



## Ocular Pharmacology & Toxicology

### Objectives:

- Not Given

[ Color index : **Important** | **Notes** | Extra ]

**Resources:** Slides+434team+Notes

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# General pharmacological principles

## Pharmacodynamics:

- Mechanism of action : it's the effect of the drug in certain area
- Most drugs act by binding to regulatory macromolecules
  - A. Neurotransmitters
  - B. Enzymes
  - C. Hormonal receptors
- Agonist or antagonist (**receptor level**)
- Activator or inhibitor (**enzyme level**)

## Pharmacokinetics:

- it is the absorption, distribution, metabolism, and excretion of the drug : how the drug reach particular area and how it will be excrete.
- A drug can be delivered to ocular tissue as:

locally	<p style="text-align: center;"><b>Eye Drop</b></p> <p>We prefer local on systemic b/c of more effect on target tissue and less side effects</p> 	<ul style="list-style-type: none"><li>● <b>most common</b> , best way ,can use it during day time.<ul style="list-style-type: none"><li>● one drop = 50 <math>\mu</math>l , more than third of the drug will wash out so one drop is more than enough.</li><li>● volume of conjunctival cul-de-sac (is the fornix of conjunctiva that act as reservoir of drug) 7-10 <math>\mu</math>l</li></ul></li><li>● measures to increase drop absorption , so increase effect :<ul style="list-style-type: none"><li>○ wait 5-10 minutes between drops , it will decrease diluted effect.</li><li>○ compress lacrimal sac, that will decrease systemic effect.</li><li>○ keep lids closed (blinking wash of the drug into lacrimal sac) for 5 minutes after instillation , increase local effect and decrease systemic effect</li></ul></li><li>● doesn't reach in high concentrate behind the lense</li><li>● once you the bottle , if it preserved like in fridge you can use it till expiry date , it it outside the fridge then you can use for 1 month only</li></ul>
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## locally

### ointments



- **Increase the contact time** of ocular medication to ocular surface thus better effect
- It has the disadvantage of vision blurring (advise pt to put it before sleep)
- The drug has to be high lipid soluble with some water solubility to have the maximum effect as ointment.
- it cover the eye at the bed time.

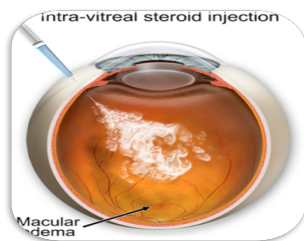
eye drop and ointments likely to affect anterior segment of the eye ( cornea , conjunctiva , anterior chamber , the iris , lens and posterior chamber , but not any further so , we need to use injection around the eye or directly to the eye

### Peri-ocular injections

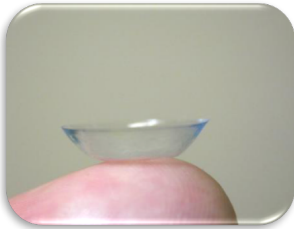
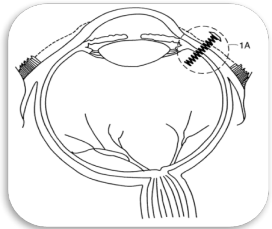


- **Reach behind iris-lens diaphragm** better than topical application. e.g. subconjunctival, subtenon (capsule surround the sclera and behind conjunctiva), peribulbar, or retrobulbar (bulbar eye globe).
- This route bypass the conjunctival and corneal epithelium : **good for drugs with low lipid solubility** (e.g. penicillins)
- Also steroid (reduce inflammation) and local anesthetics can be applied this way
- Use it when higher concentration , longer duration wanted in the anterior chamber so inject behind the eye , and use it in critical condition like Endophthalmitis which is ( inflammation inside the eye ) and give antibiotic
- Use short needle or you will puncture the glop

### Intraocular injections



- Intracameral (anterior chamber) or intravitreal, e.g:
  - intracameral acetylcholine (miochol) during cataract surgery
  - Intravitreal antibiotics in cases of endophthalmitis
  - Intravitreal steroid in macular edema
  - Intravitreal anti-VEGF for DR.

