MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology

Pharmacology of drugs acting on the eye

Objectives:

- Outline common routes of administration of drugs to the eye
- Discuss the pharmacokinetics of drugs applied topically to the eye
- Classify drugs used for treatment of disorders of the eye
- Elaborate on autonomic, anti-inflammatory drugs & drugs used for glaucoma
- Hint on ocular toxicity of some drugs

color index:

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

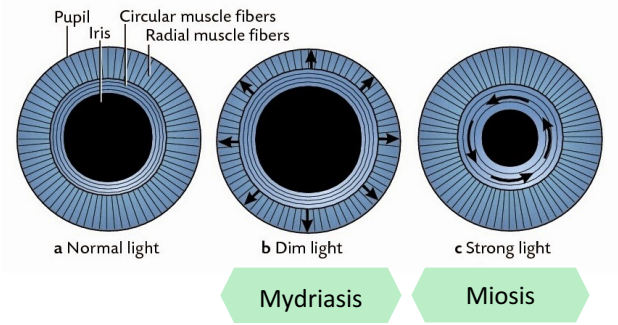
تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري

Check out the mnemonics file :
https://docs.google.com/presentation/d/1Z0Vf9oEOJSXo4JIA0mTCk5jB-OU9LP5TFCwz8iBgNac/edit?usp=sharing

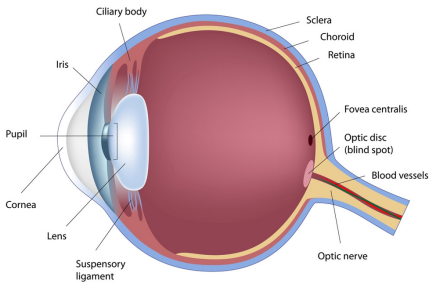
Kindly check the editing file before studying this document
https://docs.google.com/presentation/d/1_-g1vol4eBWPet5xVCkuTGFvvnhFF3PJmU0tWtEEw_o/edit?usp=sharing

To understand !

