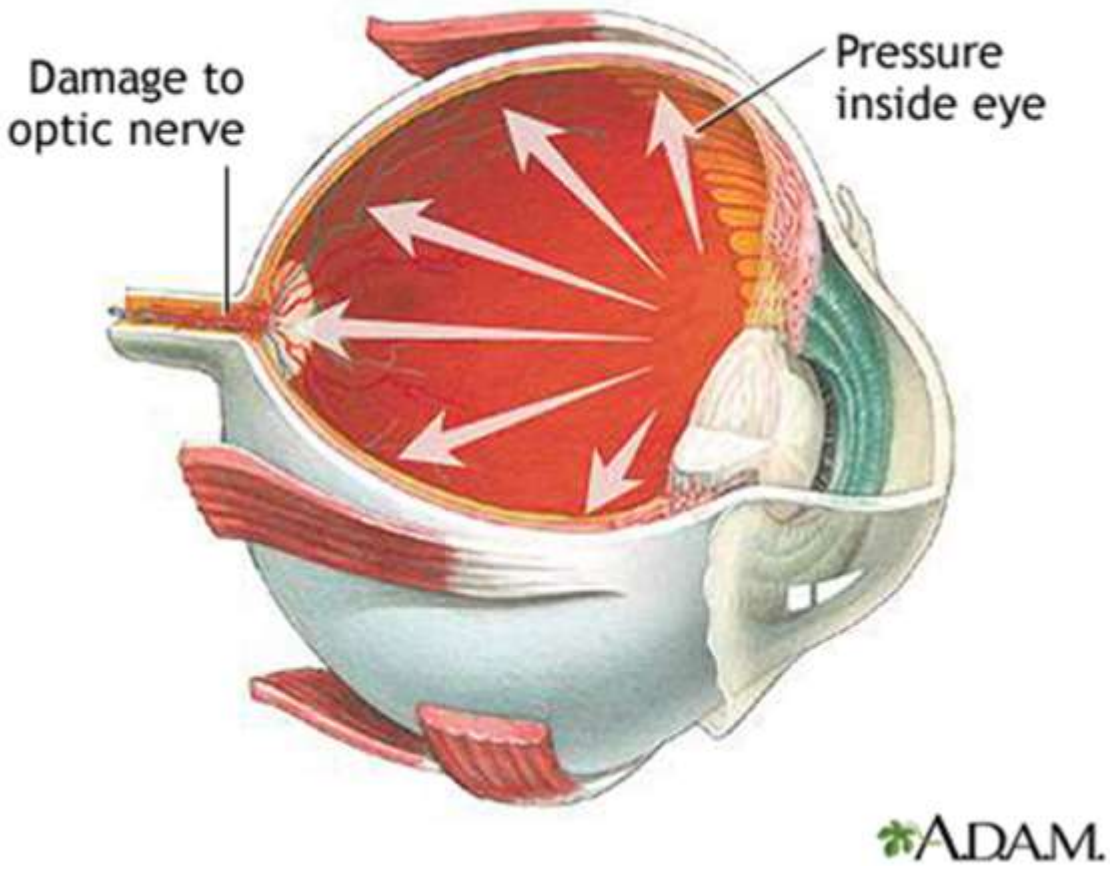
"We're hopeful the built up pressure will subside, but right now he's still in a glaucoma."

Glaucoma Pharmacotherapy

Karen Kopacek, MS, RPh

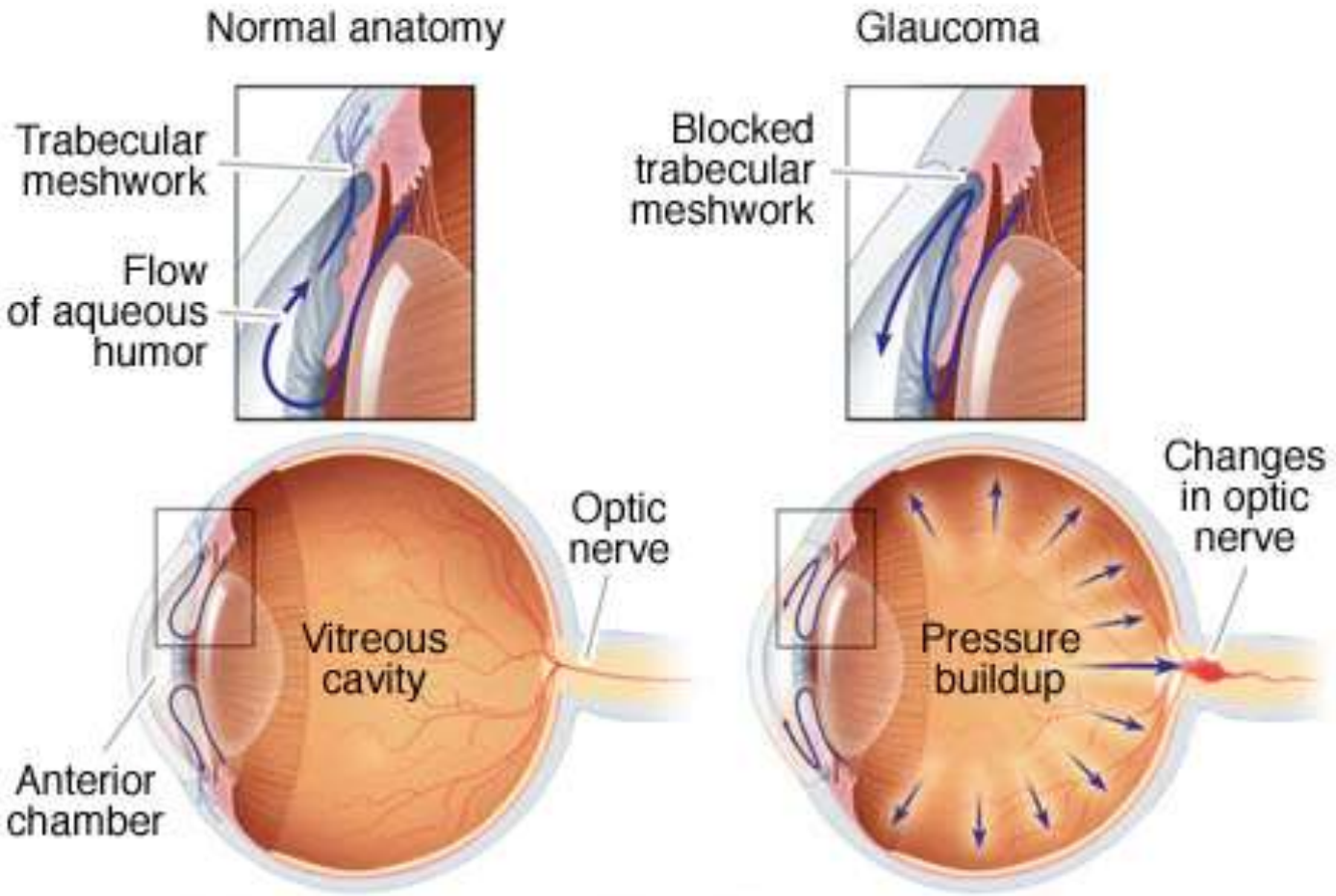
Glaucomas

- Group of optic neuropathies
- Two broad categories: Open-angle glaucoma and angle-closure glaucoma
  - Both can be primary diseases
  - Secondary glaucoma can result from trauma, certain medications, inflammation, tumor, or conditions such as pigment dispersion or pseudo-exfoliation



Weinreb RN et al. JAMA 2014;331(18):1901-11

POAG Definition



- **Primary open-angle glaucoma (POAG) is:**
  - a chronic, progressive neuropathy in adults
  - associated with an open anterior chamber angle
  - characterized by atrophy of the optic nerve and loss of retinal ganglion cells and their axons
  - Both optic nerve damage and visual field loss are present in at least one eye

Objectives

1. List key elements in the epidemiology, pathophysiology, diagnosis, and prognosis of primary open angle glaucoma (POAG).
2. Describe pharmacologic therapies for POAG: treatment goals, drug classes, MOA, efficacy, side effects, contraindications, dosing, and drug-disease state interactions.
3. Discuss the role of pharmacists in the treatment and management of POAG.

