
Glaucoma Pharmacology: Prescribing for the Patient

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Prostaglandins and Prostaglandin-like Medications

- Prostaglandins (PGAs) are chemical mediators of inflammation which have the ability to reduce IOP by increasing uveoscleral outflow (unconventional pathway as opposed to trabecular meshwork which is the conventional pathway)
- PGAs: The newest and most heralded medications in glaucoma management. Is considered by some to be revolutionary
 - Advent of PGAs has caused reduction in glaucoma surgeries performed
- 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, periorbital skin darkening, 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 to iris color changes. 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
- About 10-20% of population does not respond. 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: none
- Systemic contraindications: none besides possibly pregnancy and being a child
- Prostaglandins are not indicated in secondary inflammatory glaucoma or any clinical entity that has anterior segment inflammation as a primary component
 - Not likely to hurt, but not likely to help, either

Latanoprost 0.005%

- Trade name Xalatan
- Mean IOP reduction: 27-33.7%
 - Can exceed 50%
- Latanoprost is very oculosensitive
- 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 very low degree of systemic effects
- Initial short-term response to Xalatan is likely due to PF-2 receptor stimulation. Later response may be due to Xalatan actually changing the ground substance in the cellular matrix of the ciliary meshwork.
- Long term IOP control is excellent with Xalatan and may be better than other meds, even if patients miss dosages.
 - Xalatan is as effective at 24 hours as at 4 hours.
- Now available as a generic and the only generic PGA

Clinical Pearl: Don't be confused about PGAs- their half-life is very short, but their duration of action is very long.
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Travoprost 0.004%:

- Trade name: Travatan Z
- 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
- Travatan Z is preserved with Sofzia, which is more gentle to the ocular surface than BAK in previous iteration
- Travoprost 0.004 now available generically

Bimatoprost 0.01%:

- Trade name: Lumigan
- Hypotensive lipid- Not true prostaglandin (?) – 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 been recently approved and has replaced original 0.03% concentration
 - 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.
 - We will likely be seeing generic bimatoprost 0.03% in near future

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. Same bottle and everything. 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
 - Niche product
 - 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 actually re-seal, so it will be difficult to prevent patients from re-using vials

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 no bearing on glaucomatous patients.

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

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

Clinical Pearl: Avoid using prostaglandins in cases of uveitis.

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 cataract surgery to reduce risk of CME.

Clinical Pearl: Travoprost, bimatoprost, and latanoprost account for the vast majority of prescriptions for glaucoma written today.

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

Unoprostone isopropyl 0.15%

- Rescula
- Initially approved by the FDA in 2000 for lowering IOP in patients with glaucoma and ocular hypertension who were intolerant of other medications or who needed additional pressure reduction more than current drug therapy was providing.
- Labeled dosing is twice daily.
- Unoprostone was developed from a prostaglandin metabolite, but the compound itself was considered to be a docosanoid with properties fundamentally different from prostaglandin analogs. At the time of approval, it was felt that the mechanism of action was through increased aqueous outflow, but the true action was never fully understood.
- Though not clearly understood, it appears that the effects of unoprostone on BK and ClC-2 channels act to increase aqueous outflow through the trabecular meshwork.

Sympathetic Agents

- Adrenergic agonists
- Sympathomimetic
 - Norepinephrine based

- Adrenergic antagonist
 - Sympatholytic

Sympathetic System

- Alpha 1
 - Blood vessels of ciliary body: vasoconstriction, which reduces blood flow and aqueous production.
 - Epinephrine-like drugs
- 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 (Brimonidine)
- Beta 1
 - Heart: increased
- Beta 2
 - Lungs: relaxed- increased breathing ability
- Beta 1 & 2 on ciliary body
 - Stimulation increases aqueous production
 - Blocking B1 & 2 receptors reduces aqueous production
 - Beta blockers

Adrenergic Agonists: Brimonidine tartrate (Alphagan)

- 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
- 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)
 - Selective alpha-2 agonist
 - Seems to work via inhibition, thus no effects on heart and blood pressure as seen with sympathomimetics
- IOP reduction of approximately 4-6 mm hg (25-30%)
- TID dosing
 - 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, 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, headache
- 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.
 - At this point, Alphagan is not proven to be nor is considered to be neuroprotective. It is not responsible 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: Do not use Alphagan in children.

Clinical Pearl: Patients can have a late-onset Alphagan allergy.

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 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 hypoaesthesia
- BP decrease (beta 1)
- Bradycardia (beta 1)
- Pulmonary bronchiole contraction (beta 2)
- Depression
- Confusion
- Anxiety
- Fatigue
- Malaise
- Irritability
- Somnolence
- Confusion
- Death
 - Approximately 40 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 effectiveness 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 actually reduces mortality.
 - Reduced resistance to ejection actually 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: Topical beta blockers have the same systemic effects as 20 mg of oral beta blocker therapy.