Accommodation for light intensity

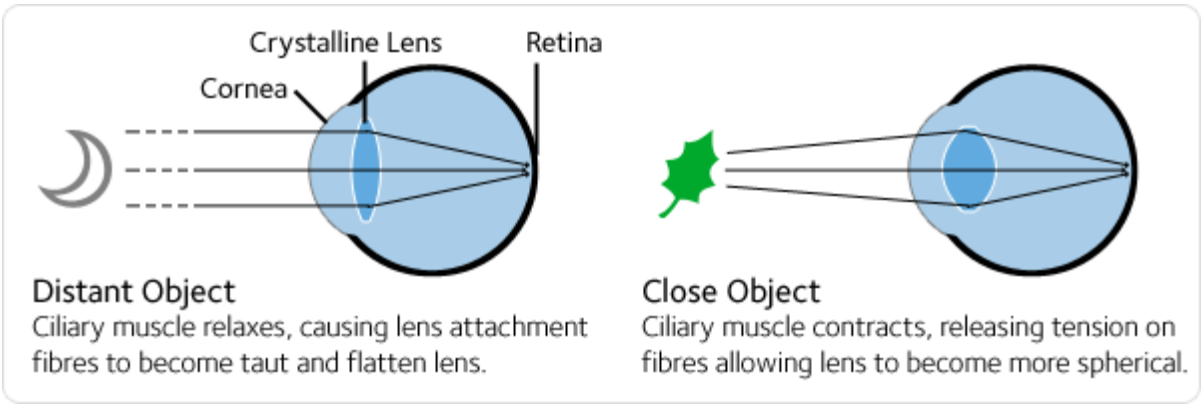


Anatomy

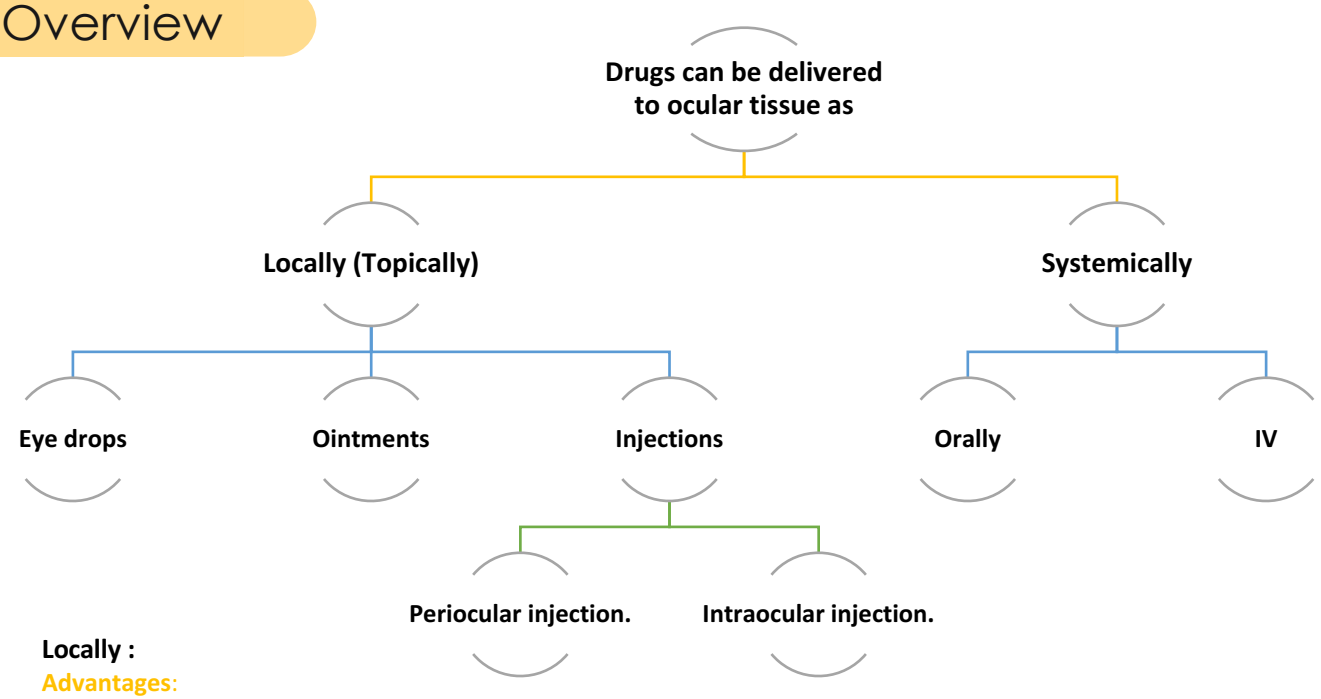


Accommodation for near/far vision:

Eye accommodation
2:05 min



Overview



Locally :

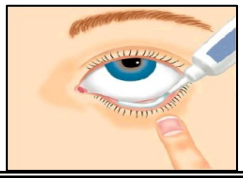
Advantages:

- Convenient, Economic, Relatively safe.

Disadvantages:

- Compliance, Corneal & conjunctival toxicity.

1-Locally: Eye drops, ointments, injections.

	Eye drops	Ointments
Definition	• Eye drops are saline containing drops "liquid" • **Most common** route of administration. • One drop = 50 µl / **4 hours (usually)**	Ointment is a smooth oily preparation, As a rule of thumb, an ointment base is more occlusive and will drive the medication into the skin more rapidly than a solution or cream base.
Advantages	Convenient, costs less, applied frequently.	Increases the **contact time** of ocular medication to ocular surface →providing **better effect.**
Disadvantages	The contact time between the drug and the eye is **low** due to fast removal by tears → Thus has to be used **several times.** One of the problems of eye drops is poor compliant of the patient. 	The drug has to be **highly lipid soluble** to have the maximum effect as ointment. t's a Greasy substance so the contact time between the medication and the tissue is longer 

Eye injections

Techniques

intra-ocular injections
For anterior segment surgery, infections & retinitis

		ADRs
1- Intra-cameral: تذكرنا بكلمة كاميرا "inside anterior or posterior chamber of the eye"	E.g. شركة لايكا وكانون للكاميرات • Intra-cameral **acetylcholine** or **lidocaine** during cataract surgery. (Leica = acetylcholine) (Canon = lidocaine)	
2- Intra-vitreal "inside the eye" vital نربطها بكلمة The Antibiotic and steroid can save our vitality	E.g. • Intravitreal antibiotics in cases of **endophthalmitis** (an inflammation of the internal coats of the eye) • Intravitreal steroid in **macular edema** (the build-up of fluid in the **macula**, an area in the center of the retina.)	-Retinal toxicity. -Intraocular toxicity. - Corneal toxicity.

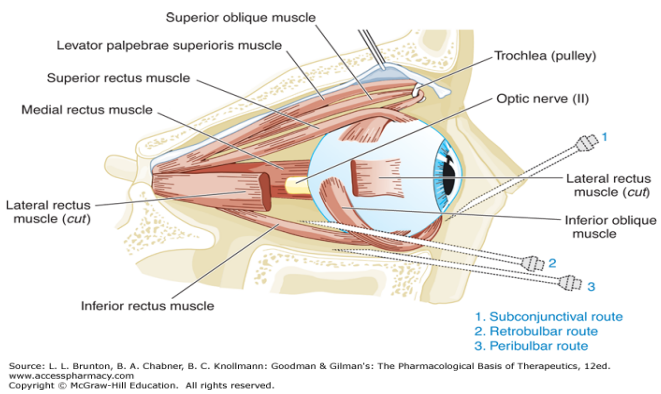
Peri-ocular injections

1-Subconjunctival
Sub= under

2- Retro-bulbar
"behind the eyeball"
Retro= behind

3- Peri-bulbar
"above and below the orbit"
Peri=around

4-subtenon



Advantages:
- They reach behind the iris-lens diaphragm **better than** topical applications.
- Drugs penetration is generally weaker for low lipid-soluble drugs, however injections can bypass the conjunctival and corneal epithelium which is good for **drugs with low lipid solubility (e.g. penicillins)**
- **Steroid and local anesthetics** can be applied this way.
- Used for infection of anterior segment and inflammation of uvea.

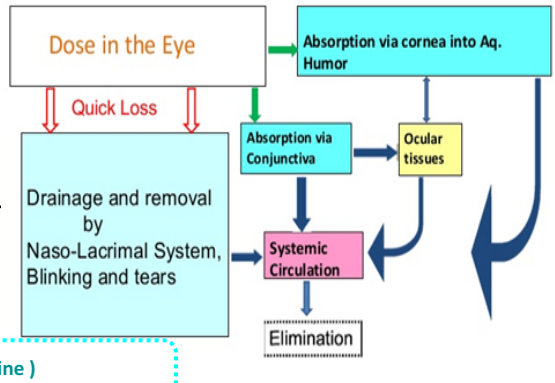
Disadvantages:
- Local toxicity, tissue injury, globe perforation, optic nerve damage.