1. Key Elements of Primary Open Angle Glaucoma (POAG)

- A. Epidemiology
- B. Pathophysiology
- C. Diagnosis
- D. Prognosis

A. Epidemiology

- Estimated 45 million people worldwide have POAG[1]
- Glaucomas (OAG and ACG) are the second leading cause of blindness worldwide[1]
- Demographics:[2,3]

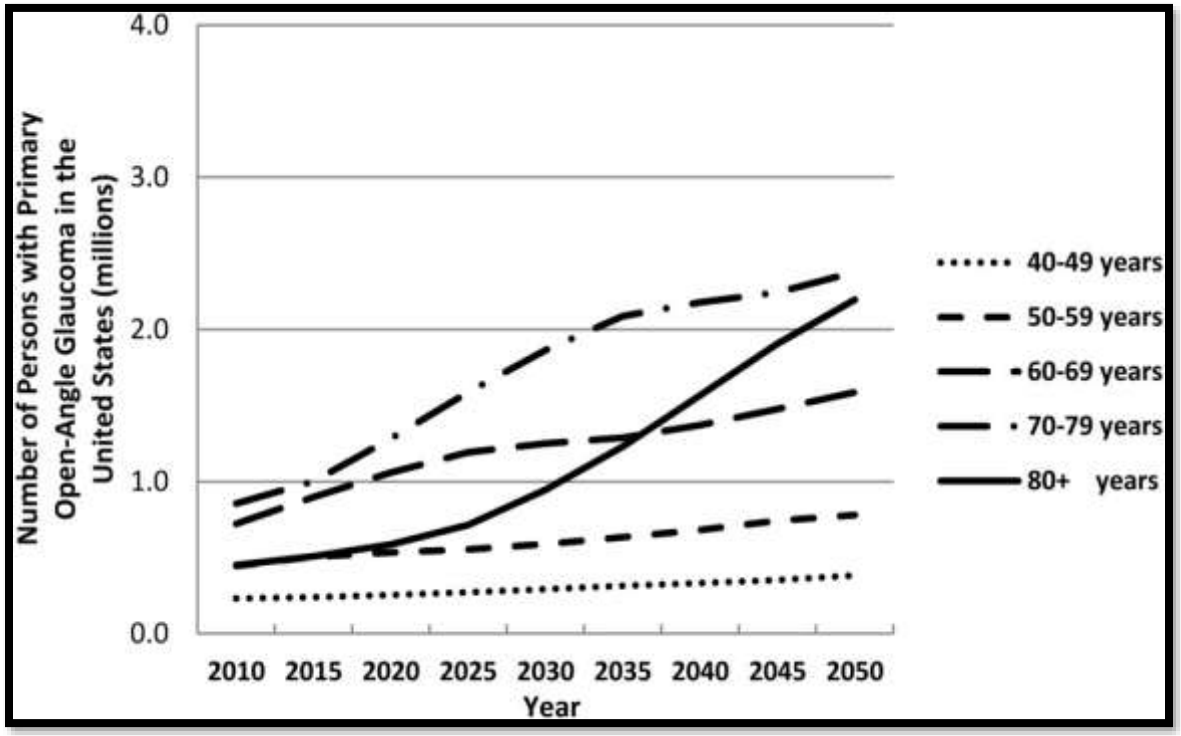
	2011	2050 estimate
Prevalence in US	**2.71 million**	**7.3 million**
Age group with highest prevalence	**70-79 years (31%)**	**same**
Sex with highest prevalence	**Women**	**same**
Ethnicity with highest prevalence	**Non-Hispanic Whites (44%)**	**Hispanic/Latino (50%)**
Largest demographic group	**White women**	**Hispanic/Latino men**

1. Am Academy Ophth 2016
2. Vajaranant T et al. Am J Ophth 2012;154:303-314
3. Quigley HA. Lancet 2011;377: 1367-77

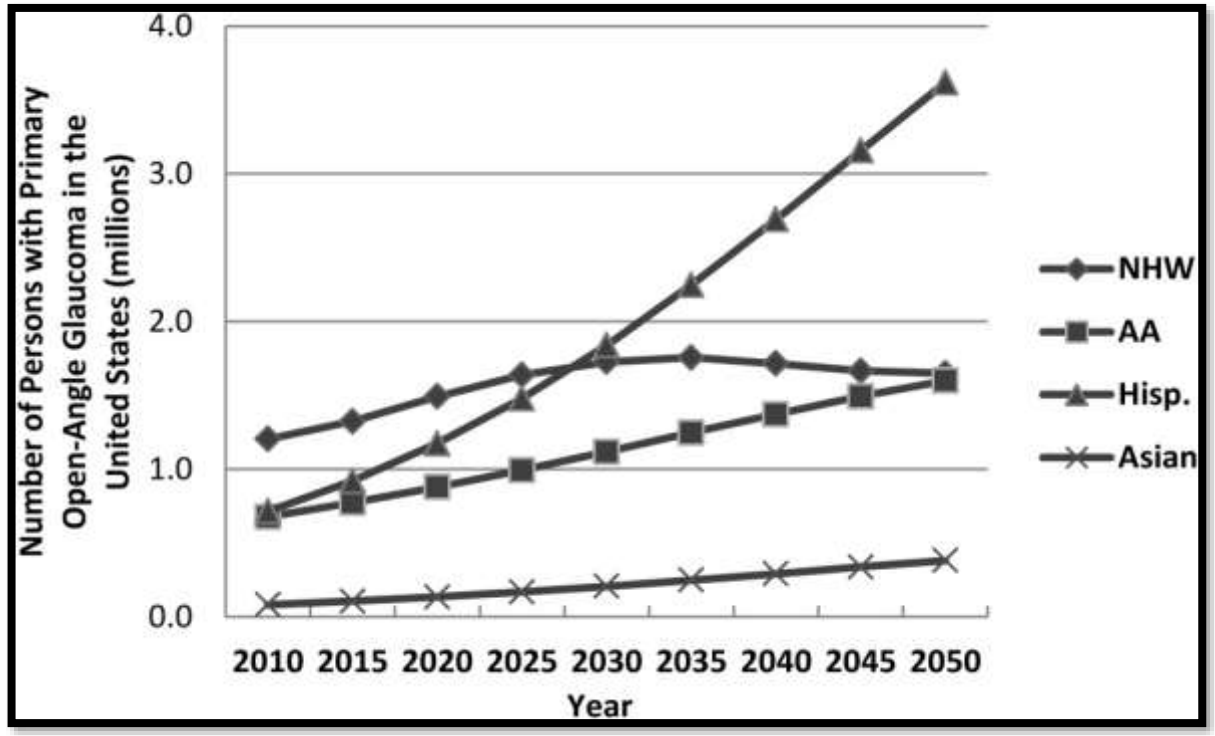
Estimated number of persons with POAG in the US by age and year (Graph 1) and race/ethnicity and year (Graph 2).

Key: NHW = non-Hispanic white; AA = African American; Hisp. = Hispanic/Latino.

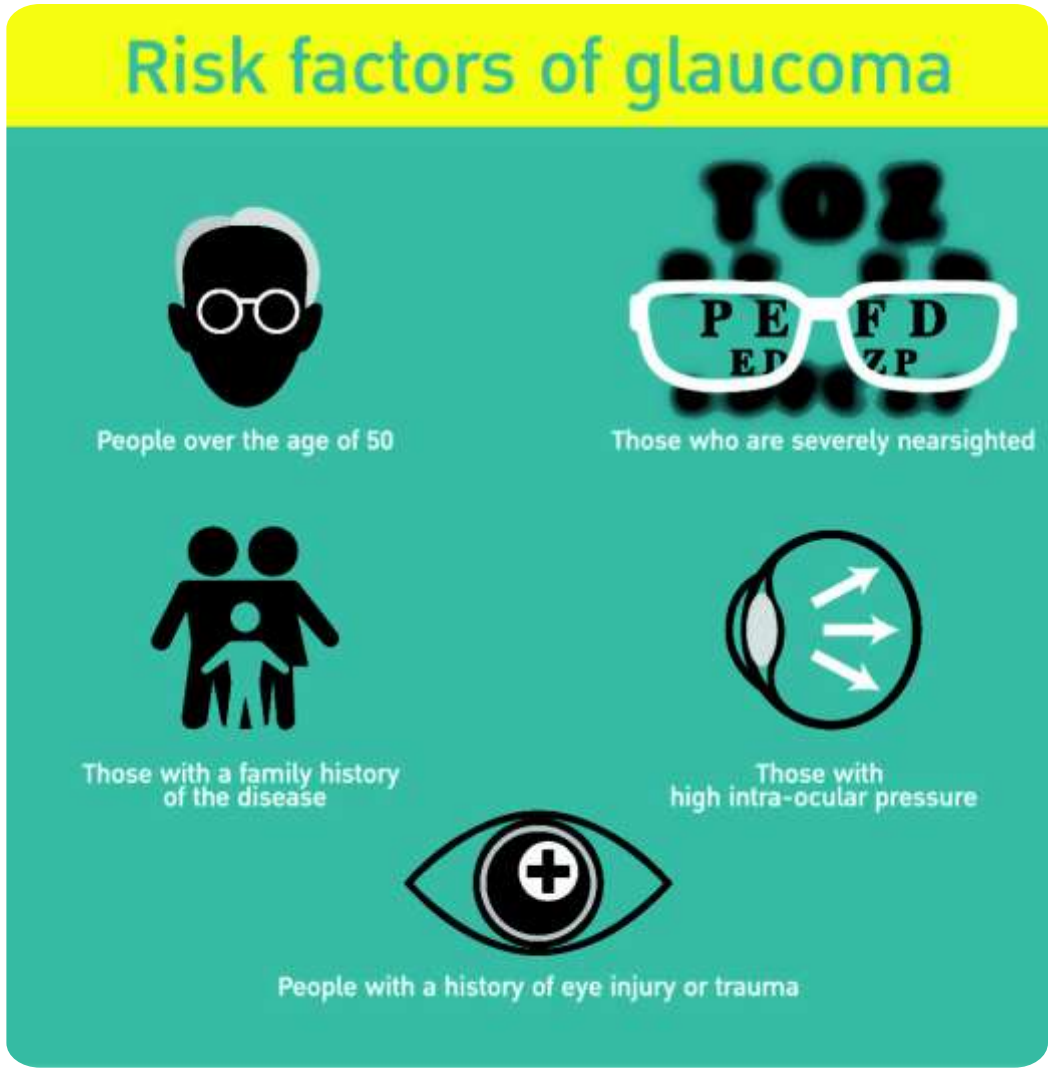
Graph 1



Graph 2



Vajaranant T et al. Am J Ophth 2012;154:303-314.