<p><b>locally</b></p>	<p><b>Sustained- release devices</b></p>	<ul style="list-style-type: none"> <li>• These are devices that deliver an adequate supply of the medication at a steady-state level ,e.g.:</li> </ul> <ol style="list-style-type: none"> <li>1. Ocusert delivering pilocarpine.</li> <li>2. Timoptic XE delivering timolol.</li> <li>3. Ganciclovir sustained-release intraocular device.</li> <li>4. Collagen shields.</li> <li>5. Liposomes.</li> </ol> <p>For pt who needs to put the drug many times per day.</p> <div style="display: flex; justify-content: space-around; align-items: center;">   </div>
<p><b>systemic</b></p>	<ul style="list-style-type: none"> <li>• Oral or IV.</li> <li>• Factor influencing systemic drug penetration into ocular tissue:</li> </ul> <ol style="list-style-type: none"> <li>1. <b>lipid solubility of the drug:</b> more penetration with high lipid solubility , Major factor : more lipid binding less effect.</li> <li>2. <b>Protein binding:</b> more effect with low protein binding</li> <li>3. <b>Eye inflammation:</b> more penetration with ocular inflammation, note -: second generation cephalosporin in normal situation doesn't cross blood brain barrier ( BBB) in adequate concentration but in meningitis even second generation can cross BBB so high concentration in the eye</li> </ol>	


❖ **Factors influencing local drug penetration into ocular tissue:**

<p><b>Drug concentration:</b></p>	<p>The higher the concentration the better the penetration e.g. pilocarpine 1-4%.</p>
<p><b>Viscosity:</b></p>	<p>Higher viscosity increases drug penetration by:</p> <ul style="list-style-type: none"> <li>• <u>increasing the contact time with the cornea.</u></li> <li>• <u>altering corneal epithelium.</u></li> </ul>
<p><b>Lipid solubility:</b></p>	<p><b>The higher lipid solubility the more the penetration</b> (lipid rich environment of the epithelial cell membranes).</p>
<p><b>pH:</b></p>	<p>the normal tear pH is 7.4 and if the drug pH is much different, this will cause reflex tearing (more drug acidity &gt;&gt; more tear &gt;&gt; more washing out of the drug ).</p>

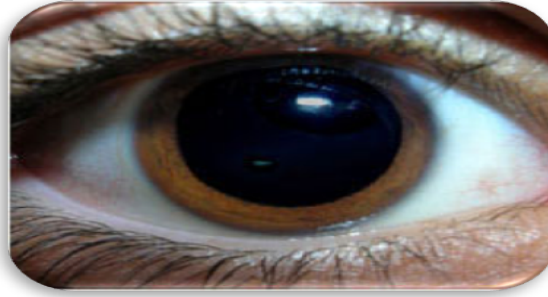
## Ocular pharmacotherapeutics:

### ❖ cholinergic agents (agonists):



<b>Directly acting agonists:</b> [e.g. pilocarpine, acetylcholine]	<b>Indirectly acting (anticholinesterases) :</b> More potent with longer duration of action	
Uses: To Induce miosis, for glaucoma.	<b>Reversible inhibitors</b> [e.g. physostigmine <b>used in the diagnosis of Myasthenia Gravis</b> ].	<b>Irreversible inhibitors</b> [e.g. phospholine iodide].
Mechanisms: <ul style="list-style-type: none"> <li>• Miosis by contraction of the iris sphincter muscle.</li> <li>• Accommodation by circular ciliary muscle contraction.</li> <li>• increases aqueous outflow (<b>inside eye to outside</b>) through the trabecular meshwork by longitudinal ciliary muscle contraction.</li> </ul>	<ul style="list-style-type: none"> <li>• Used in glaucoma and lice infestation of lashes.</li> <li>• Side effect: CNS side effects.</li> </ul>	<ul style="list-style-type: none"> <li>• Used in accommodative esotropia.</li> </ul>  <p>(<b>they have strabismus when focusing in typically farsightedness</b> )</p>
Side effects: <ul style="list-style-type: none"> <li>• <b>Local:</b> diminished vision (<b>myopia with long use</b> ), headache, cataract, miotic cysts, and rarely retinal detachment.</li> <li>• <b>Systemic side effects:</b> diarrhea, lacrimation, salivation, perspiration, bronchospasm, nausea, vomiting and urinary urgency.</li> </ul>		<ul style="list-style-type: none"> <li>• Side effect: iris cyst and anterior subcapsular cataract.</li> <li>• <b>Contraindicated :</b> in angle closure glaucoma, asthma, Parkinsonism -causes apnea if used with succinylcholine or procaine.</li> </ul>
<b>Contraindications:</b> asthma, Parkinsonism		

