucoma
- Aphakia (relative contraindication)
- Retinal breaks, retinal detachment
- Posterior subcapsular cataract present
- Pre-presbyopia
  - Not well tolerated

Pilocarpine: Potential Systemic Effects

• Arrhythmia	• Bradycardia
• Sweats and salivation	• Slight respiration decrease
• Nausea	• Headache
• Diarrhea	• Vomiting
• Hypersalivation	• Hypotension
	• Muscle weakness

Other Parasympathetic Agents:

- Carbachol, Physostigmine (Eserine- Occasionally used to treat crab louse infection of the eyelashes), Echothiopate iodide (phospholine iodide), Demarcarium bromide (Humersol)
  - These agents are virtually never used and should be considered clinically insignificant

Clinical Pearl: Never use miotics in any eye with primary inflammation such as uveitis.

Clinical Pearl: Miotics are losing popularity as glaucoma treatment, due mostly to local side effects and the advent of newer medications. Miotics are rarely used today in modern glaucoma therapy. However, any patient with primary angle closure glaucoma should be on this medication prior to laser surgery. It actually may be a good choice when surgery is not an option in advanced, end stage cases.

Clinical Pearl: Occasionally, to reduce IOP in acute situations, doctors will liberally use pilocarpine. This strategy only works if the mechanism is acute pupil block angle closure.

If the patient has uveitis, the outcome can be disastrous. In reality, pouring pilocarpine into a patient is likely only to give them diarrhea.

Clinical Pearl: Due to miosis, pilocarpine can mimic the blinding effects of glaucoma.

III. Carbonic Anhydrase Inhibitors

- Sulfonamide non-antibiotic drugs
- MOA: Aqueous suppressant- Carbonic anhydrase catalyzes the hydration of carbon dioxide to carbonic acid that then dissociates into bicarbonate ions and hydrogen.

  $CO2 + H2O \rightarrow CA \rightarrow H2CO3 \rightarrow H^+ + HCO3^-$
- Bicarbonate diffuses into the eye, making it hypertonic in relation to plasma, and fluid flows osmotically into the eye from plasma.
- Blocking carbonic anhydrase blocks bicarbonate formation - Blocks osmosis into posterior chamber
- Blocks aqueous formation by slowing production of bicarbonate in secretory neuroepithelial cells of ciliary body

Oral Carbonic Anhydrase Inhibitors: Side Effects

Acidosis	*Paresthesia*
Metallic taste (dysgeusia)	Malaise
Calculi formation	Fatigue
Depression	Impotence
Aplastic anemia	Dizziness
Confusion	Anorexia and weight loss
GI upset	Polyuria
Bone marrow toxicity and suppression of formed blood elements	Loss of libido
Nausea and vomiting	Diarrhea

Carbonic Anhydrase Inhibitors: Systemic Contraindications

- Sulfa allergies*
- Sickle cell disease
- Hypokalemia
- Renal disease
  - Predisposition to form kidney stones
- Liver disease

***Sulfa allergies explained: Allergies with sulfonamide antibiotics implies cross reactivity with other sulfonamide antibiotics, but not necessarily with sulfonamide non-antibiotics,**

due to structural differences. Non-antibiotic sulfonamides lack the same structural configuration as sulfonamide antibiotics and are less likely to result in a severe allergic reaction. Cross reactivity between sulfonamide antibiotics and sulfonamide non-antibiotics is extremely rare. Thus, it is important to determine of a patient who has 'sulfa allergies' is sensitive to sulfonamide antibiotics or sulfonamide non-antibiotics. CAIs, which are sulfonamide non-antibiotics, can be used in patients who are sensitive to sulfonamide antibiotics. When in doubt, proceed with caution and check with the patient's physician.

Oral Carbonic Anhydrase Inhibitors: Acetazolamide

- Diamox - Oral
- 125mg, 250mg, 500 mg SR (Diamox sequels)
- 1000mg QD PO
- 6-week tolerance, in most cases.
- Indicated post-surgically and for acute angle closure (250 mg tabs)

Clinical Pearl: The standard dosing of 1000 mg/day is likely the reason that Diamox is so poorly tolerated and is likely an overdose, especially in smaller patients.

Oral Carbonic Anhydrase Inhibitors: Methazolamide

- Neptazane
- 25mg, 50mg
- Dosing: 25 mg BID up to 50 mg TID maximum
- Side effects and contraindications similar to acetazolamide, but is much better tolerated.
- Is sometimes used chronically in recalcitrant cases

Topical Carbonic Anhydrase Inhibitors: Dorzolamide

- Trusopt 2%
- *Orange cap*
- 10-26% IOP reduction
- Reduces aqueous production
- Poor lipid solubility and doesn't penetrate cornea well
- Tends to be an irritating medication to use because of low pH, which is necessary to get the medication into solution form
- Dosing TID
- Binds to melanin, so it is slightly less effective in dark irides.
- Can be combined with other families of medications.