Risk Factors for POAG

- Higher IOP (> 22 mmHg)
  - Corticosteroids, anticholinergics
- Older age (> 40 years)
- Family history of glaucoma
- African race or Latino/Hispanic ethnicity
- Type 2 diabetes mellitus
- High myopia
- History of eye trauma
- Vascular disease: hypotension, vasospasm, systemic hypertension (HTN tx)
- Smoking? (higher risk in men)

Am Academy Ophth 2016; Weinreb et al. JAMA 2014;311:1901-11; Quigley HA. Lancet 2011;377:1367-77; McMonnies CW. J Optometry 2017;10:71-8..

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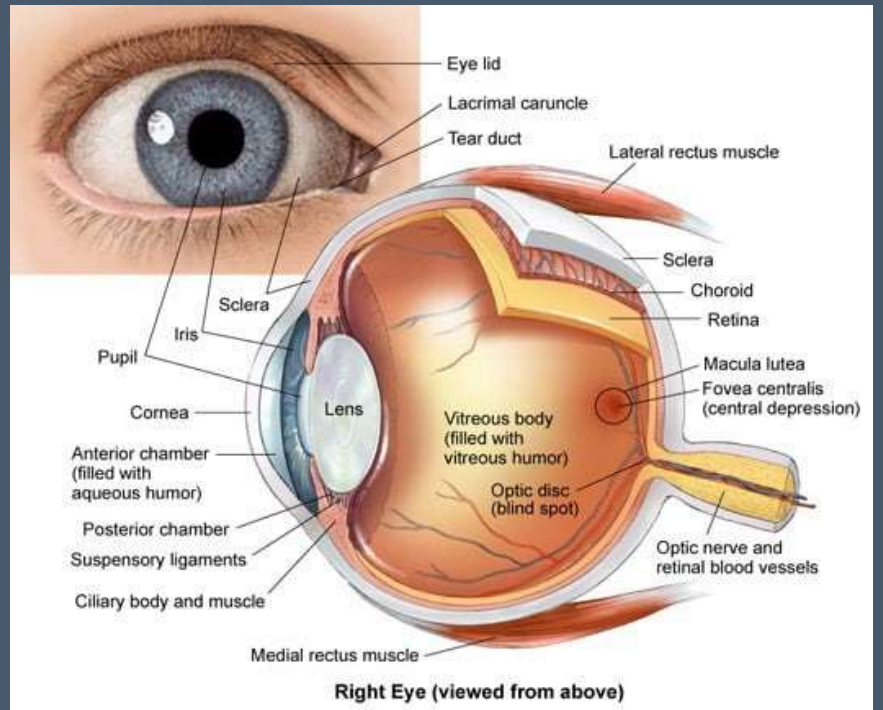
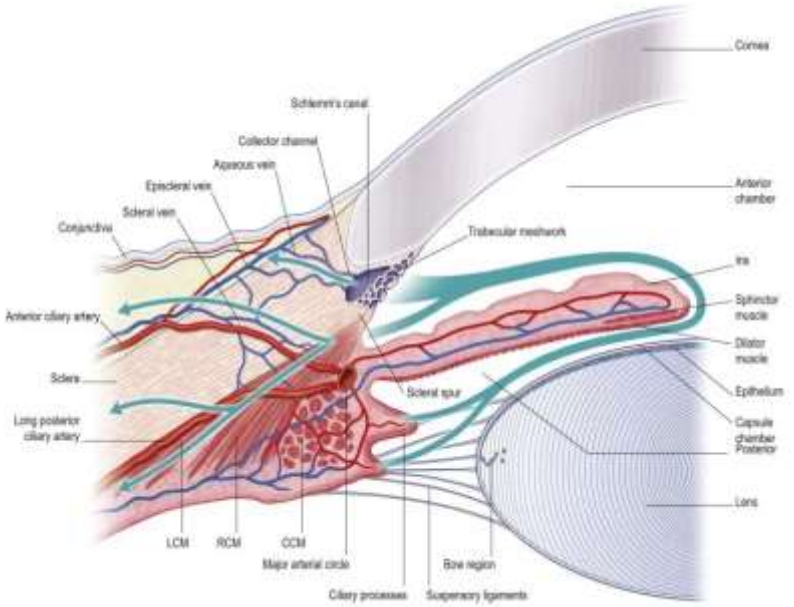
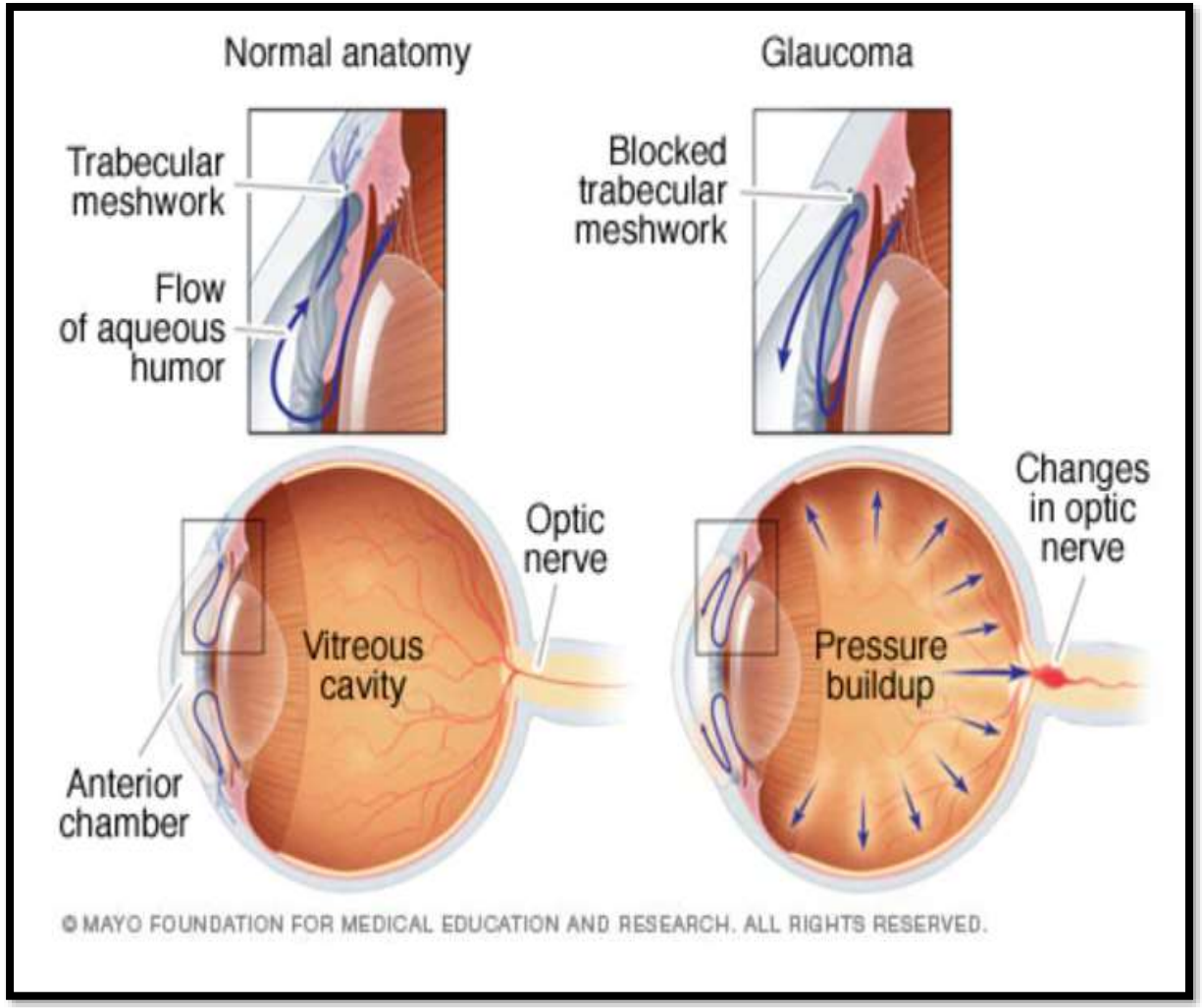