Absorption Is determined by:

Drug residence time→ the time drug remains in cul-de-sac, tear. It can be prolonged by plugging tear ducts or changing the formulation.
Metabolism → esterases
Elimination → by nasolacrimal drainage or binding to tear protein.
Diffusion → across cornea & conjunctiva.

Distribution

After corneal absorption the drug accumulates in the aqueous humor, intraocular structures or systemically distributed.
*** Melanin binding prolongs the effect of α -agonists in patients with dark pigmented iris.**



Metabolism

Significant biotransformation takes place in the eye.
Esterases activate pro-drugs, e.g.:
- **Dipivefrin → (adrenaline)**
- **Latanoprost →(PGF2α)**

(Dipivefrin = adrenaline)
(dipivefrin = Adrenaline) أو ممكن نقول أبي أدرنالين

2-Systemically: Oral, IV

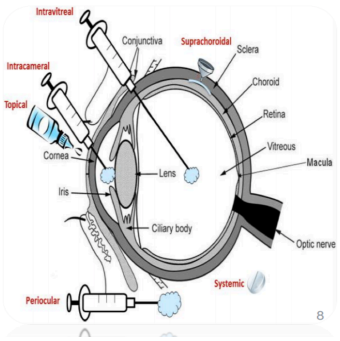
Oral or IV

- Factors influencing systemic drug penetration into ocular tissue:
- **lipid solubility of the drug:**

More penetration with high lipid solubility
- **Protein binding:** (bound drug) :Not Free to distribute all over the body, It localized in the blood

More effect with low protein binding (inverse proportion)
- **Eye inflammation:**

More penetration with ocular inflammation.

