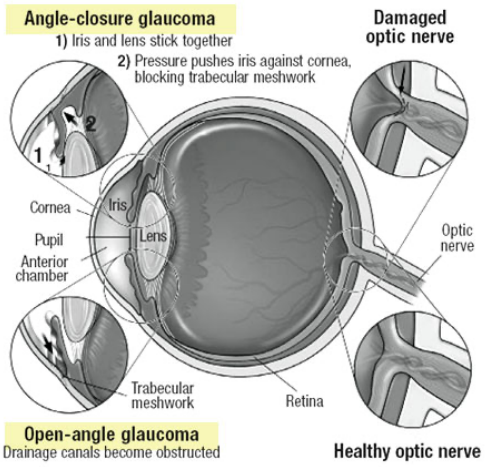
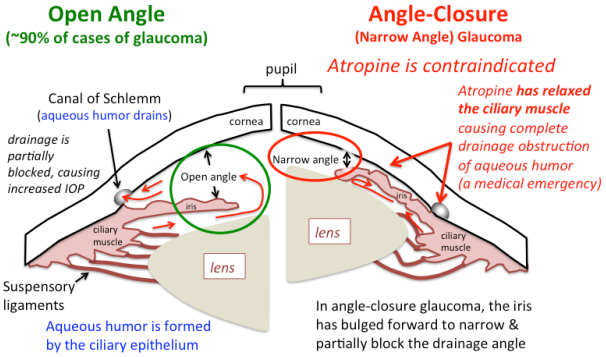
Pharmacologic Management of Glaucoma

- Glaucoma is a leading cause of irreversible blindness worldwide and is a nonspecific term used for a group of disease that can irreversibly damage the optic nerve.
- Intraocular pressure (IOP) is influenced by the production of aqueous humor by the ciliary process and the outflow of aqueous humor through the trabecular meshwork.
- An IOP > 22 mmHg should arouse suspicion of glaucoma. Ocular hypertension is defined as IOP > 21 mmHg.
- In primary open-angle glaucoma (POAG), aqueous humor outflow from the anterior chamber is subnormal primarily due to a degenerative process in outflow channels (i.e., the trabecular meshwork and Schlemm canal).
- In angle-closure glaucoma (5-10% of all glaucoma cases), the elevated IOP is due to closure of the anterior chamber angle.
  - "Acute" angle-closure glaucoma: considered a medical emergency and usually presents as an acute attack with rapid increase in IOP, blurring or sudden loss of vision, and severe pain.
  - "Chronic" angle-closure glaucoma: patients experience a gradual closure of aqueous humor outflow and may be asymptomatic until glaucoma reaches an advanced stage.
  - Permanent management of angle-closure glaucoma often requires surgical treatment (e.g., peripheral iridotomy or peripheral iridectomy).



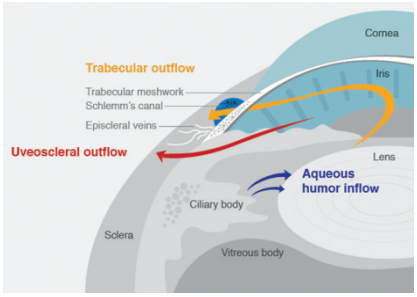


- Goal of therapy: lower IOP --> prevent disease progression --> prevent further deterioration of vision.

Open Angle Glaucoma

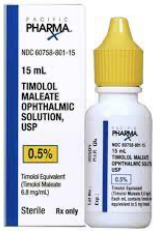
- Historically, beta-blockers (BB) were the most commonly used 1st-line agents for treatment of POAG; but in recent years, prostaglandin analogs (PGA) have exceeded BB use.
- All the ophthalmic BBs are available in generic formulations (cost savings) and some of the PGAs are available as generic products.

Beta-Blockers (BB)



- MOA: BBs block the beta-adrenergic receptors in the ciliary epithelium and lower IOP by decreasing aqueous humor production.
- BB decrease IOP by 20-35%, depending on the strength used and the frequency of administration.

Timolol (Timoptic)



- Timolol is a nonselective BB and is the most commonly used BB in POAG.
- Timolol 0.5% 1 drop OU BID produces the max decrease of IOP reduction.
- Tachyphylaxis ("escape phenomenon") can occur with timolol.
- SE: timolol is associated with a modest reduction in resting HR (5-8 bpm), worsening of heart failure (HF), airway obstruction (i.e., bronchoconstriction)

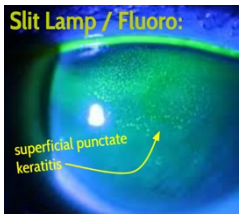
Timolol (cont.)