## ❖ cholinergic antagonists:

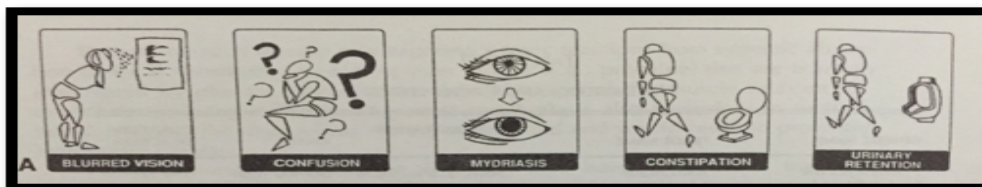


- E.g. tropicamide, cyclopentolate, homatropine, **atropine** ( stays for 2 weeks ).
- **cause:** mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle **(so there is loss of accommodation)**)
- Uses: fundoscopy, cycloplegic refraction **(procedure to measure accommodation)** , anterior uveitis **(because it's attenuate endotoxin induced uveitis )**.



### Side effects:


- local: **allergic reaction**, blurred vision
- Systemic: nausea, vomiting, pallor, vasomotor collapse, constipation, urinary retention, and confusion
- Specially **in children** they might cause flushing, fever, tachycardia, or delirium



- Treatment by DC or physostigmine
- In children ointment better than eye drop cause not going to lacrimal system so less systemic effect.

❖ **Adrenergic agonists:**

**be careful for: cardiac disease, asthma and BP**

<b>Non-selective agonists</b> ( $\alpha_1$ , $\alpha_2$ , $\beta_1$ , $\beta_2$ ) E.g. epinephrine, depevefrin (pro-drug of epinephrine)	<b>Alpha-1 agonists</b> (e.g. phenylephrine)	<b>Alpha-2 agonists</b> (e.g. brimonidine, apraclonidine)
Uses: glaucoma	Uses: <b>mydriasis (without cycloplegia)</b> , decongestant	Uses : glaucoma treatment [ treatment of the open angle not the closure angle ] and prophylaxis after glaucoma laser procedures
Side effects: headache, arrhythmia, <b>increased blood pressure, conjunctival adrenochrome</b> (pigments in conjunctival fornix in pt use adrenergic drugs), cystoid macular edema in aphakic (without lens) eyes	Adverse effect: <ul style="list-style-type: none"> <li>• Can cause significant <b>increase blood pressure</b> especially in infant and susceptible adults</li> <li>• Rebound congestion</li> <li>• Induce acute angle-closure glaucoma in patients with narrow angles</li> </ul>	Mechanism: decrease aqueous production, and increase uveoscleral (drainage 90% by canal of schlemm, 10%outflow uveoscleral)
Contraindication :in closed angle glaucoma , cardiac patient   Pic : notes the small dots if it present, you have to ask about these drug, the dots are dangerous because it is a pigmentation lesion	<b>Contraindication</b> : cardiac patient	<b>Side effects:</b> <ul style="list-style-type: none"> <li>• <b>Local:</b> allergic reaction, mydriasis, lid retraction (it activates sympathetic which innervates muller muscle)</li> <li>• <b>Systemic:</b> oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks</li> </ul> <b>Contraindications:</b> infants, MAO inhibitors users MAO : monoamine oxidase inhibitors for depression