Dorzolamide: Side Effects

- Hyperemia
- Instillation pain
- Bitter taste (dysgeusia)
- Onset of corneal edema in patients with compromised corneal endothelium
- Toxic allergy (significant)
- Aplastic anemia (rare)

- Bone marrow suppression with reduction of WBC's, RBC's, platelets (rare)
- Renal stone development (rare)
- Available generically

Topical Carbonic Anhydrase Inhibitors: Brinzolamide Ophthalmic Suspension 1%

- Azopt- Brand only
- *Orange cap*
- Reduces IOP 20%
- TID dosing
- Formulated at physiological pH because it is a suspension
    - Significantly more comfortable and better tolerated than Trusopt
- Less incidence of allergic reactions
- Clinically equivalent to Trusopt
- Same side effects as dorzolamide, but doesn't sting as much upon instillation. However, there is more blurred vision because it is a suspension.

Clinical Pearl: Topical CAI's work very well in cases of uveitic glaucoma. Also, they work very well and are well tolerated in children.

Clinical Pearl: While dosing is TID, many prescribe topical CAIs BID. This is probably acceptable as part of polytherapy, but is questionable for monotherapy.

Clinical Pearl: Avoid using topical CAI's in patients with compromised corneal endothelium, and cautiously in patients with true allergy to sulfa medications (non-antibiotics), and a history of renal stones.

Clinical Pearl: Due to the safety of topical CAI's compared to oral CAI's, the therapeutic index indicates that oral CAI's are no longer appropriate in the chronic care of glaucoma in most cases, though there are exceptions.

Clinical Pearl: Topical CAIs appear to be effective in lowering IOP at night/ during sleep. They are also seen to be the medication class which is the best additive/ adjunctive therapy to use with PGAs.

Clinical Pearl: The most common adverse effects of topical CAIs are dysgeusia, blurred vision, burning and stinging. The most notable contraindication is corneal endotheliopathy and reduced endothelial cell count.

Clinical Pearl: It is not recommended to use an oral and topical carbonic anhydrase together. However, many clinicians will do so in extreme, short-term, or unusual situations.

IV: Rho and Rho-associated protein kinase (ROCK) Inhibitors/ norepinephrine transporter inhibitor

- Newest class of medication
- The Rho family consists of three small guanosine triphosphate (GTP)-binding proteins (RhoA, RhoB, RhoC), which regulate aspects of cell shape, motility, proliferation, and apoptosis throughout the body
- ROCKs are serine/threonine kinases that regulate smooth muscle contraction, specifically in the TM
- ROCK1 and ROCK2 tend to be expressed in the majority of tissues, including human TM and ciliary muscle cells
- ROCKs appear to have several actin cytoskeletal-related targets that directly affect the contractile properties of TM outflow tissue
    - Loss of ROCK function has previously been associated with micromechanical relaxation of cells and disassembly of stress fibers and focal adhesion complexes enhancing aqueous outflow
- Multiple studies have indicated that ROCK and Rho GTPase inhibitors can increase aqueous humor drainage in TM tissue, leading to a reduction in IOP
- ROCK inhibitors induce reversible modifications to cell morphology and cell interactions in the eye that facilitate greater outflow of aqueous humor and, ultimately, result in a lower IOP.
- ROCK inhibitors exhibit a widening of the extracellular spaces and juxtacanalicular tissue morphological changes within 30 minutes of administration and lasting up to 12 hours
- ROCK inhibitors may have uses in glaucoma management other than lowering IOP. Animal studies have demonstrated increased ocular blood flow as well as potential neuroprotective effects, and ROCK inhibitors may also have the potential to reduce postoperative scarring during glaucoma-filtering surgery
- ***Rhopressa™*** (netarsudil ophthalmic solution) 0.02%- approved 12/18/17, is a novel "triple-action" eye drop that specifically targets the trabecular meshwork, enhancing trabecular outflow. Preclinical results have demonstrated that Rhopressa™ also lowers episcleral venous pressure, which contributes approximately half of IOP in healthy subjects. Further, Rhopressa™ provides an additional mechanism that reduces fluid production in the eye and therefore lowers IOP. Biochemically, Rhopressa™ is known to inhibit both Rho Kinase (ROCK) and norepinephrine transporter
- ROCKET-1 study-Rhopressa™
    - Did not meet the primary efficacy endpoint of demonstrating noninferiority of IOP lowering for once-daily Rhopressa compared to twice-daily timolol
        - Rhopressa did not meet its primary efficacy endpoint based upon IOP measurements at the end of weeks 2 and 6 and day 90
        - Rhopressa showed slight loss of efficacy at week 6 and day 90 (approximately 20%).
        - The primary adverse event was hyperemia, which was experienced by approximately 35% of the Rhopressa patients, of which 80% was reported as mild.