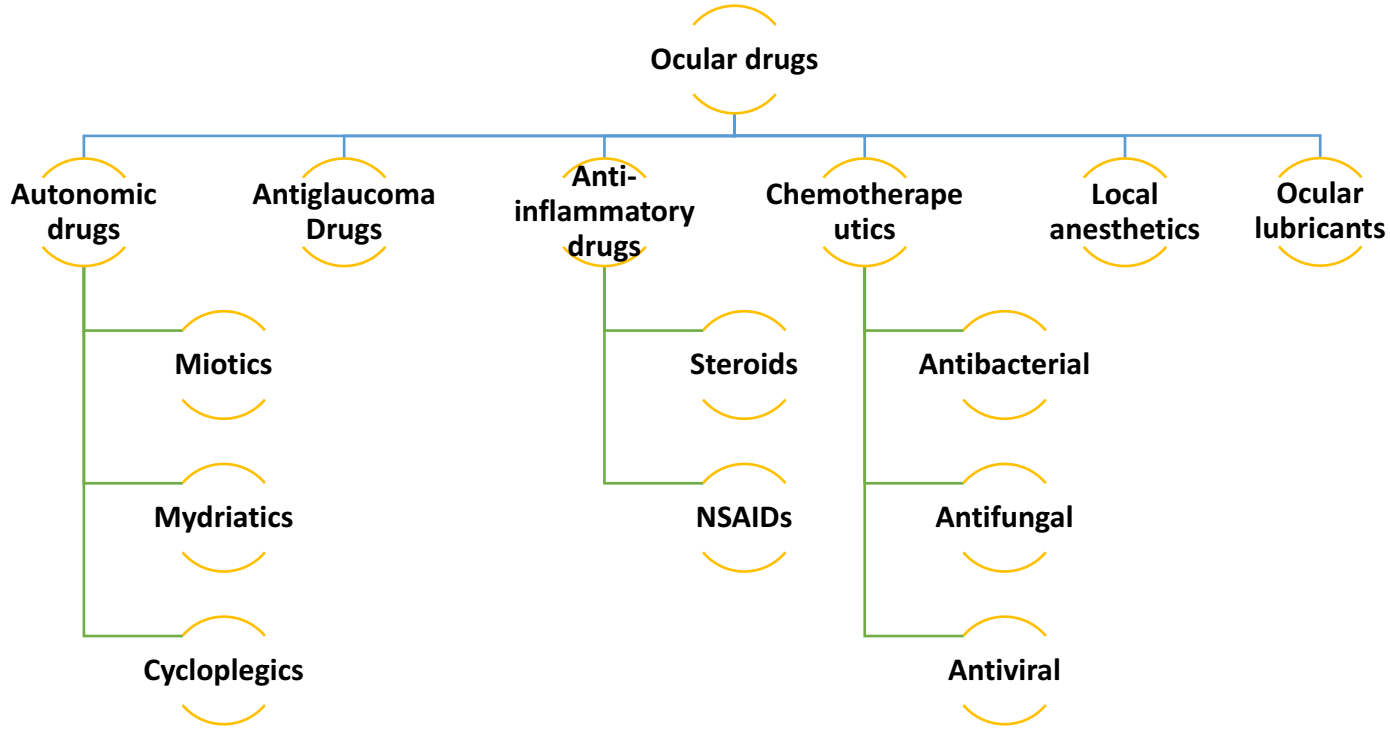


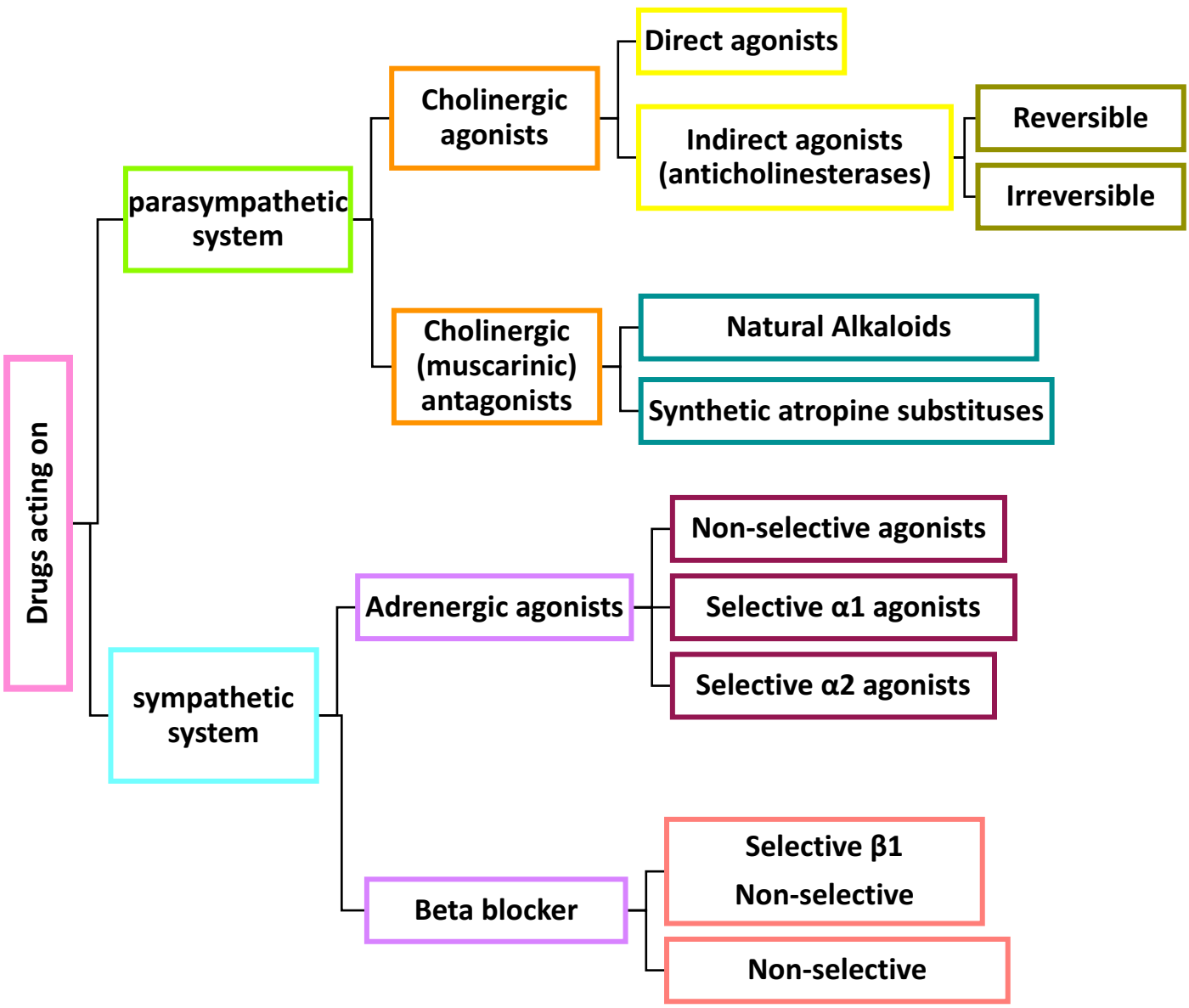
To understand !

Eye		Parasympathetic N.S.	Sympathetic N.S.
Iris	radial muscle	No effect	Contraction (Mydriasis) **(α1)**
	circular muscle	Contraction (miosis) **(M3)**	No effect
Ciliary muscle		Contraction (M3) (accommodation for near vision)	Relaxation (**β2**) هذا بيتك الثاني ارتاح
Lens		Thick, more convex	Thin, more flat
Conjunctival blood vessels		Conjunctival Vasodilatation and congestion of blood vessels	Conjunctival Vasoconstriction (α1) and decongestion of blood vessels
Accommodation		near vision	far vision
Suspensory ligaments		relaxation	contraction

*Ciliary muscle is the **opposite** of the suspensory ligament

Overview


Ocular drugs
Autonomic drugs
Antiglaucoma Drugs
Anti-inflammatory drugs
Chemotherapeutics
Local anesthetics
Ocular lubricants
Miotics
Mydriatics
Cycloplegics
Steroids
NSAIDs
Antibacterial
Antifungal
Antiviral

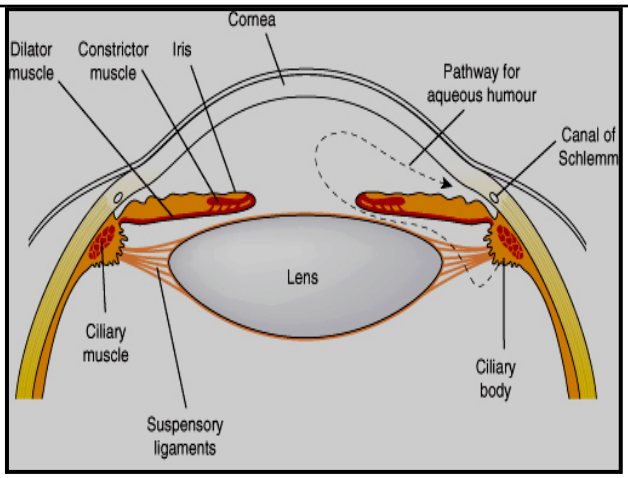

Drugs acting on
parasympathetic system
Cholinergic agonists
Direct agonists
Indirect agonists (anticholinesterases)
Reversible
Irreversible
Cholinergic (muscarinic) antagonists
Natural Alkaloids
Synthetic atropine substituses
sympathetic system
Adrenergic agonists
Non-selective agonists
Selective α1 agonists
Selective α2 agonists
Beta blocker
Selective β1
Non-selective
Non-selective