## ❖ Adrenergic antagonists:

Alpha adrenergic antagonists Not widely used	Beta-adrenergic blockers
E.g. thymoxamine, dapiprazole	E.g. <ul style="list-style-type: none"> <li>• nonselective : timolol (commonly used to treat glaucoma), carteolol</li> <li>• selective: betaxolol (beta 1 “cardioselective”) (Good for asthmatic)</li> </ul>
<b>Uses:</b> to reverse pupil dilation produced by phenylephrine (better not to be used because of the risk of retinal detachment )	<b>Uses:</b> glaucoma (by suppressing aqueous production)
	<b>Mechanism:</b> reduce the formation of aqueous humor by the ciliary body
	<b>Side effects:</b> bronchospasm (less with betaxolol) (non-selective:exacerbates bronchial asthma, COPD ) , cardiac impairment

## ❖ Carbonic anhydrase inhibitors:

**(carbonic anhydrase have a role in producing aqueous humor) :**

- E.g. acetazolamide, dorzolamide
- Uses: glaucoma, cystoid macular edema, pseudotumor cerebri
- Mechanism: aqueous suppression
- Side effects: myopia, paresthesia, GI upset, headache, altered taste and smell (decreases CSF production) , Na and K depletion, metabolic acidosis, renal stone, bone marrow suppression “aplastic anemia”
- Contraindication: sulpha allergy, digitalis user's , pregnancy



## ❖ Osmotic Agents:

(used to suppress IOP as fast as possible in Acute attacks) :

- Dehydrate vitreous body which reduce IOP significantly
- E.G.
  1. Glycerol 50% syrup (cause nausea, hyperglycemia)
  2. Mannitol 20% IV (cause fluid overload, avoid in heart failure) (screen CVS before use)
- Use in case of acute angle closure glaucoma to reduce IOP rapidly.

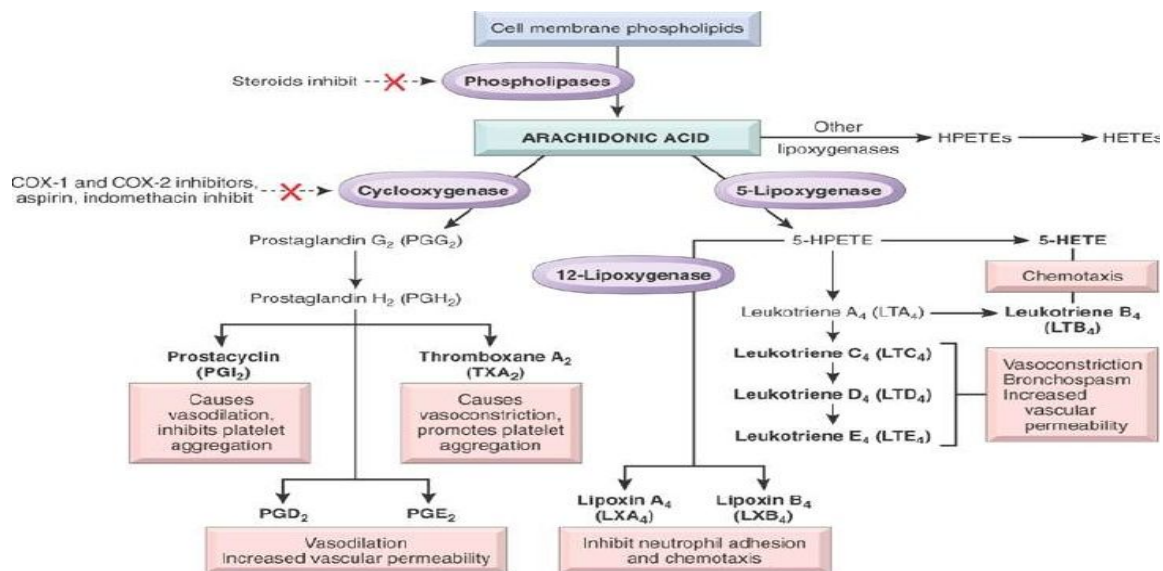
## ❖ Prostaglandin analogues:



- E.g. latanoprost, bimatoprost, travoprost, unoprostone.
- **Uses:** glaucoma.
- **Mechanism:** increase uveoscleral aqueous outflow.
- **Side effects:** darkening of the iris (heterochromia iridis), lengthening and thickening of eyelashes, intraocular inflammation, macular edema.