    - Other adverse effects have been conjunctival hemorrhages and corneal verticillata
- Once-daily dosing with hyperemia the main adverse effect
- White cap
- Brand only

Clinical Pearl: Though the clinical trials of Rhopressa showed some unimpressive results, the medication appears to be outperforming these trials in clinical practice. That is, clinicians are anecdotally reporting great success stories.

V. Fixed Combination Agents

Topical Beta Blocker/Carbonic Anhydrase Inhibitor: Cosopt
- Combination of 0.5% Timoptic and 2% Trusopt
- Generically called dorzolamide/ timolol; Trade name is/was Cosopt
- *Yellow/orange cap & label for Cosopt; dark blue for generic version (dorzolamide/timolol)*
- BID dosing
- Slightly less effective than using each separate drug in combination
- Better convenience and compliance
- This is a popular and important medication currently
- Available as generic except for preservative free version called Cosopt PF
- Cosopt PF is unit dose, non-preserved Cosopt
    - Non-resealable unit dose vials with 4-6 drops/vial

Topical Beta Blocker/ Alpha Adrenergic Agonist: Combigan
- Combination of 0.5% Timoptic and 0.2% Alphagan
- Trade name Combigan. Not available generically yet
- *Dark blue cap*
- BID dosing
- Better convenience and compliance and less somnolence than alphagan
    - The decreased somnolence was the reason that Combigan eventually received FDA approval.
- Not available generically

Alpha adrenergic Agonist/Carbonic Anhydrase Inhibitor: Simbrinza
- Trade name: Simbrinza: Brinzolamide 1% (Azopt) and brimonidine 0.2% (Alphagan)
- TID dosing
    - Often used BID but this is off label
- Adverse effects same as individual components
- 1-3 mm Hg additional IOP reduction compared to individual components
- 22-35% IOP reduction from baseline
- Approved as 1st line therapy
- Used as primary, adjunctive, and replacement therapy
- Only FC medication without beta blocker

    - Fair tolerance- dropout rate is around 11%
- Brand only- no generic
- *Light green cap*

Rho Kinase inhibitor/norepinephrine transporter inhibitor/prostaglandin analog: Rocklatan

- Netarsudil/latanoprost 0.02%/0.005% (Rocklatan)
- Contains latanoprost and Rhopressa
- White cap- brand only
- Targets both the uveoscleral and trabecular outflow pathways
- Very effective at reducing IOP (Duh! It's got latanoprost in it.)
    - Superior to latanoprost and timolol alone
    - Hyperemia, verticillata, blurred vision, conjunctival petechial hemorrhage are reported adverse effects
    - Appears poised to be a major glaucoma med- most significant issue beyond adverse effects is cost and coverage.

Clinical Pearl: It is extremely difficult to get FDA approval for combination agents. The FDA demands that a combination agent reduce IOP by a select amount compared to either sole agent throughout every time period tested. Most combination agents cannot demonstrate this degree of efficacy.

Clinical Pearl: There are several other combination medications such as Azarga (timolol/ Brinzolamide), Ganfort (timolol/ bimatoprost), DuoTrav (timolol/ travoprost), and Krytan Tek (dorzolamide, timolol, brimonidine) that patients from other countries may be using but are not available here. Many are manufactured in the USA but cannot get FDA approval. They are likely very good medications, however.

Others: Osmotics

- Osmotic dehydration
- Nauseating
    - Emesis
- Glycerine (Osmoglyn)
- Emergency care-acute angle closure
- Not for use in chronic care at all – one time only

Issues with Preservatives:

- Chronic exposure to topical glaucoma medications containing preservatives, especially benzalkonium chloride (BAK) can lead to disruption of corneal integrity, chronic low-grade conjunctival inflammation, burn out of goblet cells, and ultimately dry eye and ocular surface disease. True issue vs. marketing ploy?

Available generically: latanoprost, travoprost, bimatoprost 0.03%, pilocarpine, 1%, 2%,

4% timolol, betaxolol, carteolol, brimonidine 0.2%; brimonidine 0.15%; dorzolamide/ timolol FC, dorzolamide.

Medications shown to reduce IOP at night: PGAs and topical CAIs. Those shown ineffective at night: beta blockers and alpha agonists.

Preservative free options: Zioptan, Cosopt PF, Timoptic Ocudose. Non-BAK options: Xelpros, Travatan Z, Alphagan P

Clinical Pearl: Generics account for 90% of the glaucoma market today. Branded medications cost from $175-$250/ month each.

Current Therapy:

Used Commonly:	**Available, but not used commonly**	**Not Used:**
Prostaglandins	Pilocarpine	all other miotics
Alphagan/ brimonidine	Iopidine	epinephrines
Topical CAI's	oral CAI's	
Beta blockers		**Up-and-Coming**
Fixed Combinations		ROCK inhibitors
		NO-donating PGAs

Resource: WWW.GOODRX.COM