B. Pathophysiology of POAG: Normal Physiology

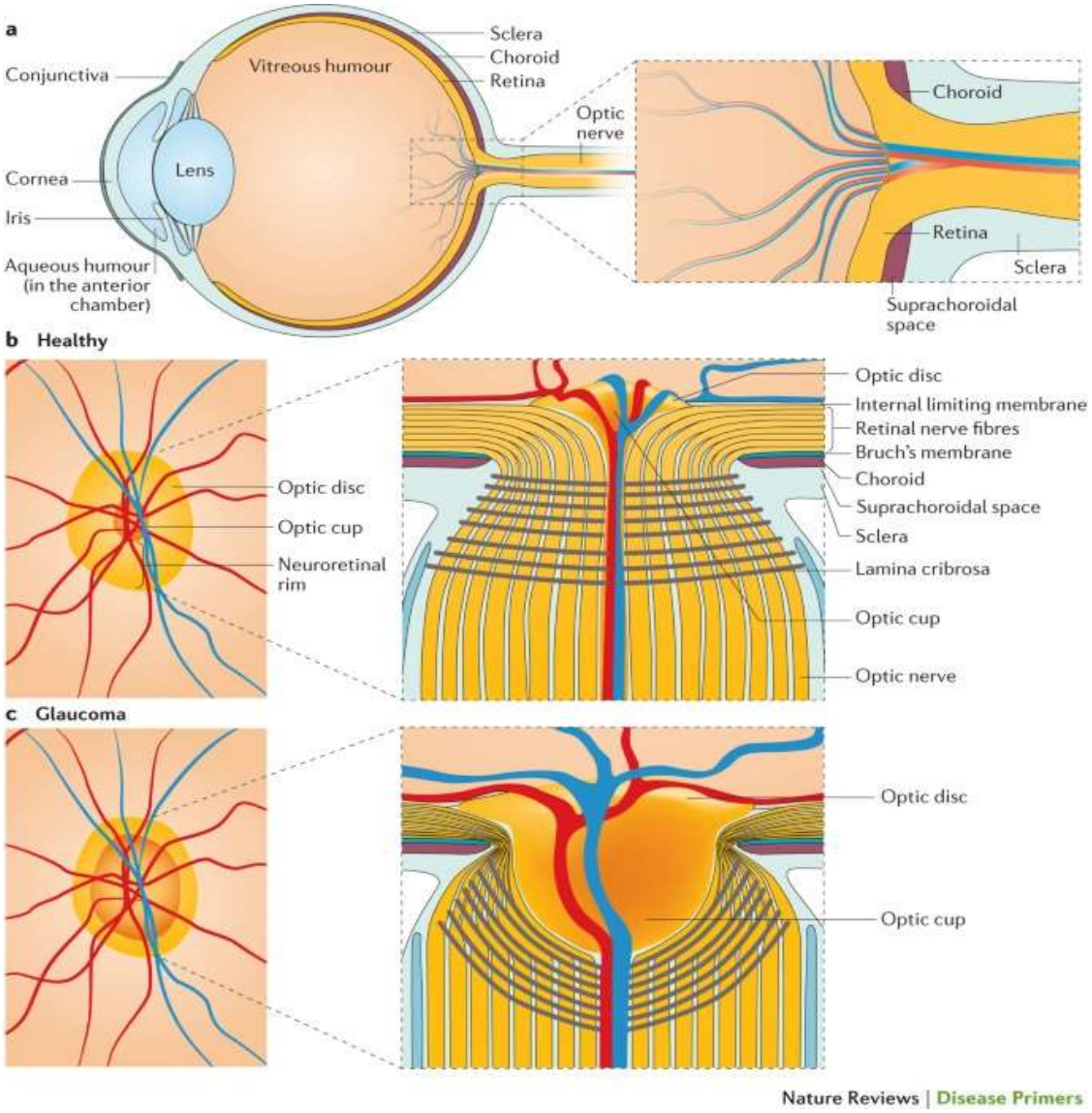
- Aqueous humor (AH) formed in ciliary body and its epithelium
- ***Carbonic anhydrase, α- and β-adrenergic receptors***, and sodium- and potassium-activated adenosine triphosphatases found on ciliary epithelium are involved with secretion
- Pressure in posterior chamber pushes AH between the iris and lens then through the pupil into anterior chamber.
- AH leaves the eye by filtration through trabecular meshwork to the Schlemm's canal (conventional outflow) and through the ciliary body and suprachoroidal space (uveoscleral or unconventional outflow).
- **Normal IOP 12-22 mmHg**

B. Pathophysiology of POAG



- Increased IOP in all types of glaucoma results from the decreased outflow of AH through trabecular meshwork
- ***Level of IOP is not the defining criterion for POAG!***
  - Increased IOP is associated with higher risk of glaucomatous damage
  - However, increased IOP is an insensitive and nonspecific diagnostic and monitoring tool
  - Patients with normal IOP also develop POAG
  - Patients with IOP > 22 may not develop POAG

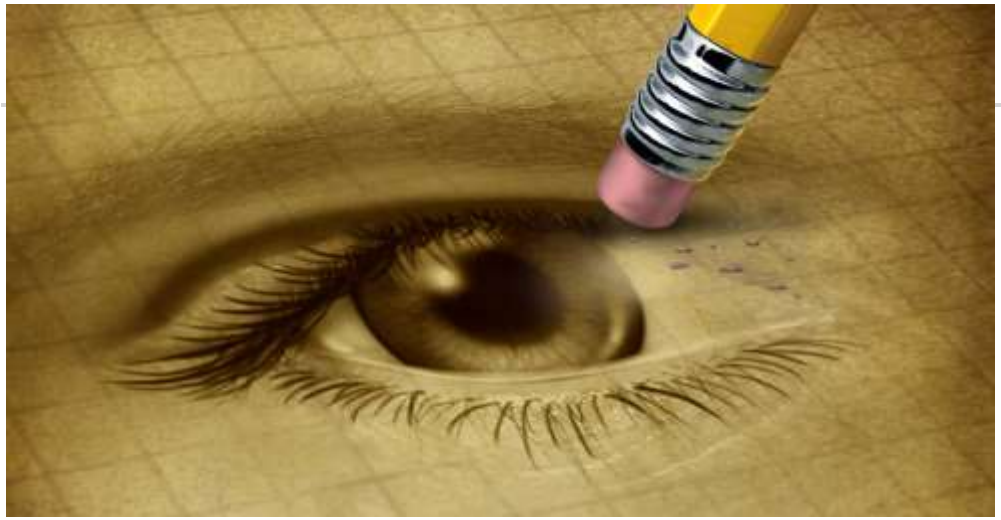
B. Pathophysiology of POAG



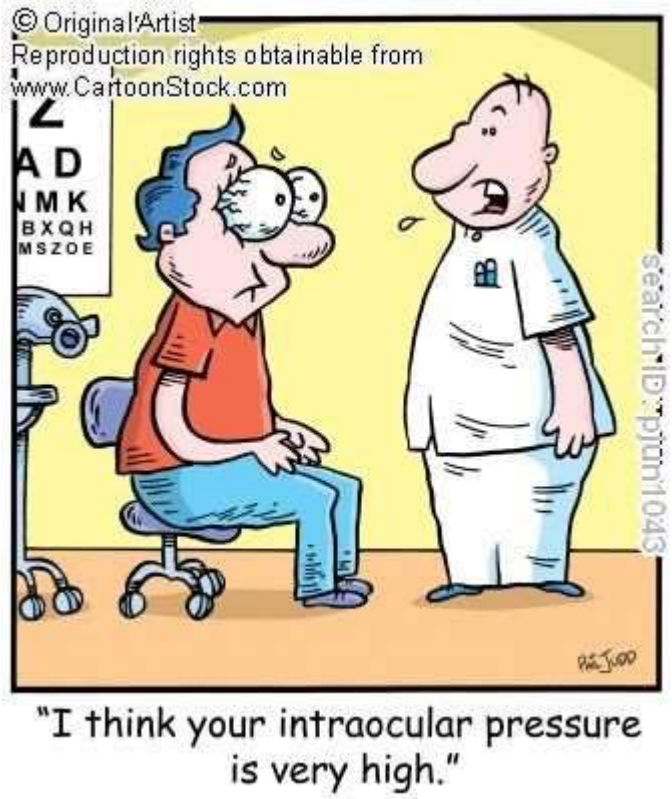
- Increased IOP causes mechanical stress and strain on posterior structures of the eye- optic disk, cup, optic nerve fibers
- Optic nerve cells and fibers (or retinal ganglion cells and axons) degenerate and die
- As ganglion nerve cells die and axon loss increases, cup becomes larger compared to the whole disk
- Progression leads to gradual reduction (constriction) in the peripheral visual field, development and enlargement of blind spots
- Typically affects both eyes

