The Eye and Related Drugs:

Objectives:
The undergraduate student should be aware of:

- Ocular effects, proper dosages, local and systemic complications of the commonly used eye drops.
- Ocular complications of systemically prescribed drugs and how to recognize and prevent.
- To know and practice the proper technique of instilling eye drops in the eye

Topical Medications:

For topical medications installed in the eye, you may need to use diagnostic drugs to perform a complete ocular examination, and to aid in the proper diagnosis of a certain ocular condition, or you may apply local therapeutic agents to treat a specific pathology.

Proper technique to instill eyedrops

1. Wash your hands; wear disposable gloves if desired.
2. Instruct the seated patient to tilt the head back and to look up.
3. Expose the palpebral conjunctiva by gently pulling downward on the skin over the cheekbone. Avoid direct pressure on the eyeball.
4. Instill the correct amount of medication into the lower conjunctival fornix. Avoid applying drops directly to the cornea, which is the most sensitive part of the eye, and avoid touching the tip of the applicator to the patient's lids or eye.
5. Instruct the patient to close both eyes gently for a few seconds. Wipe any excess medication from the patient's skin with a tissue.
**Topical Diagnostic Drugs:**

1. **Fluorescein Dye:**

Sodium fluorescein is a water-soluble, non-irritant orange-yellow dye. It turns into green when diluted. When blue light is used, the green color becomes more brilliant (fluoresces).

**It is helpful in:**
- detecting corneal epithelial abrasions and corneal ulcers as fluorescein stains the spots denuded from epithelium.
- diagnosis of dry eye (tear break-up time)
- In measuring the IOP by applanation
- clinical evaluation of the lacrimal drainage system. Normally, if the dye is instilled in the conjunctival sac it passes to the nose.

**Side effects:**
To avoid discoloration, contact lenses should be removed before the fluorescein is instilled. Freshly prepared dye or sterile strips should be used to avoid contamination with bacteria especially pseudomonas.

2. **Topical Anesthetics:**

Topical anesthetic drops (proparacaine hydrochloride 0.5% and tetracaine 0.5%) are useful to make surface manipulations painless such as when we need to remove a superficial corneal foreign body or perform tonometry.

*Intact corneal sensation is one of the protective mechanisms of the eye, so patients should be warned against self medication with topical anaesthetics. They are **ONLY** to be used by doctors in the office.*
### 3. Mydriatics:

<table>
<thead>
<tr>
<th>Parasympatholytics (Cycloplegic /mydriatics )</th>
<th>Sympathomimetics (Mydriatics)</th>
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<tr>
<td><strong>Action</strong></td>
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<tr>
<td>- Paralysis of iris sphincter (pupil dilatation)</td>
<td>- Stimulation of pupillary dilator muscle (pupil dilatation)</td>
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<td>- Paralysis ciliary muscle (paralysis of accommodation)</td>
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<td><strong>Uses</strong></td>
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<tr>
<td>- Refraction in children (cycloplegic refraction)</td>
<td>- Ophthalmoscopy</td>
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<tr>
<td>- Relieve spasm of ciliary muscles (relieve pain in corneal ulcer &amp; iridocyclitis)</td>
<td>- Prevent synechea formation</td>
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<td><strong>Drugs</strong></td>
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<tr>
<td>- Tropicamide (0.5% - 1%)</td>
<td>- Phenylephrine hydrochloride 2.5%</td>
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<tr>
<td>- Cyclopentolate (0.5% - 2%)</td>
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<tr>
<td>- Atropine sulfate (0.5% - 1%)</td>
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<tr>
<td><strong>Side Effects</strong></td>
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<tr>
<td>- Defective near vision</td>
<td>- Acute hypertension</td>
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<td>- Nausea, vomiting and vasomotor collapse.</td>
<td>- Myocardial infarction (with 10% conc)</td>
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<td>- Atropine hypersensitivity in children (skin flush, fever, dizziness, convulsions)</td>
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*To minimize the risk of Atropine hypersensitivity especially in young children*
- Use the lowest concentration (0.5%)
- Ointment preparation is more preferable (because of its slow absorption)
- Digital punctual occlusion may be used in order to minimize systemic absorption

Atropine is not used to dilate the pupil for a fundus exam since its mydriatic/cycloplegic effect extends up to 2 weeks.
Topical Therapeutic Drugs:

A. Decongestants:

Decongestants are most commonly used eye drops. They produce vasoconstriction that reduces hyperaemia in the eye due to minor eye irritations caused by smoke, dust, wind, glare, swimming, contact lenses, or fatigue.

Decongestants are weak concentrations of sympathomimetic or alpha-adrenergic agonists that include adrenaline (epinephrine), naphazoline hydrochloride, and phenylephrine hydrochloride.

The most frequent complication of ocular decongestants arises from overuse, with rebound vasodilation of conjunctival vessels. In rare instances, acute angle-closure glaucoma may be precipitated in susceptible eyes by the use of sympathomimetic drugs because they can dilate the pupil.