Healthy Eye

Superficial Punctate Keratitis

Main symptoms: red eyes, excessive tearing, photophobia, blurry vision, eye discomfort

- Systemic absorption after topical administration does occur, esp in the elderly (due to overdosing associated with poor admin technique) --> timolol should be used with caution in patients with sinus bradycardia, heart failure (HF), and COPD.
- Chronic use of timolol may cause "corneal anesthesia" (i.e., superficial punctate keratitis) --> corneal inflammation characterized by punctate (i.e., scattered) epithelial loss or damage. Symptoms include redness, tearing, photophobia, slightly decreased visual acuity.
- Cost: $9-11 (generic) / $46-50 (brand)



- Timoptic XE (gel-forming solution) is administered once daily --> prolongs corneal residence time and increases ocular bioavailability.
  - Cost: $39-$53 (generic) / $58-64 (brand)

Levobunolol (Betagan)

- Levobunolol is a nonselective BB ophthalmic product approved for either once-daily or BID dosing.
- Levobunolol 0.5%-1% is comparable to timolol in lowering IOP with similar SEs. (Cost: $12 generic)

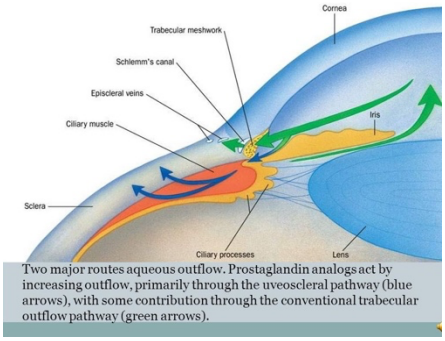
Betaxolol (Betoptic)

- Betaxolol is a selective beta-1 blocker --> less adverse effects on pulmonary function than non-selective BBs.
- Betaxolol is less effective than timolol in IOP reduction and usually requires adjunctive therapy with other agents for glaucoma. (Cost: $12.68 generic / $39.13 brand)

Carteolol (Ocupress)

- Cardiolol is a nonselective BB with partial beta-adrenergic agonist activity, which should minimize bronchospastic and cardiac effects; however, no clinical differences and SEs were seen with carteolol compared to other nonselective BBs. (Cost: $9-24 generic)

Prostaglandin Analogs (PGA)



Two major routes aqueous outflow. Prostaglandin analogs act by increasing outflow, primarily through the uveoscleral pathway (blue arrows), with some contribution through the conventional trabecular outflow pathway (green arrows).

- MOA: PGAs increase uveoscleral outflow of aqueous humor --> decrease IOP.
- PGSs are prescribed as 1st-line agents for treatment of POAG for the following reasons: (1) PGAs are as effective as the BBs, (2) PGAs are dosed once daily, and (3) PGAs are associated with minimal systemic side effects.
- PGAs include: latanoprost (Xalatan), travoprost (Travatan Z), bimatoprost (Lumigan) and tafluprost (Zioptan).
- Local SEs: Iris pigmentation; eyelid skin darkening; eyelash lengthening, thickening, pigmentation and misdirected growth; conjunctival hyperemia; ocular irritation; superficial punctate keratitis.
  - Note: different PGAs may differ in SEs. Example: Latanoprost tends to have the lowest incidence of hyperemia (24%), while bimatoprost tends to have the highest (59%).

- Tafluprost is available in single-use packets requiring refrigeration --> causes less local irritation (itching, dryness) due to corneal irritation from benzalkonium chloride (preservative).

Prostaglandin Analogs (cont.)

- FDA approved the cosmetic use of bimatoprost solution (Latisse), which is applied with an applicator to the base of the upper eyelashes for the treatment of hypotrichosis. Eyelash lengthening, thickening, and darkening or pigmentation is seen after 8-16 weeks.
- PGAs have additive effects when used with BBs (e.g., timolol), carbonic anhydrase inhibitors (e.g., dorzolamide), and alpha-2 adrenergic agonists (e.g., brimonidine, apraclonidine).
  - Latanoprost decreases IOP an additional 2.9-6.1 mm Hg when used as an adjunctive agent in patients who are unable to lower their IOP with a single agent.
  - Latanoprost 0.005% is administered once daily at bedtime, since more frequent administration is actually less effective.
- Cost of latanoprost: $32 (generic) / $112 (brand); Cost of tafluprost: $172 (brand) – no generic.