Understanding Glaucoma - Video posted in Canvas

Vision Changes with Glaucoma
-Video posted in Canvas



Pathophysiology Summary



Imbalance in aqueous humor production and drainage

Increased intraocular pressure

Optic nerve damage*

Vision loss*

1. Key Elements of Primary Open Angle Glaucoma (POAG)

A. Epidemiology

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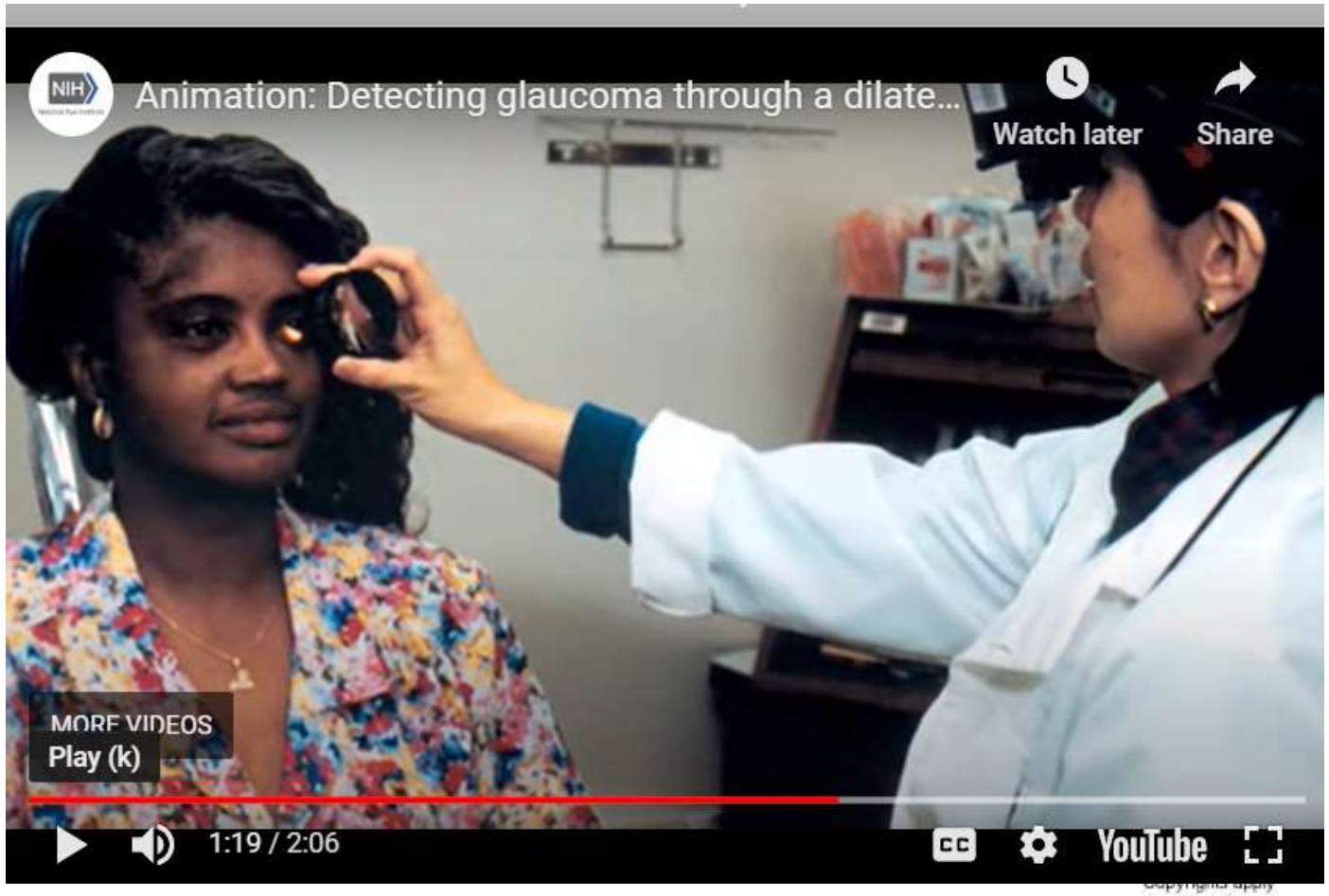
Glaucoma Diagnosis: Tonometry

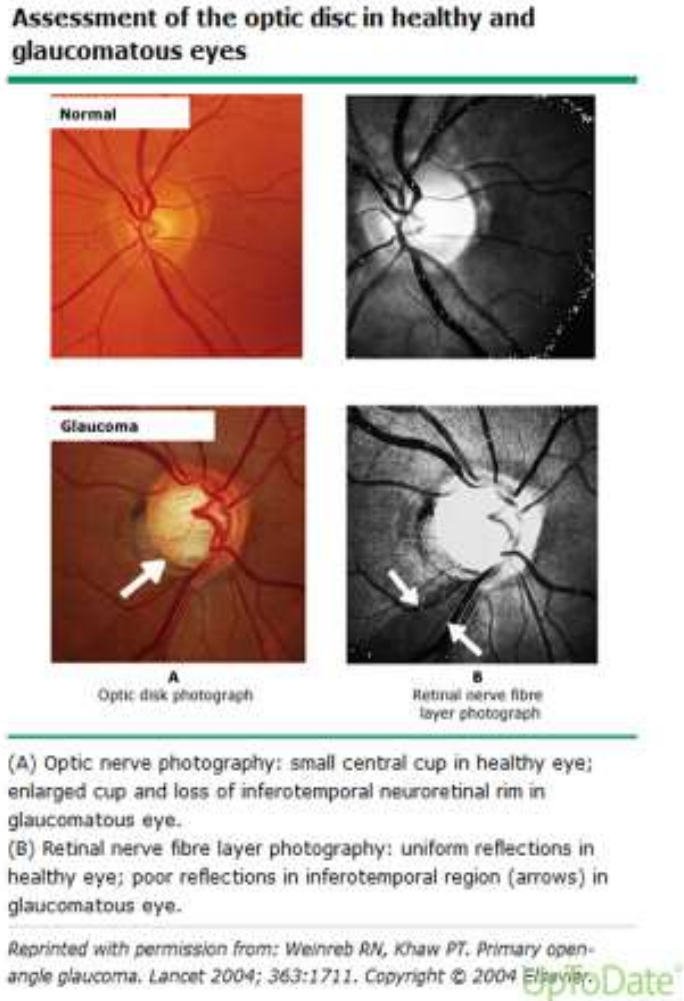

Applanation tonometry. UK. © Richard Scawn

- Methods to measures IOP:
  - Tonometry
  - Air pulse (non-contact)

Stevens S et al. Comm Eye Health. 2012;25:60.

Ophthalmoscopy- Fundus Exam

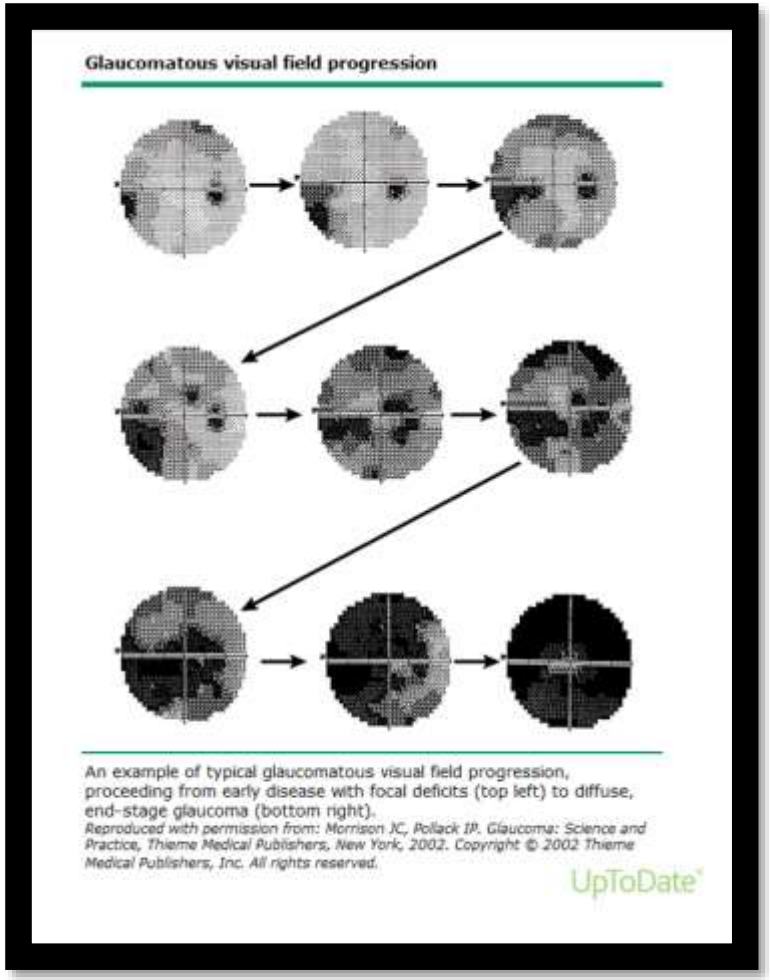




Spokes D. BMJ 2004;329;s56.