B. Tear substitutes:

Treatment of dry eye is usually with lubricating eyedrops or gels.

- 1) The methyl and hydroxypropyl cellulose derivatives are widely used in artificial tear formulations. They work on the simple principle of lubricating the ocular surface in order to promote its integrity.

- 2) Some brands that include sodium hyaluronate as an inactive ingredient aids in a gradual release of water molecules, which increases the duration of wettability.

- 3) Polyvinyl alcohol (PVA) based artificial tears is a hypotonic solution which helps to counteract the hyperosmolarity seen in dry eyes,

- 4) Oil based brands of tear substitutes use oils in their composition. These has been shown to increase the thickness of the lipid layer of the tear film.
C. **Topical antibiotics**: *(see chapter 7)*

Topical antibiotics are often used to treat common bacterial conjunctivitis. The dosage and duration of treatment are variable according to the severity as well as the active drug ingredient. Risks of *topical allergic sensitivity* and *development of antibiotic resistant organisms* is significant with long-term and inappropriate antibiotic use.

D. **Topical antiviral agents**: *(see chapter 7)*

Topical antivirals are very effective in treating ophthalmic herpes viral infections. The most preferred topical medications are *acyclovir ointment* (commonly used in Europe and in Egypt) and *ganciclovir gel* (commonly used in the U.S). Both are selective antivirals which only attack the virus infected cells. Their toxicity is very low.

Other non selective topical antivirus medications such as trifluorothymidine (TFT), iodoxy uridine (IDU) and vidarabine are almost equally effective but long term use can result in toxicity in the form of corneal epithelial punctate keratitis or conjunctival congestion and dryness.
E. Topical Corticosteroids:

Topical corticosteroids preparations are very useful as anti-inflammatory and antiallergic in the management of various ocular situations as conjunctival allergic reaction, uveitis, scleritis and post-surgical inflammatory reaction. However, these can induce serious ocular complications;

i. Activation of viral, bacterial, and fungal infections.
ii. Complicated cataract.
iii. Secondary open angle glaucoma

Nonsteroidal anti-inflammatory agents do not potentiate these complications but alone are generally not potent enough to control significant intraocular inflammation, however. They are also used for other specific indications, such as ocular itching, macular edema, or prevention of miosis during cataract surgery or when steroids are contraindicated.

- Never use or prescribe a topical ocular corticosteroid unless you have a precise diagnosis for which the drug is specifically indicated.
- You must be prepared to monitor the patient for serious side effects, such as glaucoma, cataract, or infection.

In genetically predisposed individuals, the use of topical corticosteroids preparation can induce acute rise of intraocular pressure, i.e. steroid responders

F. Topical anti-glaucoma drugs: (see chapter 5)

The topically administered anti-glaucoma drugs may have local or, most seriously, systemic side effects. The systemic side effects may be more
prominent in the elderly, many of whom have multiple systemic conditions and are taking multiple other medications.

a) **β-Adrenergic Antagonists** (timolol, levobunolol, metipranolol, carbachol) 
These are nonselective β-adrenergic antagonists (beta-blockers) that reduce the formation of aqueous humor by the ciliary body and thereby reduce IOP. They are highly effective and widely used in the management of open angle glaucoma. These drugs induce **bronchospasm**. Therefore, they are contraindicated in patients with asthma or chronic obstructive pulmonary disease. They may also precipitate or worsen cardiac failure and must be used with caution if bradycardia or systemic hypotension.

- **Topical betaxolol**, a cardio-selective β-adrenergic antagonist, was developed to avoid the cardiac complications of timolol.
- **Still caution should be used when this drug is employed in patients with excessive impairment of pulmonary function due to its pulmonary effects.**

Pilocarpine systemic toxicity occurs only at 5 to 10 times the usual ocular dosage.

b) **Cholinergic-Stimulating Drugs** (Topical pilocarpine) 
Pilocarpine lowers IOP by increasing aqueous outflow through the trabecular meshwork. Local side effects, include diminished vision due to induced myopia and headaches from ciliary muscle spasm. Systemic side effects are rare in the form of lacrimation, salivation, perspiration, nausea, vomiting, and diarrhea may occasionally occur, especially with overdosage.

c) **α₂-Adrenoceptor Agonists:**

i. **Topical brimonidine**: is a relatively selective α₂ agonist that lowers IOP by a dual mechanism of decreased aqueous production and increased uveoscleral aqueous outflow. **It may cause a local allergic reaction. Systemic side effects**
include oral dryness, headache, fatigue, and drowsiness as it is lipid soluble and crosses the blood-brain barrier.

**Brimonidine must not be used in infants due to risk of severe hypotension and apnea**

ii. Topical apraclonidine decreases aqueous formation and increases uveoscleral outflow. It can cause local sensitivity reaction and contact dermatitis of the lids and conjunctiva. Systemic side effects include promotion of orthostatic hypotension and vasovagal episodes.

d) **Prostaglandin Analogues:** (Topical latanoprost, bimatoprost, travoprost)

    Lowers the IOP through increasing uveoscleral aqueous outflow, with no major systemic toxic effects. They have the advantage of once daily application which increases the patient compliance. However, ocular effects in the form of; *darkening of the iris, eyelid skin hyper-pigmentation, lengthening and thickening of the eyelashes* may occur after several months of therapy (figure 1). Moreover, the use of these topical preparations may promote *ocular and periocular inflammation* (uveitis, macular edema) especially in those predisposed to this condition after cataract surgery or following vascular disease in the eye (as central retinal vein occlusion).