Drugs acting on parasympathetic system:
cholinergic agonists, cholinergic antagonists

Cholinergic agonists

	Direct agonists		Indirect agonists (anticholinesterases)	
Drug	**Acetycholine** M receptor **Methacholine** M+N receptor **Carbachol** من كثرة الكرب (Carb) صار شخص اكول (achol)	**Pilocarpine** M receptor	**Reversible** Bind for short time with Ach esterase then leave it	**Irreversible**
			Physostigmine **Demecarium**	**Echothiophate** **Isoflurophate**
Indications	Specific uses : 1-Induction of miosis in surgery 2- Open angle glaucoma *Acetylcholine has very short duration of action so no medical application for it .	Open angle glaucoma Why not for closed as well ? Closed angle glaucoma is an emergency case which required surgery	**Specific uses:** 1- Glaucoma 2- Accommodative esotropia	
	General uses: 1- Glaucoma (open & closed angle). 2- Counteract action of mydriatics. after funduscopic examination 3- To break iris-lens adhesions. Sequences of mydriatics drugs followed by miotics drugs (Contraction followed by relaxation) 4- In accommodative esotropia (ecothiophate). الحول: Ecothiophate = Esotropia 5- in lice infestation of lashes (physostigmine)			
Mech. Of action	**2 contractions :** 1- Constriction of the pupillary Circular muscle (sphincter muscle) **(miosis)** drugs causes constriction are Preferred in treatment of glaucoma 2-Contraction of the ciliary muscle **(accommodation for near vision)** **Decrease** in intraocular pressure ↓ **IOP.** **increases aqueous outflow** through the trabecular meshwork into canal of Schlemm** **Increased lacrimation** Conjunctival **Vasodilatation** may Lead to congestion in eye			
ADRs	- Diminished vision (myopia). - Headache			

**The aqueous humor is secreted by the epithelium of ciliary body.
Produced by a combination of active transport of ions and ultrafiltration of interstitial fluid.
The fluid flows over the surface of the lens, out through the pupil into the anterior chamber. Flows through the trabecular meshwork into Schlemm's canal by ciliary muscle contraction. and is collected in the scleral veins.
As a result of miosis of the iris muscle which pulled away from the canal of Schliemann so the angle of filtration will increase



Drugs acting on parasympathetic system:
cholinergic agonists, cholinergic antagonists

Cholinergic (muscarinic) antagonists		
	Natural alkaloids	**Synthetic atropine substitutes**
Drug	**1- Atropine** Not used because it has very long duration of action **2- Scopolamine (Hyoscine)**	**1- Homatropine** أي مرض بالعين بسبب كربة وهم للشخص **2- Tropicamide** Eye drop are coming **3- Cyclopentolate** It to late to treat the glaucoma
Duration	Long duration of action **1- Atropine:** 7-10 days **2- Scopolamine (Hyoscine) :** 3-7 days	Short duration of action **1- Homatropine:** 1-3 days **2- Tropicamide:** 6 hours Widely used **3- Cyclopentolate:** 24 hours
Mech.of action	**2 Relaxations:** 1- **Passive*** mydriasis →due to relaxation of circular muscles. 2- **Cycloplegia** (loss of near accommodation) →due to relaxation of ciliary muscle. (This effect is due to blocking of paraS only!) **- Increased IOP** → glaucoma. (especially angle closure glaucoma) **- Decreased lacrimal secretion** →**sandy eye**. - Loss of light reflex.	
Indications	1- To prevent adhesion in uveitis & iritis. (because they are doing mydriasis) 2- Funduscopic examination of the eye. 3- Measurement of refractive error. (problem with focusing of light on the retina due to the shape of the eye)	
Contra-indications	Glaucoma (angle closure glaucoma) →Because there is no miosis →which makes the filtration C.I easier > IOP may rise dangerously → acute attack of eye pain.	

Ocular actions of drugs acting on sympathetic system

- **Contraction** of dilator (radial) Pupillae **(Active mydriasis)** → **α1**
- mean the iris go to the back.
- **Relaxation** of ciliary muscles (accommodation for **far vision**) **β2**** = reduce filtration angle.
- **Increase** in intraocular pressure **IOP**
- Lacrimation **α1**
- **Vasoconstriction** of conjunctival blood vessels **α1** . (used as decongestion drug)
- **α & β** receptors in the blood vessels of the ciliary processes help in regulation of aqueous humour formation

*Active vs. passive mydriasis:
• Atropine (anticholinergic): **Blocking** muscarinic receptors→ **relaxing circular** muscles → **Passive Mydriasis**
• Sympathetic stimulation: **activation** of α receptors in **radial muscles** → **contraction** →**Active mydriasis**
** in the sympathetic system, activation of α receptors leads to smooth muscle contraction, and activation of β**2** receptors leads to smooth muscle relaxation