Perimetry: Visual Field Progression with Glaucoma

https://www.aao.org/eye-health/tips-prevention/visual-field-testing



- Functional loss is assessed by measuring light sensitivity at located in the 30° of vision
- Perimetry produces a map of complete field of vision
- Initial visual field exam makes diagnosis and completed longitudinally to measure disease progression

1. Key Elements of Primary Open Angle Glaucoma (POAG)

A. Epidemiology

B. Pathophysiology

C. Diagnosis

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D. Prognosis

- POAG typically has a slow progression over months to years
  - Progresses without causing symptoms until the disease with substantial amounts of neuronal damage
- Functional loss is not reversible
- Prognosis is excellent when discovered early and treated adequately
  - Estimated progression to bilateral blindness in treated pts: 4-22%
- Goal: preserve remaining visual field, maintain/improve QOL
  - Early intervention is essential
  - Only proven treatment is reducing IOP using eye drops, oral meds, laser therapy, and surgery

Objectives

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2. **Describe pharmacologic therapies for POAG: treatment goals, drug classes, MOA, efficacy, side effects, contraindications, dosing, and drug-disease state interactions.**
3. Discuss the role of pharmacists in the treatment and management of POAG.

A. Treatment Goals

- Am Academy of Ophthalmology guidelines recommend lowering IOP (irrespective of whether IOP is abnormal at baseline) to a target level at which the clinician believes that the rate of disease progression will be slowed sufficiently to avoid functional impairment
  - Initial target aims for 20-50% reduction in IOP from pretreatment pressure level
  - Target must be continuously reassessed during follow-up, depending on evolution of disease
- Target IOP should be achieved with fewest medications and minimal adverse effects
- Medication choice may be influenced by cost, adverse effects, and dosing schedules

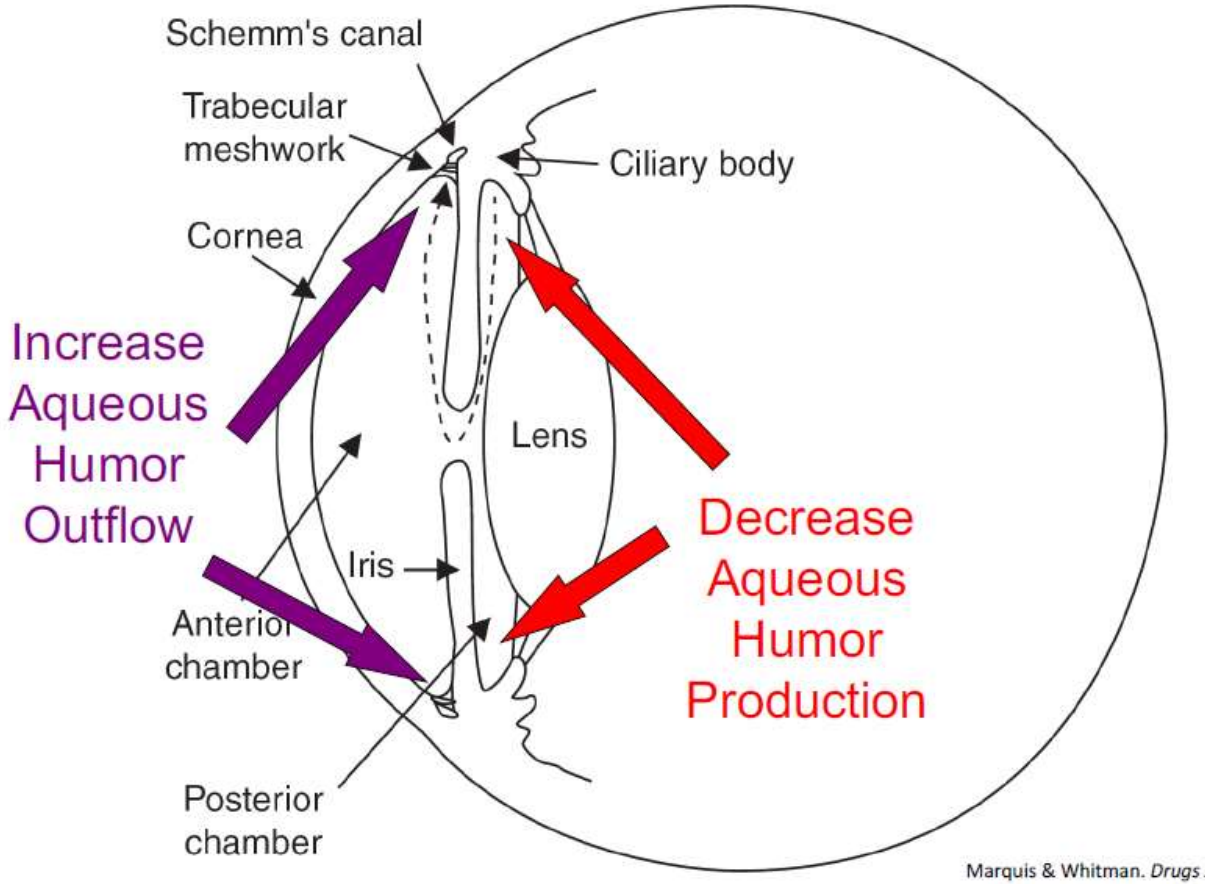
Weinreb RN et al. JAMA 2014;311(18):1901-11

B. Drug Classes

- Prostaglandin analogues
- β-adrenergic blockers
- α-adrenergic agonists
- Carbonic anhydrase inhibitors
- Cholinergic agonists

Pharmacology Approaches to Glaucoma

- Prostaglandin analogues
- α-adrenergic agonists
- Cholinergic agents



Marquis & Whitman. *Drugs Aging*. 2005;22(1):1-21.

- α-adrenergic agonists
- B-adrenergic blockers
- Carbonic anhydrase inhibitors

Prostaglandin Analogues

MOA	↓ IOP	ADEs	Considerations	Drugs	Dosing
Increase in uveoscleral (and lesser extent trabecular) outflow of AH	**25-35%**	*Ocular* Blurry vision Burning/stinging Dry eyes Eyelash changes Hyperpigmentation Herpes virus activation Keratitis Macular edema Uveitis *Systemic* Headache	Well tolerated and produce few systemic ADE Darkens hazel irises Conjunctival hyperemia (redness) is common May reactivate herpes simplex virus keratitis Avoid in uveitic glaucoma and pregnancy	Bimatoprost **Latanoprost** Tafluprost (PF) Travoprost	QHS QHS QHS QHS

Prostaglandin Analogue Adverse Effects

Non-treated eye Treated eye

Eyelash lengthening/bristling with bimatoprost administration. Note: Reprinted from Inoue K, Shiokawa M, Higa R, et al. Adverse periocular reactions to five types of prostaglandin analogs. Eye. 2012;26(11):1465–1472.19