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 (Generic)
 - 0.25% (blue cap)
 - 0.50% (yellow cap)
- Ocudose- non-preserved in unit dose vials
 - Only non-preserved beta blocker, but at \$330/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
 - Same cost as timoptic BID soln.
 - 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%: QD dosing approval

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

Timolol hemihydrate

- Betimol 0.25% and 0.5%- generic

Levobunolol

- Brand name Betagan no longer available. Only available as generic
 - 0.25% (blue cap) and 0.5% (yellow cap)

- Clinically equivalent to Timoptic
- BID dosing
- Same side effects and contraindications as Timoptic

Betaxolol

- Betoptic S 0.25% suspension – blue cap
- Beta 1 selective
- 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)
- 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 agonist 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
- Generic

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.

Carbonic Anhydrase Inhibitors

- Carbonic anhydrase catalyzes the hydration of carbon dioxide to carbonic acid that then dissociates into bicarbonate ions and hydrogen.

$$\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{CA}} \text{H}_2\text{CO}_3 \xrightarrow{} \text{H}^+ + \text{HCO}_3^-$$
- 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

Carbonic Anhydrase Inhibitors: Side Effects

Acidosis	Paresthesia
Metallic taste	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
- Sick cell disease
- Hypokalemia
- Renal disease
 - Predisposition to form kidney stones
- Liver disease

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)

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.

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 (low pH)
- 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
- Bitter taste
- Toxic allergy (significant)
- Aplastic anemia
- Bone marrow suppression with reduction of WBC's, RBC's, platelets
- Renal stone development
- Onset of corneal edema in patients with compromised corneal endothelium
- Available generically

Topical Carbonic Anhydrase Inhibitors: Brinzolamide Ophthalmic Suspension 1%

- Azopt
- Orange cap
- Reduces IOP 20%
- TID dosing
- Formulated at physiological pH
- Significantly more comfortable and better tolerated than Trusopt
- Less incidence of allergic reactions
- Clinically equivalent to Trusopt

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, an allergy to sulfa medications, 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 orals CAI's are no longer appropriate in the chronic care of glaucoma.

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.

Miotics: Contraindications

- Uveitic glaucoma
 - Any significant ocular inflammation
- Neovascular glaucoma
- Aphakia (relative contraindication)
- Retinal breaks, RD
- Posterior subcapsular cataract present
- Pre-presbyopia

- Not well tolerated

Parasympathetic Agents: Pilocarpine

- Direct acting cholinergic agonist
- Miotic
- Ciliary body contraction
- Increases outflow of aqueous through trabecular meshwork (conventional pathway). Tends to decrease outflow through uveoscleral pathway (unconventional pathway).
- 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
- Green cap
- 4% Pilocarpine 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 synechia 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
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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.

Fixed Combination (FC) Agents: Topical Beta Blocker/Carbonic Anhydrase Inhibitor

- Combination of 0.5% Timoptic and 2% Trusopt

- Generically called dorzolamide/ timolol; Trade name is/was Cosopt
- Yellow/orange cap & label
- 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 only 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

Fixed Combination (FC) Agents: Topical Beta Blocker/ Alpha Adrenergic Agonist

- Combination of 0.5% Timoptic and 0.2% Alphagan
- Trade name Combigan. Not available generically
- BID dosing
- Better convenience and compliance
- This is a popular and important medication currently

Fixed Combination (FC) Agents: Alpha adrenergic Agonist/Carbonic Anhydrase Inhibitor

- Brinzolamine 1% (Azopt) and brimonidine 0.2% (Alphagan)
- TID dosing
- 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

Clinical Pearl: It is extremely difficult to get FDA approval for combination agents. The FDA demands that a combination agent reduce IOP by more than 2 mm Hg compared to either sole agent throughout every time period tested. Most combination agents cannot demonstrate this degree of efficacy.

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.

Available generically: latanoprost, pilocarpine, timolol, betaxolol, carteolol, brimonidine 0.2%; brimonidine 0.15%; dorzolamide/ timolol, travoprost

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.

Current Therapy:

Used Commonly:

Prostaglandins
Alphagan
Topical CAI's
Beta blockers
Fixed Combinations

Available, but not used commonly

Pilocarpine
Iopidine
oral CAI's

Not Used:

all other miotics
epinephrines

Medically Managing Glaucoma:

The goal of treatment in open angle glaucoma is to reduce IOP to a level below which optic nerve and visual field damage will not occur or progression of existing damage is prevented.