Drugs acting on sympathetic nervous system

Adrenergic agonists

	Non-selective agonists (α1 , α2 , β1 , β2)	Selective α1 agonists	Selective α2 agonists
Drug	**1- Epinephrine** **2- Dipivefrin (pro-drug of epinephrine)** Dipivefrin = Epinephrine	**Phenylephrine**	**Apraclonidine** **(eye drop)** تذكرنا بمعجزة عيس ى (إبراء الأكمة)
Mechanism of action	- Increase uveoscleral outflow of aqueous humor.	- Active Mydriasis (without cycloplegia). because their effect is on the radial muscle, not the ciliary muscle which is innervated by parasympathetic *no loss of accommodation	- **Decrease** production of aqueous humor. - **Increase**uveoscleral outflow of aqueous humor. - Inhibits sympathetic working.
Route of administration	Used locally as eye drops.		Eye drops
Indications	**Open angle glaucoma.**	1- Funduscopic examination of the eye. 2- To prevent adhesion in uveitis & iritis. 3- Decongestant in minor allergic hyperemia of eye.	1- Open angle glaucoma treatment 2- Prophylaxis against IOP spiking after glaucoma laser procedures.
ADRs	1- Headache. 2- Arrhythmia. 3- **Increased blood pressure.**	1- May cause significant **increase in blood pressure.** 2- Rebound congestion. 3- Precipitation of acute angle-closure glaucoma in patients with narrow angles.	1- Headache. 2- Bradycardia. 3- **Hypotension.**
Contra-indications	In patients with **narrow angles** (low drainage) as they may precipitate **closed angle glaucoma**. (α1 effect) →because it is doing mydriasis.		

Drugs acting on sympathetic nervous system

Adrenergic agonists: Beta blockers

Drug	Non-selective	Selective β1 Non-selective (cardio-selective) لووول (lol) باب البيت(beta) طلع مقفل (blockers) !
	1- Timolol جاء وقت قطرة العين 2- Carteolol الجزر مفيد للعين	Betaxolol بيتك من جماله كسر عين العدو
Mech. Of action	• Act on ciliary body to decrease production of aqueous humor. • Blocking of β2 > blocking the relaxation effect on the ciliary muscle.	
Rout of admin.	Given topically as eye drops Timolol = long time	
Indications	- Can be used in patients with hypertension & ischemic heart disease. - Used in treatment of open angle glaucoma. - β-adrenergic blocker timolol, are effective in treating chronic glaucoma but are not used for emergency lowering of intraocular Indications pressure.	
ADRs	Ocular irritation.	
Contra-indications	1- In asthma patients. (because the effect of β2 > bronchospasm) 2- Patients with CVS disorders. (because the effect of β1 on the heart)	
Notes	**B blockers** are the most popular & effective treatment of open angle glaucoma **AFTER prostaglandins** .	

Summary: Autonomic Nerve supply of the Eye

Ocular actions		
Parasympathetic N.S.		**Sympathetic N.S.**
Cholinergic agonists	**Cholinergic (muscarinic) antagonists**	
*** These 2 are opposite to each other**		• **Contraction** of dilator (radial) Pupillae **(Active mydriasis)** → α1 • **Relaxation** of ciliary muscles (accommodation for **far vision**) →β2
2 contractions : 1- Constriction of the pupillary Circular muscle (sphincter muscle) (miosis) drugs causes constriction are Preferred in treatment of glaucoma 2-Contraction of the ciliary muscle (accommodation for near vision).	**2 relaxations:** 1- **Passive** *mydriasis →due to relaxation of circular muscles. 2- **Cycloplegia** (loss of near accommodation) →due to relaxation of ciliary muscle.	
Decrease in intraocular pressure ↓ **IOP.**	**Increased IOP** → glaucoma. (especially angle closure glaucoma)	**Increase** in intraocular pressure **IOP**
increases aqueous outflow		α & β receptors in the blood vessels of the ciliary processes help in regulation of aqueous humour formation
Increased lacrimation	**Decreased lacrimal secretion** →**sandy eye**.	Lacrimation α1
Conjunctival **Vasodilatation** may Lead to congestion in eye	Loss of light reflex.	**Vasoconstriction** of conjunctival blood vessels α1 (used as decongestion drug)

Treatment of open angle glaucoma (chronic)

Watch it from 4:30

How glaucoma occurs ? 1- open : angle of filtration is open (canal of Schlemm) but the problem is increasing in the production of aqueous humor.
2- closed angle glaucoma :here the angle of filtration is narrow by mydriatic drugs need surgery to treat it.

The main goal is to decrease IOP by:

(Beta قدام بيتك ؟ (Carbonic anhydrase inhibitors) اني سيارة (Alpha(1+1=2)) فيه ألف وحدة ووحدة blockers)

(Adrenergic) أدري إن فيه دجاج بروست (Prostaglandins) برا ((increase عشان كذا تبي تصرفني بسرعة Parasympathomimetics) ouflow)

Decreasing production of aqueous humor:

- Beta blockers.
- Alpha-**2** agonists.
- Carbonic anhydrase inhibitors.

Increasing outflow of aqueous humor:

- Prostaglandins.
- Adrenergic agonists, nonspecific.
- Parasympathomimetics.

Prostaglandins and Beta blockers are the most popular

Carbonic anhydrase inhibitors & prostaglandin analogues

Drug	**Carbonic anhydrase inhibitors** E.g. acetazolamide (**oral**) dorzolamide (**topical**) preferred	**Prostaglandin analogues** E.g. latanoprost, travoprost
Mech. of action	Decrease production of aqueous humor by blocking carbonic anhydrase enzyme required for production of bicarbonate ions → (transported to posterior chamber, carrying osmotic water flow).	Increase uveoscleral aqueous outflow. Latanoprost is preferred due to lesser adverse effects. They have replaced beta blockers They are used topically as eye drops & once a day. جربت دجاج البروست (Prost) مرة وحدة بحياتي(once a day)
Indi-cation	**open angle glaucoma**	
ADRs	• Myopia (Nearsightedness), malaise, anorexia, • GI upset, headache. • Metabolic acidosis, renal stone. Ops! I can not see any Cars =(carbonic anhydrase) because I have Myopia	• Pigmentation of the iris (heterochromia iridis) • Intraocular inflammation. • Macular edema. I rise up with Big broast= (iris) (Pigmentation) (Prostaglanin)
Contra-indication	• **Sulfa allergy** because they are sulfa derivatives. • **Pregnancy** • **Digitalis** users.	