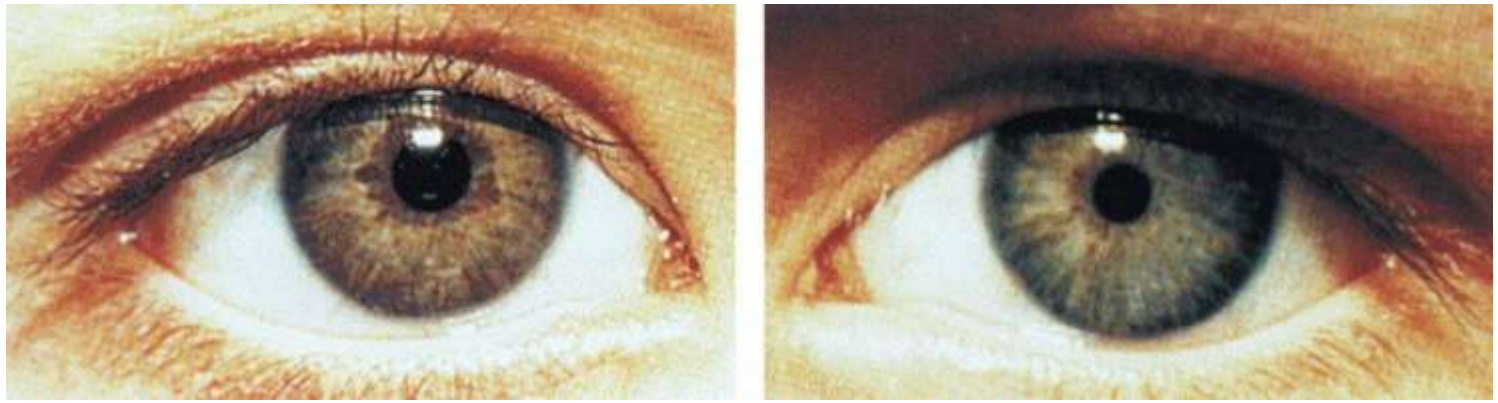
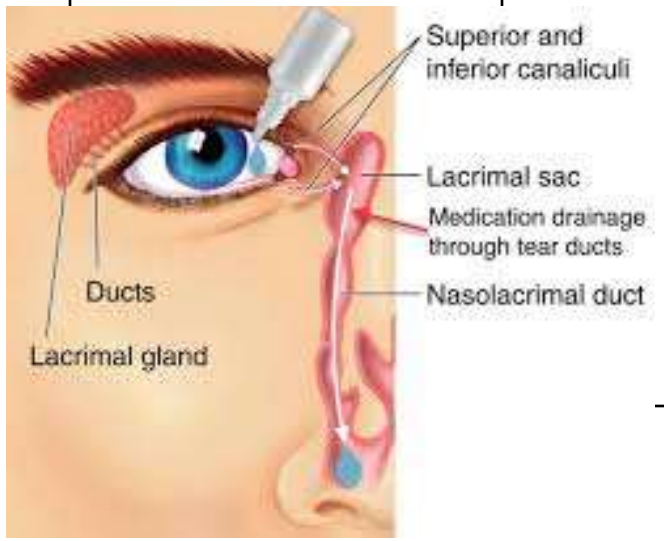


Fig. 3. Latanoprost-induced iris pigmentation in a 1-year-old child. The eye on the left side has been treated for 5 months. The eye on the right side has not been treated.

Stjernschantz JW et al. Surv Ophthal 2002;47;S162-S175

B-Adrenergic Blockers

MOA	↓ IOP	ADEs	Considerations	Drugs	Dosing
Reduction of AH production by ciliary body without producing effects on AH outflow	**20-30%**	*Ocular* Burning/stinging Dry eyes Keratitis Uveitis *Systemic* Bradycardia Bronchospasm (NS) Depression Fatigue Hypotension Syncope	*Use with caution** **Asthma (NS)** **COPD (NS)** **Cardiovascular: Bradycardia, heart block, heart failure** ***Nasolacrimal occlusion reduces risk or severity of systemic adverse effects**	*Selective* **Betaxolol** *Non-selective* Carteolol Levobunolol Metipranolol **Timolol**	 BID BID BID BID QD-BID



α-Adrenergic Agonists

MOA	↓ IOP	ADEs	Considerations	Drugs	Dosing
Decrease AH production (A, B) Increased uveoscleral outflow (B, D)	**18-27%**	*Ocular* Blepharitis Blurry vision Burning/stinging Conjunctivitis Allergic-type rxn: lid edema, eye discomfort, itching, hyperemia (A, B) *Systemic** Dry mouth/nose Fatigue GI upset Headache Hypotension Somnolence	Cardiovascular disease Renal disease Cerebrovasc disease DM HTN, other CV drugs **MAOIs** **TCAs** ***Nasolacrimal occlusion reduces risk or severity of systemic adverse effects**	*Selective* Apraclonidine **Brimonidine** *Non-selective* Dipivefrin	 BID-TID* BID-TID* BID ***Nasolacrimal occlusion may improve response and allow for longer dosing interval (BID)**

Carbonic Anhydrase Inhibitors

MOA	↓ IOP	ADEs	Considerations	Drugs	Dosing
Decrease AH formation via directly antagonizing ciliary epithelium carbonic anhydrase	**15-20%**	*Ocular* Blurry vision Burning/stinging Corneal edema Keratitis *Systemic** Anorexia Blood dyscrasias Depression Diarrhea electrolyte imbalances Kidney stones Malaise Bitter/metallic taste	*Ocular* Corneal endothelium compromise *Systemic** Aplastic anemia Hepatic impairment Kidney stones Renal impairment Sickle cell disease **Sulfonamide allergy** Thrombocytopenia	*Ocular* **Brinzolamide** **Dorzolamide** *Systemic** Acetazolamide Methazolamide *** Primarily due to oral agents**	 BID-TID BID-TID BID-QID BID-TID

Cholinergic (Miotic) Agents

MOA	↓ IOP	ADEs	Considerations	Drugs	Dosing
Contraction of ciliary muscle causes scleral spur to unfold trabecular Meshwork → Increased aqueous humor outflow	**20-30%**	*Ocular* Angle closure Blurry vision Burning/stinging Cataract Ciliary spasms Conj scar/shrink Corneal edema Keratitis Retinal detachment *Systemic* Bronchospasm Diaphoresis N/V/D Salivation	*Ocular* **Acute inflammation** Cataracts Hx retinal detach Severe myopia *Systemic* Asthma Bladder dsyfxn Cardiovascular COPD GI disease	Carbachol **Pilocarpine**	TID-QID TID-QID* ***Nasolacrimal occlusion may improve response and allow for longer dosing interval (BID)**

Initiation of Drug Therapy

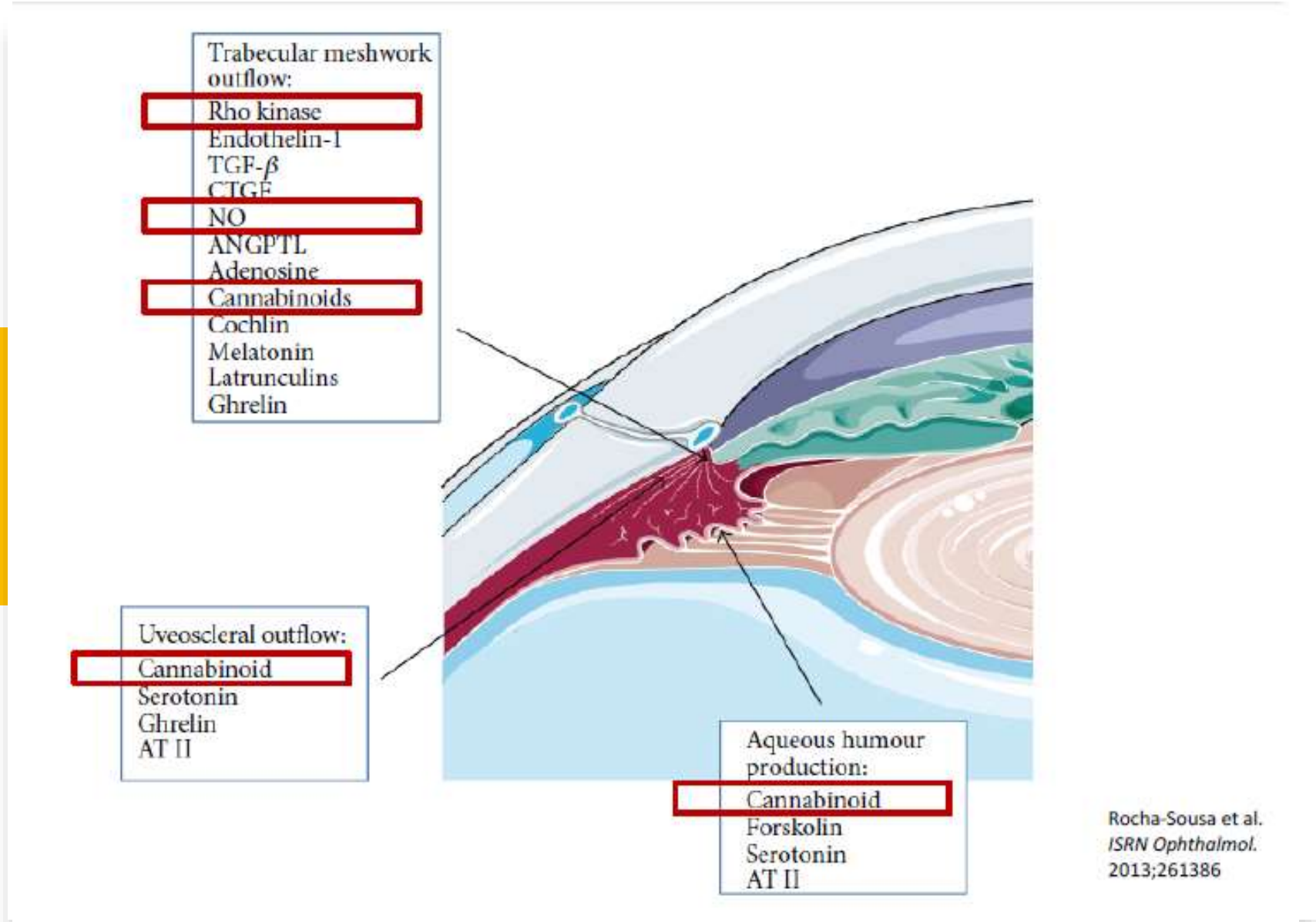
- First line: **prostaglandin analogues**, beta-blockers
- Second line: alpha agonists, carbonic anhydrase inhibitors, cholinergics
- Third line: dipivefrin