## ◆ Anti-Inflammatory:

	Corticosteroids		NSAIDs
	Topical	Systemic	
<b>Example</b>	<ul style="list-style-type: none"> <li>Fluorometholone</li> <li>remixolone</li> <li>prednisolone</li> <li>Dexamethasone</li> <li>hydrocortisone</li> </ul>	<ul style="list-style-type: none"> <li>Prednisolone</li> <li>cortisone</li> </ul>	<ul style="list-style-type: none"> <li>ketorolac,</li> <li>Diclofenac</li> <li>flurbiprofen</li> </ul>
<b>uses</b>	<ul style="list-style-type: none"> <li>postoperatively</li> <li>anterior uveitis</li> <li>severe allergic conjunctivitis</li> <li>vernal keratoconjunctivitis</li> <li>prevention and suppression of corneal graft rejection</li> <li>Episcleritis</li> <li>scleritis</li> </ul>	<ul style="list-style-type: none"> <li>posterior uveitis</li> <li>optic neuritis</li> <li>temporal arteritis with anterior ischemic optic neuropathy</li> </ul>	<ul style="list-style-type: none"> <li>postoperatively</li> <li>mild allergic conjunctivitis</li> <li>episcleritis</li> <li>mild uveitis</li> <li>cystoid macular edema</li> <li>preoperatively to prevent miosis during surgery "to inhibit prostaglandin which is known to constrict the pupil"</li> </ul>
<b>Mechanism</b>	<ul style="list-style-type: none"> <li>inhibition of arachidonic acid release from phospholipids by inhibiting phospholipase A2</li> </ul>		<ul style="list-style-type: none"> <li>inactivation of cyclo-oxygenase enzyme (prevent formation of PG which causes miosis, so we use it in cataract surgery)</li> </ul>
<b>Side Effects</b>	<ul style="list-style-type: none"> <li>susceptibility to infections</li> <li>glaucoma</li> <li>cataract</li> <li>ptosis</li> <li>mydriasis</li> <li>scleral melting</li> <li>skin atrophy</li> </ul>	<ul style="list-style-type: none"> <li>Local: posterior subcapsular cataract, glaucoma, central serous retinopathy</li> <li>Systemic: suppression of pituitary-adrenal axis, hyperglycemia, osteoporosis, peptic ulcer, psychosis</li> </ul>	<ul style="list-style-type: none"> <li>Stinging</li> </ul>



**Anti Allergics (Patient must present with itching; Avoid allergens, cold compress, lubrications)**

Type	Example	Mechanism and Uses	Side Effect
<b>Anti-Histamines</b>	<ul style="list-style-type: none"> <li>● Pheniramine</li> <li>● levocabastine</li> </ul>	Work by <b>blocking histamine</b> that is produced by the body in response to allergens or irritants	<ul style="list-style-type: none"> <li>● Drowsiness.</li> <li>● bradycardia and overdose may lead to sleep disorders.</li> </ul>
<b>Decongestants</b>	<ul style="list-style-type: none"> <li>● naphazoline</li> <li>● phenylephrine</li> <li>● tetrahydrozoline</li> </ul>	used to relieve redness, puffiness, and itchy/watering eyes due to colds, allergies, or eye irritations	<ul style="list-style-type: none"> <li>● Stinging.</li> <li>● Redness.</li> <li>● widened pupils, or blurred vision.</li> </ul>
<b>Mast cell stabilizers</b>	<ul style="list-style-type: none"> <li>● cromolyn,</li> <li>● lodoxamide</li> <li>● pemirolast</li> <li>● nedocromil</li> <li>● olopatadine</li> </ul>	They <b>block a calcium channel</b> essential for mast cell degranulation, stabilizing the cell and thereby <b>preventing the release of histamine</b> and related mediators.	
<b>NSAID</b>	<ul style="list-style-type: none"> <li>● Ketorolac</li> </ul>		<ul style="list-style-type: none"> <li>● Stevens Johnson syndrome.</li> </ul>
<b>Corticosteroids</b>	<ul style="list-style-type: none"> <li>● Fluorometholone</li> <li>● remixolone</li> <li>● prednisolone</li> </ul>		<ul style="list-style-type: none"> <li>● Posterior subcapsular cataract.</li> <li>● Glaucoma.</li> <li>● Papilledema.</li> <li>● Predisposition to fungal infections.</li> </ul>