Alpha$_2$-Adrenergic Agonists: Apraclonidine (Iopidine) and Brimonidine (Alphagan)

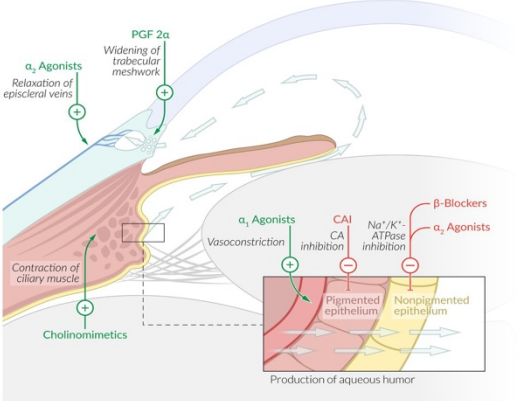
- MOA: Alpha$_2$-agonists decrease production of aqueous humor and increase uveoscleral outflow --> decrease IOP.
- Brimonidine is more selective for alpha$_2$ receptors than apraclonidine and should be associated with fewer ocular side effects
- Ocular (localized) SEs are more common with apraclonidine: allergic conjunctivitis, hyperemia, and pruritus.
- Systemic SEs (more common with brimonidine than apraclonidine): dry nose and mouth, mild hypotension, decreased pulse, and lethargy.
- Brimonidine 0.2% BID lowers IOP comparable to timolol 0.5% BID and may be considered as an alternative 1st-line agent in POAG.
  - Brimonidine is usually considered as an adjunctive therapy in patients not responding to other agents or when there is intolerance or formulary/cost issues. Cost of brimonidine: $32 (generic) / $47 (brand).
  - Combigan is a popular combination product containing brimonidine 0.2% with timolol maleate 0.5% --> Cost: $43-44 (generic) / $49 (brand).

Topical Carbonic Anhydrase Inhibitors (CAIs): dorzolamide (Trusopt) and Brinzolamide (Azopt)

- MOA: CAIs decrease bicarbonate production in ciliary processes and retina --> decrease flow of bicarbonate, sodium, and water into the posterior chamber --> decrease aqueous humor secretion by 40-60% --> decrease IOP.
- CAIs are generally considered as adjuncts in the management of POAG, since they do not appear as effective as other agents in lowering IOP.
- Brinzolamide, the most effective CAI, decreases IOP by 2.49 mmHg after 3 months. Cost: $8-16 (generic)
- SE: ocular burning, stinging, discomfort, allergic reactions, bitter taste, and superficial punctate keratitis.
- Note: Dorzolamide and brinzolamide are sulfonamides and may cause similar reactions attributable to sulfonamides (e.g., allergies, intolerance).

Cholinergic Agonists (ACh Agonists): Pilocarpine (Isopto Carpine) and Carbachol (Isopto Carbachol)

- MOA: ACh agonists are direct-acting cholinergic that cause contraction of the ciliary muscle fibers attached to the trabecular meshwork and scleral spur --> opens the trabecular meshwork to enhance aqueous humor outflow.
  - ACh agonists also cause miosis by contraction of the iris sphincter muscle, but miosis is not related to the decrease in IOP.

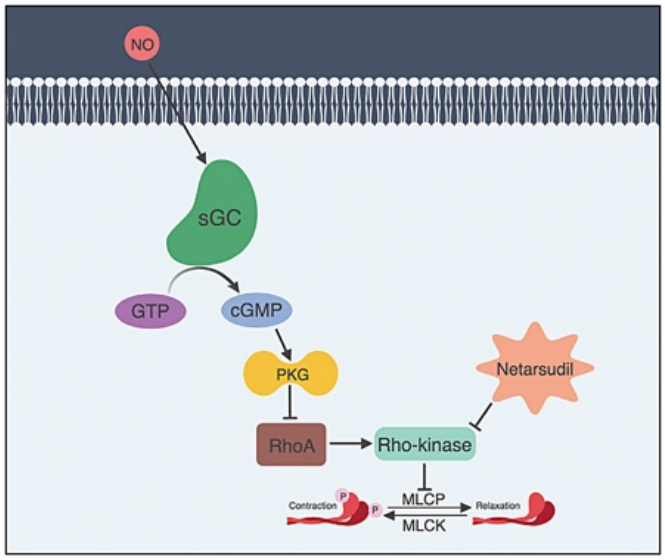


Cholinergic Agonists (cont.)