**The cosmetic side effect of prostaglandin analogues preparations is marketed in an alternate eyelash application formula of bimatoprost (Latisse)**

**Prostaglandin-associated periorbitopathy** (PAP) is another annoying local side effect of the prolonged use of this drug group, secondary to periorbital fat atrophy resulting in enophthalmos and ptosis, that can be reversed by discontinuation of the drug).

*Figure 1: Left sided PAP and hypertrichosis*
e) **Carbonic Anhydrase Inhibitors** (Oral acetazolamide, methazolamide, dichlorphenamide).

The prolonged use of this drug group may cause systemic side effects, which include *paresthesias, anorexia, gastrointestinal disturbances, headaches, altered taste and smell, sodium and potassium depletion,* and a predisposition to form *renal calculi,* and rarely, *bone marrow suppression.*

*In order to minimize the side effect of oral carbonic anhydrase inhibitors, Potassium containing supplements are prescribed.*

**Ocular Side Effects of Systemic Drugs**

The drugs covered in this section are systemically administered medications that may have profound ocular side effects.

**Amiodarone**

Amiodarone is a cardiac anti arrhythmic drug that has been *reported to induce* optic neuropathy presents with mildly decreased vision, visual field defects, and bilateral optic disc swelling. Amiodarone also produces whorl-shaped, pigmented deposits in the corneal epithelium (verticillata) that rarely cause visual symptoms (Figure 2). These changes are dosage-related and reversible if the dosage is decreased or the drug is discontinued entirely.

![Fig 2: cornea verticillata.](image)
**Corticosteroids:**

The long-term oral systemic corticosteroids given in moderate dosage, may produce *posterior subcapsular cataracts*. Moreover, the use of systemic or inhaled corticosteroids is associated with *elevated IOP* (steroid-induced glaucoma) in susceptible individuals.

**Chloroquines:**

Chloroquine and hydroxychloroquine (Plaquenil) are used to treat malaria, rheumatoid arthritis, lupus erythematosus and other autoimmune disorders. Chloroquines can produce asymptomatic *corneal deposits*, which can cause glare and photophobia, and usually regress when the drug is discontinued. Chloroquine-induced retinal damage (*Bull's eye maculopathy*) is insidious, and usually irreversible (Figue 3).

![Fig 3: Chloroquine induced maculopathy (Bull's eye maculopathy)](image)

The typical *bull's-eye* macular lesions do not become visible by ophthalmoscopy until serious retinal damage has already occurred.
- All patients beginning hydroxychloroquine therapy should have a complete ophthalmic examination including visual acuity, color vision, Amsler grid, visual field testing, fundus photography and OCT. This examination is repeated with follow up.
- Low-risk patients may be followed at a minimum of 2 years from baseline, patients at higher risk should be screened at intervals determined by their level of risk based on the patient's age, physique, drug dosage and duration of use, and any presence of renal or liver disease.
- Patients on hydroxychloroquine with visual complaints should be referred to an ophthalmologist for ocular examination.

**Interferon**

Interferon is used in the treatment of hepatitis C, leukaemia and lymphoma. Drug-induced *retinopathy* (*cotton wool spots, intraretinal haemorrhages*) can develop in some patients on high-dose therapy, which usually resolves spontaneously with cessation of therapy.

**Ethambutol:**

Ethambutol is a useful chemotherapeutic for tuberculosis. As a side effect, ethambutol produces a *dosage-related optic neuropathy*, with the onset of vision loss may be within 1 month of starting the drug.

Recovery usually occurs when the drug is stopped, but it may take months; although, vision loss may occasionally be permanent.

> At dosages of 15 mg/kg/day, optic neuropathy occurs in less than 1% of patients, but it increases to 5% of patients receiving 25 mg/kg/day and to 15% receiving 50 mg/kg/day.

**Sildenafil** *(Viagra):*

Sildenafil *(Viagra)* and its related compounds is used primarily for the treatment of men with erectile dysfunction and Raynaud’s phenomena. Patients may experience transient, mild impairment of color discrimination, often noted as *blue color tinge of vision*. The ocular effects of sildenafil are not reported, despite a few case reports of *nonarteritic ischemic optic neuropathy* and *central serous retinopathy*,

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**Topiramate** (Topamax):

Topiramate, a drug used for the treatment of seizure disorder and has been shown to induce *acute bilateral angle-closure glaucoma*.

**Digitalis:**

Intoxication with this widely used cardiovascular drug almost always produces *blurred vision* or *abnormally colored vision* (ie, chromatopsia). Classically, normal objects appear yellow with the overdosage of digitalis.