❖ **Antibiotic:**

**Penicillins**

**Cephalosporins**

**Sulfonamides**

**Tetracyclines**

**Chloramphenicol**

**Aminoglycosides**

**Fluoroquinolones**

**Vancomycin**

**Macrolides**

- Used **topically** in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.
- Used **orally** for the treatment of preseptal cellulitis e.g. amoxicillin with clavulanate, cefaclor.
- Used **intravenously** for the treatment of orbital cellulitis e.g. gentamicin, cephalosporin, vancomycin, flagyl.
- Can be injected **intravitreally** for the treatment of endophthalmitis.
- **Trachoma** can be treated by topical and systemic tetracycline or erythromycin, or systemic azithromycin.
- **Bacterial keratitis** (bacterial corneal ulcers) can be treated by topical fortified penicillins, cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones “hourly”.
- **Bacterial conjunctivitis** is usually self-limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used.



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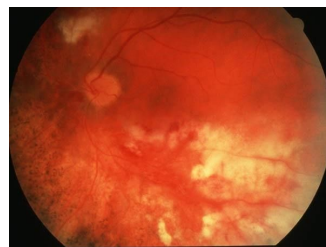
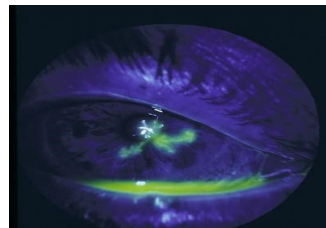


## ❖ Anti-Fungal:

- Uses: fungal keratitis, fungal endophthalmitis.
- Polyenes
  - Damage cell membrane of susceptible fungi.
  - E.g. amphotericin B, natamycin.
  - Side effect: nephrotoxicity.
- Imidazoles
  - Increase fungal cell membrane permeability.
  - E.g. miconazole, ketoconazole.
- Flucytosine
  - Act by inhibiting DNA synthesis

## ❖ Anti-Viral:

- Acyclovir
  - interact with viral thymidine.
  - Kinase (selective).
  - Used in herpetic keratitis.
- Trifluridine
  - More corneal penetration.
  - Can treat herpetic iritis.
- Ganciclovir
  - Used intravenously for CMV Retinitis.



## ❖ Ocular Diagnostic Drugs:

### Fluorescein dye

Available as drops or strips

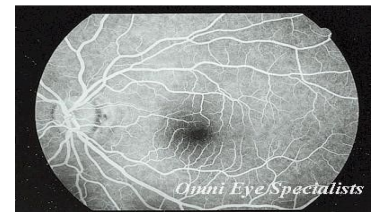
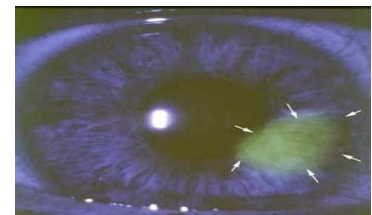
o Uses: stain corneal abrasions, applanation tonometry, detecting wound leak, NLD obstruction, fluorescein angiography

#### Caution!

- o Stains soft contact lens.
- o Fluorescein drops can be contaminated by Pseudomonas sp.

### Rose Bengal Stain

- Stains devitalized epithelium.
- Uses: severe dry eye, herpetic keratitis



## ❖ Local Anesthetic:

### ● Topical

E.g. propacaine, tetracaine.

Uses: applanation tonometry, gonioscopy, removal of corneal foreign bodies, removal of sutures, examination of patients who cannot open eyes because of pain.

Adverse effects: toxic to corneal epithelium, allergic reaction rarely.

### ● Orbital infiltration

Peribulbar or retrobulbar.

Cause anesthesia and akinesia for intraocular surgery.