- Considerations:
  - Initiate therapy with single agent
  - If target IOP not reached, substitute initial drug with another before adding another drug with different MOA
  - If second drug for mono-therapy is ineffective, then add a second agent
  - If two drugs not effective, add third agent with different MOA
  - Combination products reduce exposure to preservatives (BAK) in patients taking > 2 ophth meds
  - Check IOP 4-6 weeks after initiation of new drug
  - Consider laser procedure or surgery if drug therapy not effective

Fixed Combination Products

- Daily Dosing
  - PA & BB: Latanoprost/Timolol (Xalacom)
  - PA & BB: Bimatoprost/Timolol (Ganfort)
  - PA & BB: Travoprost/Timolol (Duotrav)
- BID Dosing
  - BB & CAI: Timolol/Dorzolomide (Cosopt)
  - BB & AA: Timolol/Brimonidine (Combigan)
- TID Dosing
  - CAI & AA: Brinzolamide/Brimonidine (Simbrinza)

Sambhara & Aref. *Ther Adv Chronic Dis.* 2014;5(1):30-43.



Rocha-Sousa et al.
ISRN Ophthalmol.
2013;261386

New Therapeutic Targets

Cannabinoids and Marijuana

- Smoking marijuana has been found to lower IOP for 3-4 hours
  - Need to smoke a marijuana cigarette 8-10 times/day in over to control IOP over 24hrs!
  - Tolerance develops with repeated doses
- Smoking marijuana may increase HR and lower BP, cause conjunctival hyperemia, impair short-term memory and motor coordination
- Cannabinoids have potential in treatment of glaucoma as they have neuroprotective properties and effectively lower IOP
- Challenges include unwanted systemic SE (psychotropic, reduction of BP), possible tolerance, and difficulty in formulating a stable product

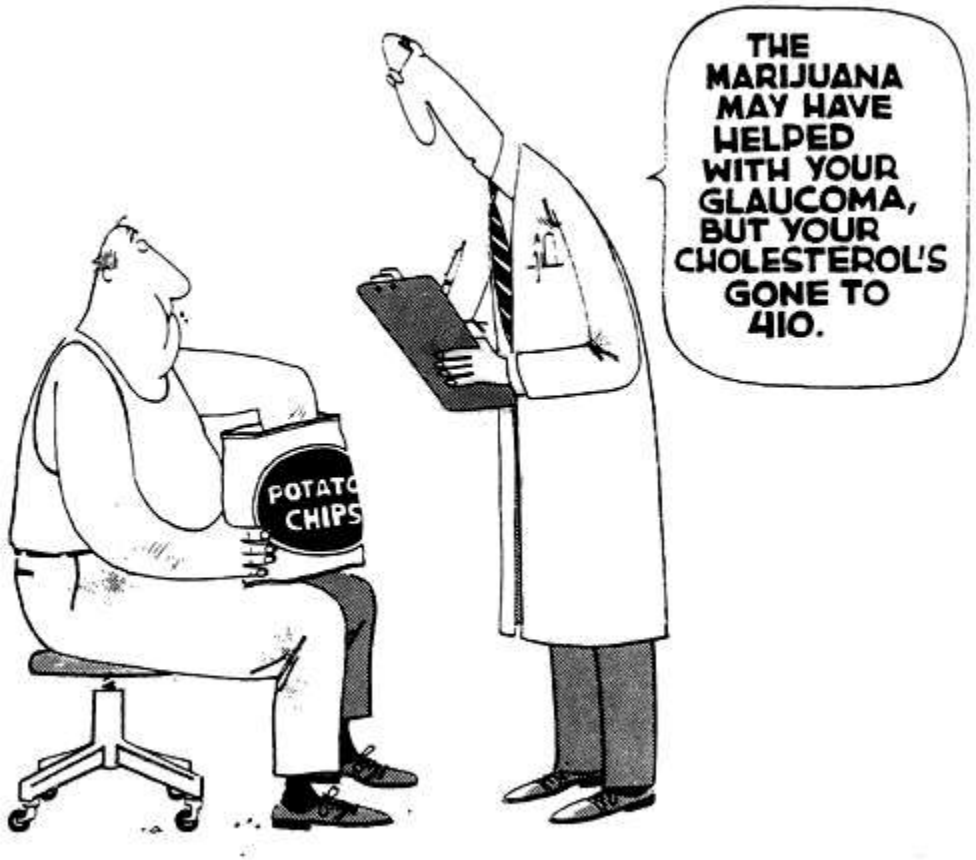


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Table 2

Suggestions for the Medical Management of Primary Open Angle Glaucoma and Ocular Hypertension*

1. Determine whether therapy is indicated for either OH or OAG. For OH, this may include performing a risk assessment analysis.
2. Rule out any secondary forms of glaucoma that may affect the therapy or prognosis.
3. Determine appropriate target pressure and readjust when necessary.
4. Use the fewest medications in the lowest concentrations needed to achieve the target pressure.
5. When the treatment is ineffective, initially substitute, rather than add, medication.
6. Continually stress, with the patient, the need for treatment compliance.
7. Make the treatment regimen as convenient for the patient as possible.
8. Teach the patient the correct method of instilling eyedrops.
9. Write down the treatment regimen for the patient, including time of day, number of drops, and color of bottle cap.
10. Communicate with the patient's family doctor.
11. Always ask the patient about changes in medical history and any side effects or adverse reactions to medications.
12. Continually educate the patient about risks and prognosis of the disease and side effects and adverse reactions of medications.

AOA (2011). OAG Optometric Clinical Practice Guideline.

Color Codes For Topical Ocular Medications
Anti-infectives
Anti-inflammatories/steroids
Mydriatics and cycloplegics
Non-steroidal anti-inflammatories
Miotics
Beta-blockers
Beta-blocker combinations
Adrenergic agonists
Carbonic anhydrase inhibitors
Prostaglandin analogs

Instilling Eye Drops - Video posted in Canvas

Other Tips:

- If you need to take more than one type of eye drop at the same time, **wait three to five minutes** between the different kinds of medication.
- Ask your ophthalmologist or pharmacist if it's OK to keep the drops in the refrigerator. **When the drops are cold it might be easier to feel the drop when it hits the eye,** so you can tell where it has landed.

https://www.aao.org/eye-health/tips-prevention/how-to-put-in-eye-drops

Patient Administration and Adherence

- Overall adherence is < 80% to glaucoma meds[1]
  - ~ one-half of patients do not instill drops correctly
- Barriers to adherence and administration[2]
  - Cognition, musculoskeletal problems (arthritis)
- Technique missteps[3]
  - Contaminating the bottle (18.2-80%)
  - Instilling more than one drop (11.3-60.6%)
  - Drop missing the eye (6.8-37.3%)
  - Washing hands before instillation (59%)
  - Not closing the eye after instillation (60%)
  - Not compressing tear duct after instillation (70%)

Autodrop Eye Drop Guide

1. Carpenter DM et al. Health Commun 2016;31(8):1036-42
2. Budenz DL. Ophthalmol 2009;116(1): S43-48
3. Davis SA et al. Curr Opinin Ophthalmol 2018;29(2):171-7

Six Tips to Avoid Eye Drop Mix-Ups

- **Keep them apart**. Do not store eye drops with any other drop bottles (like ear drops, superglue, or your pet's medication drops).
- **Keep them in their boxes**. Leave your eye drops and ear drops in their original boxes. There are often pictures of an ear or eye on the boxes, but not on the bottles.
- **Know your eyedrop names and cap colors**. Learn the name and cap color of your medications so you take them correctly. If you can't see your eyedrop bottles clearly enough to tell them apart, tell your doctor.
- **Check your medicine—out loud**. Read the dropper label out loud to help avoid mistakes.
- **Take eye and ear drops at different times**. This can help reduce the risk of mixing them up as you put them in your eyes/ears.
- **Throw away leftover drops**. Get rid of any leftover drops once you are through using them. The fewer the bottles, the fewer to get mixed up.

https://www.aao.org/eye-health/tips-prevention/eye-medication-mix-ups

Thank you!

Save Your EYES

JANUARY IS GLAUCOMA AWARENESS MONTH

"I'd hazard a guess there's an 'E' on there somewhere."