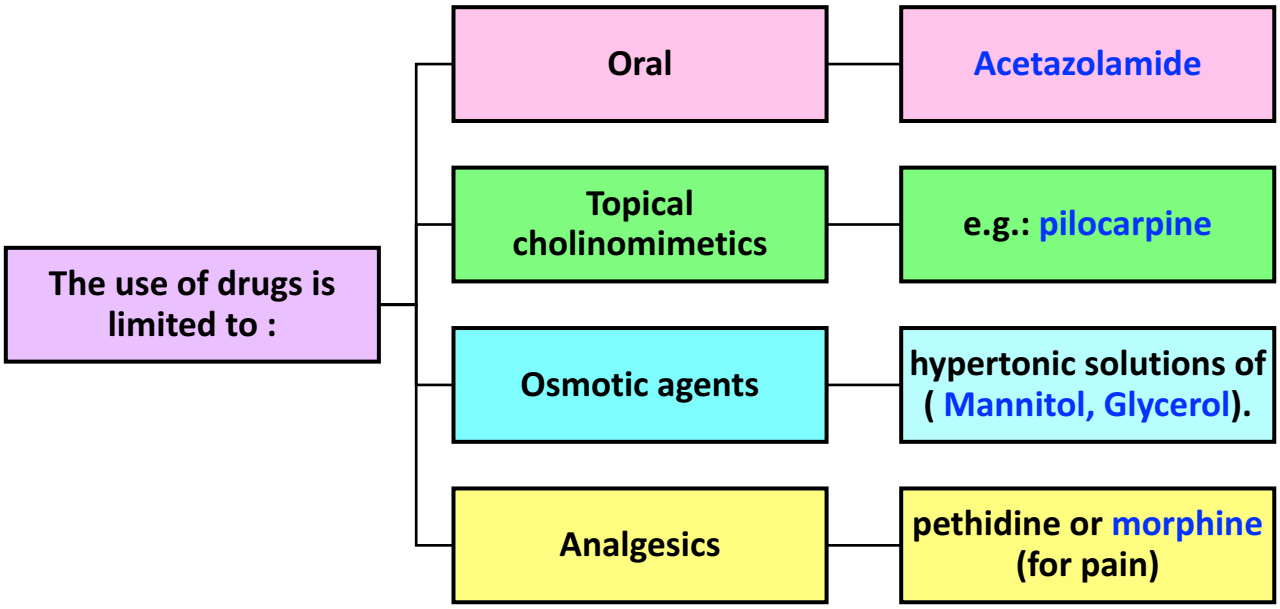
Closed Angle Glaucoma (acute)

Development of angle closure glaucoma and its reversal by miotics:

1. Mydriasis occurs in an eye with narrow iridocorneal angle, and the iris makes contact with the lens blocking passage of the aqueous from the posterior to the anterior chamber.
2. Possibly builds up behind the iris which bulges forward and closes the iridocorneal angle thus blocking aqueous outflow.
3. Miotic makes the iris thin and pushes it away from the lens removing the pupillary block and restoring aqueous drainage.

Treatment of narrow closed angle glaucoma (acute):

- **Acute, painful** increases of intraocular pressure due to occlusion of the outflow drainage pathway.
- **The only way to treat it** is Surgery, but before surgery we give him treatment to decrease IOP.
- **Emergency situation** that require treatment before surgery (**Iridectomy**).



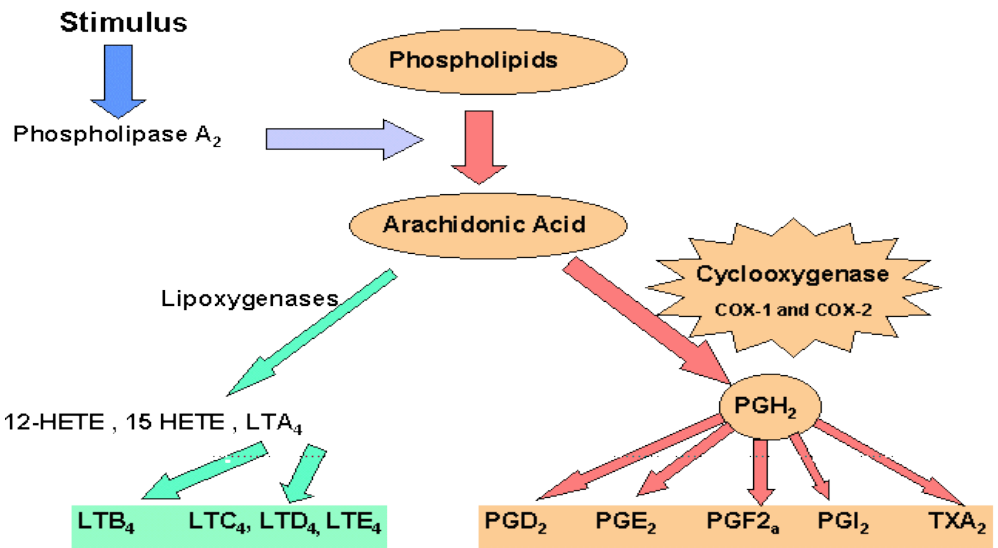
Systemic Osmotic agents (Dehydrating agents)

Mech. of action	1. Can rapidly ↓ IOP by ↓ vitreous volume. 2. Glycerol 50% syrup, orally (cause nausea, hyperglycemia). 3. Mannitol 20% IV (cause fluid overload and not used in heart failure). 4. Dehydrate vitreous body which reduce IOP prior to anterior surgical procedures 5. IV infusion of hypertonic solution (mannitolol,Glycerol)
Indi-cations	Used only in acute situations to temporarily reduce high IOP until more definitive treatments can be rendered. (prior to anterior surgical procedure)
ADRs	- Diuresis, circulatory overload, pulmonary edema - Heart failure - Central nervous system effects such as seizure, and cerebral hemorrhage.