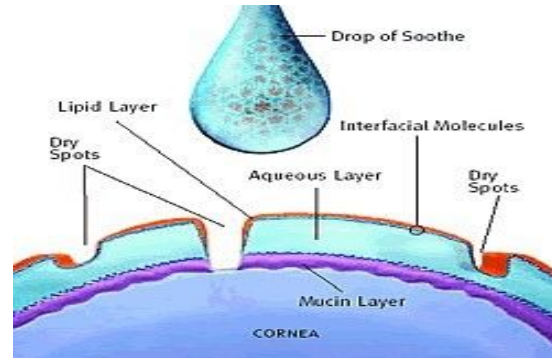
E.g. lidocaine, bupivacaine.

## ❖ Lubricants:

Drops or ointments.

Polyvinyl alcohol, cellulose, methylcellulose.

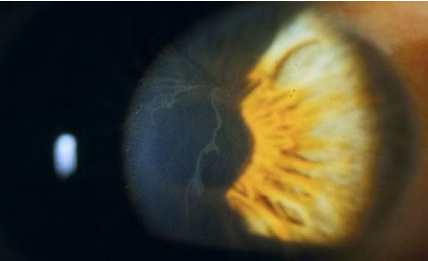



Preserved or preservative free.



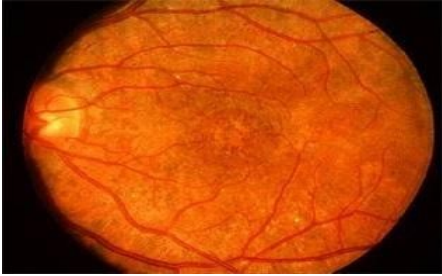
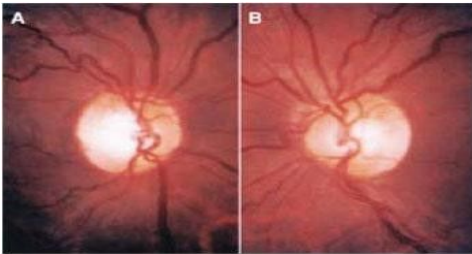
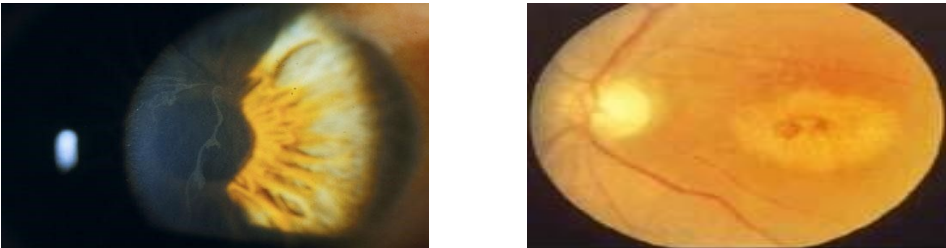
# Ocular Toxicology:

## ❖ Complications of Topical Administration:

- Mechanical injury from the bottle e.g. corneal abrasion.
- Pigmentation: epinephrine adrenochrome.
- Ocular damage: e.g. topical anesthetics, benzylkonium.
- Hypersensitivity: e.g. atropine, neomycin, gentamicin.
- Systemic effect: topical phenylephrine can increase BP.

Drug	Effect
<p>Amiodarone</p>	<ul style="list-style-type: none"> <li>● A cardiac arrhythmia drug.</li> <li>● Causes optic neuropathy (mild decreased vision, visual field defects, bilateral optic disc swelling).</li> <li>● Also causes corneal vortex keratopathy (corneal verticillata) which is whorl-shaped pigmented deposits in the corneal epithelium.</li> </ul> <div style="display: flex; justify-content: space-around; align-items: center;">   </div>
<p>Digitalis</p>	<ul style="list-style-type: none"> <li>● A cardiac failure drug.</li> <li>● Causes <b>chromatopsia</b> (objects appear yellow) with overdose.</li> </ul> <div style="display: flex; justify-content: space-around; align-items: center;">   </div>
<p>Chlorpromazine</p>	<ul style="list-style-type: none"> <li>● A psychiatric drug</li> <li>● Causes corneal punctate epithelial opacities, lens surface opacities</li> <li>● Rarely symptomatic</li> <li>● Reversible with drug discontinuation</li> </ul>