- Pilocarpine historically was an initial treatment of choice for POAG, but with widespread use of the newer agents, pilocarpine has fallen out of favor.
- Pilocarpine is administered QID and Carbachol is administered TID.
- SE (Ocular): fixed, small pupils; myopia, and increased visual disturbance with coexistent cataract disorder.
- ACh agonists are rarely used, except when newer agents may be too expensive or unavailable.
- Cost of pilocarpine 1-4%: $6-7 (generic)

Rho-Kinase Inhibitor: Netarsudil (Rhopressa)

- MOA: (1) Netarsudil decreases actin and myosin contractions --> increases aqueous outflow through the trabecular meshwork --> decreases IOP; and, (2) Netarsudil inhibits the norepinephrine (NE) transporter --> increases NE levels and activation of alpha$_2$ receptors --> decreases aqueous humor secretion.



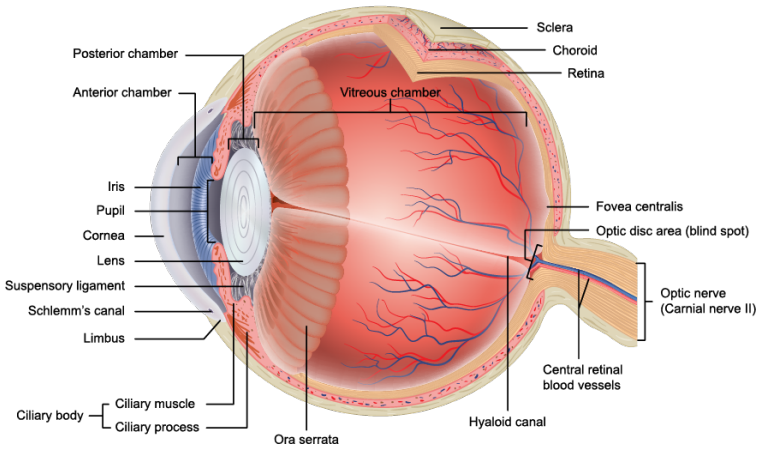
Myosin light chain phosphatase (MLCP) is responsible for the dephosphorylation of the regulatory light chain (RLC) of the motor protein myosin-II, and so negatively regulates actomyosin-based contractility.

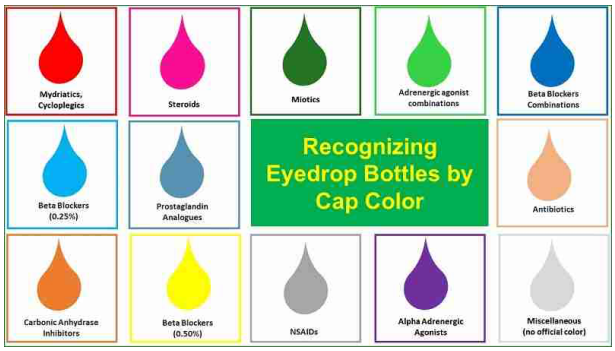
- Netarsudil was approved in 2017 by the FDA to topical use for POAG.
- A 2022 review of 17 trials concluded that the ocular hypotensive effect of netarsudil may be inferior to latanoprost and slightly inferior to timolol in POAG.
- SE: (1) Conjunctival hyperemia (53%) d/t relaxation of conjunctival blood vessels. Conjunctival hyperemia tends to be reduced with continued use. Administration at bedtime helps mitigate this hyperemia. (2) Conjunctival hemorrhage (20%) are tiny petechial micro hemorrhage. This SE is self-limiting in most patients and typically resolved with continued use. (3) Corneal deposits (20%; verticillata --> vortex keratopathy) usually resolves with discontinuation of netarsudil. 4) Erythema of eyelid (5-10%), lacrimation (5-10%) blurred vision and decreased visual acuity (5-10%).
- Dosage: Instill 1 drop into affected eye QHS.
- Cost: Netarsuil 0.02% 2.5 ml ($142.61) – brand, with no generic equivalence