Anti-inflamatory Drugs

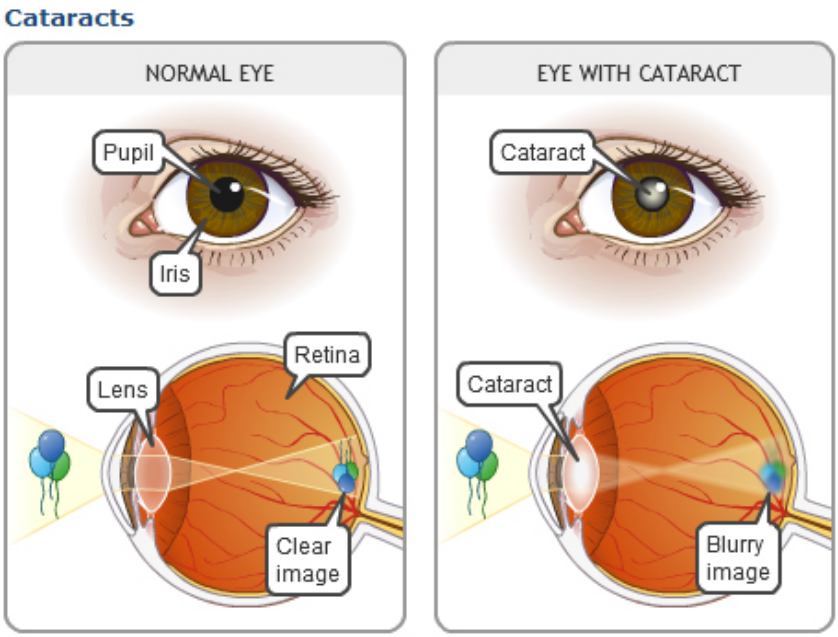
	Corticosteroids		NSAIDs
	Topical	Systemic	
Drug	**1- Prednisolone** **2- Dexamethasone** **3- Hydrocortisone**	**1- Prednisolone** **2- Cortisone**	**1- Ketorolac** **2- Diclofenac** **3- Flurbiprofen**
Mech. of action	- Inhibition of arachidonic acid release from MOA phospholipids by inhibiting phosphlipase A2		- COX (cyclo-oxygenase) inhibitors
Indications	1- Anterior uveitis. 2- Severe allergic conjunctivitis. 3- Scleritis. 4- Prevention and suppression of corneal graft rejection. 5-postoperatively	2- Posterior uveitis. 1- Optic neuritis.	**1- Ketorolac:** Cystoid macular edema occurring after cataract surgery. **2- Diclofenac:** Postoperative inflammation, mild allergic conjunctivitis, mild uveitis. **3- Flurbiprofen:** Preoperatively to prevent miosis during cataract surgery. * Because they inhibit prostaglandins which produce miosis without action of cholinergic.
ADRs	- Glaucoma, cataract, mydriasis (especially if it is used for a long time) - Skin atrophy. - Secondary infection. - Delayed wound healing. (healing is slow because it is an immune suppression)		- Stinging (irritation) - Sterile corneal melt & perforation.

Figure 2 : Biosynthesis of eicosanoids



Toxicity : Drugs causing corneal deposits

Amiodarone **Chloroquine** الملكة أمي تلبس تاج ومصابة بالعمى	1- Pigmented deposits of cornea. 2- Optic neuropathy (mild decreased vision + visual field defects) 3- Retinopathy.
Digitalis 	1- Ocular disturbances 2- Chromatopsia (objects appear **yellow**, overdosing can cause ocular disturbances) (FACT: Van gogh used to take digitalis)
Phenothizines	3- **Brown** pigmentary deposits in the cornea, conjunctiva & eyelid. نقرا اسم الدرق (كانو دا زيتي لونه) زيتي مو بعيد عن بني)
Steroids	1- Cataract formation 2- Increase IOP 3- Glaucoma (long term use)
Ethambutol (TB Medication) إثم بتول سبب لها العمى	1- Optic neuropathy Characterized by gradual Progressive central scotomas and vision loss.
Sildenafil تذكرنا بسلايدز الدكاترة دايم لونها أزرق	1- Causes a **bluish** haze 2- Light sensitivity It Inhibits PDE5 in the corpus cavernosum to achieve penile erection It also mildly inhibits PDE6 which controls the level of cyclic GMP in the retina→ seeing a bluish haze & causing light sensitivity



إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

قادة فريق علم الأدوية :

لين التميمي & عبدالرحمن ذكري

الشكر موصول لأعضاء الفريق المتميزين :

ريم الشثري

رنا باراسين

جواهر الخيال

شذا الغيهب

روان سعد القحطاني

آمال الشيبي

References :

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2- Team 435

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pharma436@outlook.com

@pharma436

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