<p><b>Thioridazine</b></p>	<ul style="list-style-type: none"> <li>• A psychiatric drug</li> <li>• Causes a pigmentary retinopathy after <u>high dosage</u></li> </ul> 
<p><b>Diphenylhydantoin</b></p>	<ul style="list-style-type: none"> <li>• An epilepsy drug</li> <li>• Causes dosage-related cerebellar-vestibular effects:</li> <li>• Horizontal nystagmus in lateral gaze</li> <li>• Diplopia, ophthalmoplegia</li> <li>• Vertigo, ataxia</li> <li>• Reversible with the discontinuation of the drug</li> </ul>
<p><b>Topiramate</b></p>	<ul style="list-style-type: none"> <li>• A drug for epilepsy</li> <li>• Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes).</li> <li>• Treatment of this type of acute angle-closure glaucoma is by cycloplegia and topical steroids (rather than iridectomy) with the discontinuation of the drug</li> </ul>
<p><b>Ethambutol</b></p>	<ul style="list-style-type: none"> <li>• An anti-TB drug</li> <li>• Causes a dose-related optic neuropathy</li> <li>• Usually reversible but occasionally permanent visual damage might occur</li> </ul> 
<p><b>Chloroquine</b></p>	<ul style="list-style-type: none"> <li>• E.g. chloroquine, hydroxychloroquine</li> <li>• Used in malaria, rheumatoid arthritis, SLE</li> <li>• Cause vortex keratopathy (corneal verticillata) which is usually asymptomatic but can present with glare and photophobia &amp; retinopathy (bull's eye maculopathy)</li> </ul> 



## ❖ Agents that can cause Toxic Optic Neuropathy:

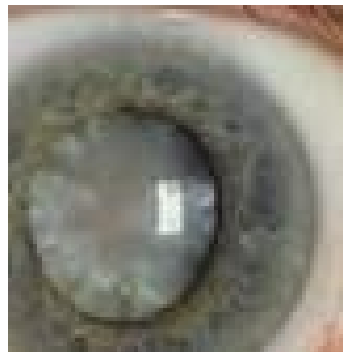
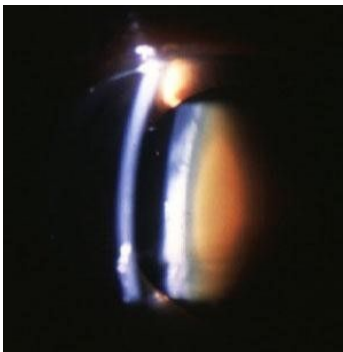
- **Methanol (IMP!!!)** Ethylene glycol (antifreeze) **Chloramphenicol**
- **Isoniazid** high-protein diet **Carbon monoxide**
- **Lead** **Mercury** **Ethambutol**
- **Digitalis** Chloroquine **Streptomycin**
- Thallium (alopecia, skin rash, severe vision loss)
- Malnutrition with vitamin B-1 deficiency
- **Amiodarone** Quinine methotrexate
- Pernicious anemia (vitamin B12 malabsorption phenomenon)
- Vincristine and methotrexate (chemotherapy medicines)
- Sulfonamides Melatonin with Zoloft (sertraline Pfizer) Radiation unshielded exposure to >3,000 rads).

## ❖ HMG-CoA REDUCTASE INHIBITORS (STATINS):

Cholesterol lowering agents.

E.g. pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin.

**Can cause cataract in high dosages specially if used with erythromycin**



## ❖ Other Agents:

Methanol	Optic atrophy and blindness (Patient presents with history of alcohol drinking).
Contraceptive pills	Pseudotumour cerebri (papilledema), and dryness (CL intolerance).
Chloramphenicol and streptomycin	Optic atrophy
Hypervitaminosis A	Yellow skin and conjunctiva, pseudotumor cerebri (papilledema), retinal hemorrhage.
Hypovitaminosis A	Night blindness (nyctalopia), keratomalacia.