Summary: Characteristics of Glaucoma Drugs

Drug Class	Mechanism of Action	Dosage	Efficacy	Local Side Effects	Systemic Side Effects	Advantages
Prostaglandin analogues	Increase uveoscleral outflow	Once daily	Most efficacious drug class; reduce IOP by 30% to 35% from baseline	Increased iris pigmentation, conjunctival hyperemia, hypertrichosis, exacerbation of herpes keratitis, cystoid macular edema, uveitis	Almost nil; some patients may have joint pains and flu-like illness	Most efficacious, minimal systemic side effects, first-line treatment choice worldwide
Beta-blockers	Decrease aqueous production through blockade of beta-adrenergic receptors on the ciliary body	Once or twice daily	Reduce IOP by 25% to 30%; extended use may reduce effectiveness	Punctate keratitis, allergy, corneal anesthesia	Bronchospasm, increased heart block, hypotension, depression, masking of hypoglycemic symptoms in diabetic patients	Relatively cheap, easily available, second-line treatment choice
Alpha-adrenergic agonists	Decrease aqueous production and increase uveoscleral outflow	Two or three times daily	Reduce IOP by 20% to 25% from baseline	Follicular conjunctivitis, contact dermatitis, blepharitis	Tachyphylaxis, crosses the blood-brain barrier, can cause central nervous system symptoms such as apnea and hypotension; contraindicated in infants	Particularly useful in reducing short-term IOP rise after anterior segment laser surgery
Carbonic anhydrase inhibitors	Decrease aqueous production by inhibiting carbonic anhydrase enzyme in the ciliary processes	Two or four times daily	Reduce IOP by 20% to 25% from baseline	Ocular surface irritation, corneal endothelial decompensation	Paresthesia, abdominal discomfort, weight loss, aplastic anemia; contraindicated in sulpha allergy	Only class with oral formulation; IOP-lowering effect seen within 1 hour; topical drug has good lipid solubility and easy corneal penetration
Cholinergic agonists	Increase trabecular outflow	Four times daily	Reduce IOP by 20% to 25% from baseline	Induced myopia, browache, miosis, iris cyst	Abdominal cramps, sweating, bronchospasm, diarrhea	Relatively inexpensive, easily available, acute treatment of angle closure attack

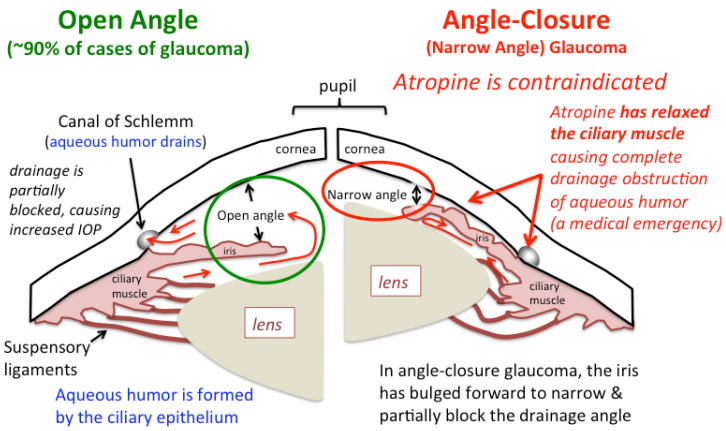
Anatomy of the Eye





Medical Management of Acute Angle-Closure Glaucoma

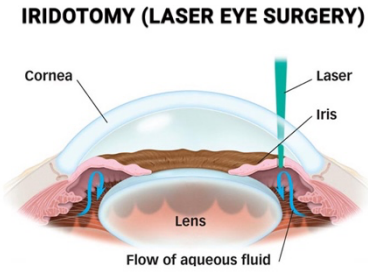
- If a patient admitted to the ED with an acute attack of angle-closure glaucoma cannot be emergently treated by an ophthalmologist within an hour, empiric treatment should be initiated if IOP is > 40 mmHg.

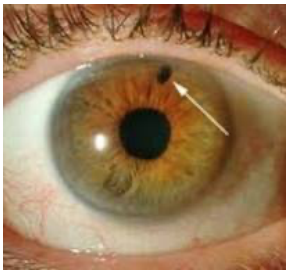


- Empiric treatment involves the prompt administration of pressure-lowering eye drops, given in one minute apart, plus acetazolamine 500 mg IV.
  - Timolol (Timoptic) 0.5% → 1 drop
  - Apraclonidine (Iodipine) 1% → 1 drop
  - Pilocarpine (Pilocar) 2% → 1 drop
  - Acetazolamine (Diamox) 500 mg IV → decreases production of aqueous humor → decreases IOP
  - Mannitol 1.5-2 GM/kg IVPB over 60 minutes may be given if needed under the guidance of an ophthalmologist. Mannitol is an osmotic diuretic → increases urinary output (UOP) → decreases IOP.

- If IOP remains persistently elevated, the ophthalmologist may perform an anterior chamber paracentesis to remove aqueous humor → decrease IOP.

- The treatment of choice for angle-closure glaucoma is a peripheral iridotomy, a procedure which uses laser technology to create a tiny hole in the peripheral iris.





- If a peripheral iridotomy does not remain patent, surgical peripheral iridectomy is performed to surgically remove some iris tissue to allow aqueous humor to reach the angle and Canal of Schlemm.