- Based upon diagnostic evaluation, weighing risk factors, and considering risk-to-benefit ratio of treatment, the decision to initiate medical therapy is made. Once the decision to treat is made, a goal of therapy is set. In some cases, a target pressure is chosen. This pressure (or range) is the one that is felt to be a safe level for a given patient.
 - This must be periodically re-evaluated with considerations as to severity of disease, risk of visual impairment and disability, general health of the patient, and life expectancy.
 - The target pressure may be adjusted either up or down depending upon factors considered.
- Glaucoma suspects/ocular hypertensive patients who have normal discs and fields and no other associated risk factors could be followed without medical treatment. As numbers of risk factors increase, then the decision to treat may be initiated.
- Treatment (or therapy amplification) is recommended when visual field and/or optic nerve changes occur which are consistent with glaucoma independent of the IOP level.
- Based upon age, expected life span, and degree of damage, some patients with glaucoma may be followed without therapy.
- Once patient is controlled, examine Q3-4months. If patients remain stable for a period of time (several years) it may be safe to follow every 6 months. Always record the exact time that the patient used the medications on the day of follow-up (a surprisingly high number of glaucoma patients believe that they should skip their medications on the day that they are scheduled to come in for a visit).
- Always measure pulse rate and BP if patient is using beta blockers
- Use a flow sheet to facilitate care
- Noncompliance is the biggest cause of treatment failure
- Never change therapy based upon one bad IOP reading
- Monocular trials do not give valuable information. That is, historically medication has been added to one eye with the fellow eye being untreated for the initial period of medication evaluation as a 'control'. Thus, if the IOP lowered in the 'treated' eye compared to the untreated 'control' eye, the medication was deemed effective. However, this concept was based upon a number of assumptions which have been subsequently proven to be incorrect:
 - The diurnal IOP is identical between eyes
 - The diurnal IOP is similar between days, weeks and months

- The response of a medication in one eye is identical to the response in the other
 - These assumptions have all been proven to be erroneous
 - Also remember regression to the mean. That is, if IOP is very high, the next reading could be much lower merely by chance. In this case, medication addition may seem effective and it truly is not.

Clinical Pearl: When starting a medication, if both eyes need treatment, then use the medication in both eyes. The true test of medication effectivity is to examine the untreated IOP over several visits and compare to the treated IOP over several visits. Monocular trials are not useful.

Therapeutic Considerations

- Medical contraindications necessitate your choosing different therapeutic paths.
- Synergy/non-synergy
 - Each *family* of glaucoma medications can potentiate pressure-lowering effects.
 - There is no synergy within families, only increasing side effects.
 - **You can't mix 2 beta blockers or two prostaglandins together and expect a better effect than with either one alone.**
 - **Remember diminishing returns when adding medications.**
- If IOP is lowered with a drug, but not sufficiently, add another drug to the initial drug. If the initial drug fails to reduce IOP (i.e., is ineffective), discontinue the initial drug and move on to another.
- Sequential monotherapy- a practice where each medication family is tried independently to see which one works best in each individual patient and if one medication can control IOP adequately
 - Time consuming
- Never add more than one drug at a time
 - Can't tell if a single drug is effective or not

Climbing the Therapeutic Ladder

1. Start with one of the commonly used medications (typically a prostaglandin analog)
2. If IOP not controlled, add beta-blocker or a topical carbonic anhydrase inhibitor or alpha-2 agonist
3. If IOP not controlled, add another choice from #2 and continue until IOP acceptable
 - If CAI and beta blocker are both effective, they can be both discontinued and replaced with a fixed combination.
 - If alpha-2 agonist and beta blocker are both effective, they can be both discontinued and replaced with Combigan
 - Pilocarpine and oral CAI's, while available, are not great choices and are not typically used
 - Some practitioners will not put patients on any more than two medications and others will use three or four
 - Laser trabeculoplasty is an option if medications are insufficient
 - Surgery is an option if medications and/or laser fail

- Each medication added has diminishing returns
 - A medication that may reduce IOP by 25% as primary therapy may only reduce IOP by 15% when added to another medication already being used

Clinical Pearl: There is not “standard” medical regimen that is appropriate for every patient.

Clinical Pearl: While Alphagan, a beta blocker, a prostaglandin analog, and a topical CAI are considered maximal medical therapy, many practitioners will not use this much medication. Some practitioners consider three medications and sometimes two medications to be the maximal tolerable therapy for patients and feel that laser or surgery should be used beyond that point.

Clinical Pearl: Target pressure can be considered a range of IOP level, which must not be consistently breached if optic nerve damage is to not occur. This has been seen with zero tolerance. This is not necessary. Any pressure reduction will buy the patient some time.

Clinical Pearl: Medications don’t fail instantaneously. That is, if the treated IOP at last visit was 18 mm and today it is 37 mm, the cause is failure to use the medication, regardless of what the patient says.

Clinical Pearl: Glaucoma is not like pregnancy. You can have a ‘little’ glaucoma. You must take into account the detrimental effects on a patient’s life that IOP lowering is likely to have, especially when compared to a small visual field loss that the patient doesn’t notice. You must take into account the side effects of the medications as well as other factors such as cost that reduce the quality of life when treating a patient when you pick a target pressure. The quality of the patient’s life can go down as you force the IOP lower.

Clinical Pearl: What if you don’t reach the target IOP? Did you fail? The most important mm Hg is not the last mm Hg, but the first mm Hg, and the second...and so on.

So, what is the most important thing that we can say about target pressures?
 A target pressure is that pressure at which the sum of the impact of the glaucomatous vision loss upon the patient and the impact of treatment upon the patient is minimized. Once treatment is started, the goal is not to make the IOP ‘normal’, but safe for the patient.

Clinical Pearl: Unless the patient is at risk of imminent vision loss from an undiagnosed case of advanced glaucoma, get several untreated IOP readings over time before beginning therapy.

Clinical Pearl: There is absolutely no reason to heroically lower IOP in office in patients with chronic glaucoma.