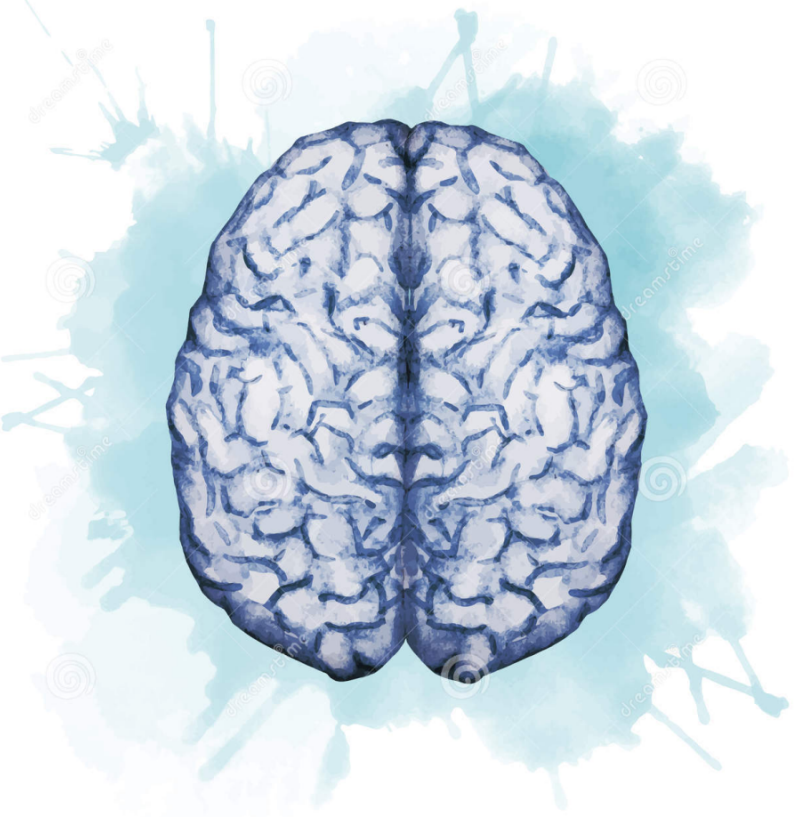

Pharmacology team 436

Mnemonics file

If you have any suggestions , contact us

هذا العمل وجد فقط للربط من باب التيسير والتسهيل لنا كدفعة ٤٣٦ ولمن خلفنا أو حتى للترويح عن النفس من خلال الربط بين أسماء الأدوية وبعض المعاني الحياتية لتكون أرسخ في الذاكرة، ولا نقصد منه أبداً انتقاص شيء من المادة العلمية أو استسخافها. ولذلك تم وضعها بملف منفصل، كل الشكر والتقدير لكل من ساهم معنا فيه بناءه ولو بكلمة طيبة، سائلين من المولى لنا ولهم التوفيق والتيسير

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@pharma436

Your feedback:

https://docs.google.com/forms/d/e/1FAIpQLSc57qjDXLPcQLYftI27W91gCKD2RgH0OzQDdDxsiLYmH9DKtw/viewform

436

MEDICINE

KING SAUD UNIVERSITY

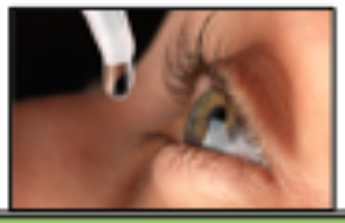
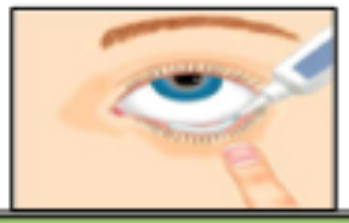
436 team pharmacology

Pharmacology of drugs acting on the eye

(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(3)

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 ليكا وكانون للكاميرات • Intra-cameral **acetylcholine** or **lidocaine** during cataract surgery. (Leica = acetylcholine) (Canon = lidocaine)	
2- Intra-vitreal "inside the eye" تربطها بكلمة vital 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.

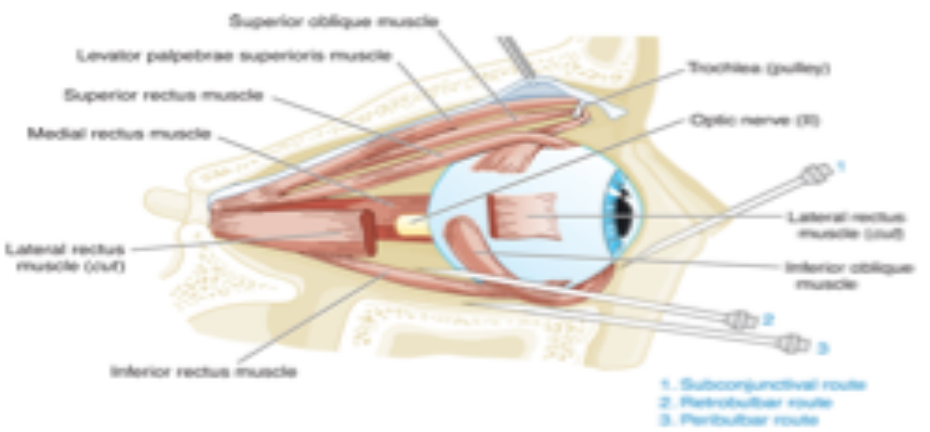
Peri-ocular injections

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.

(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(4)

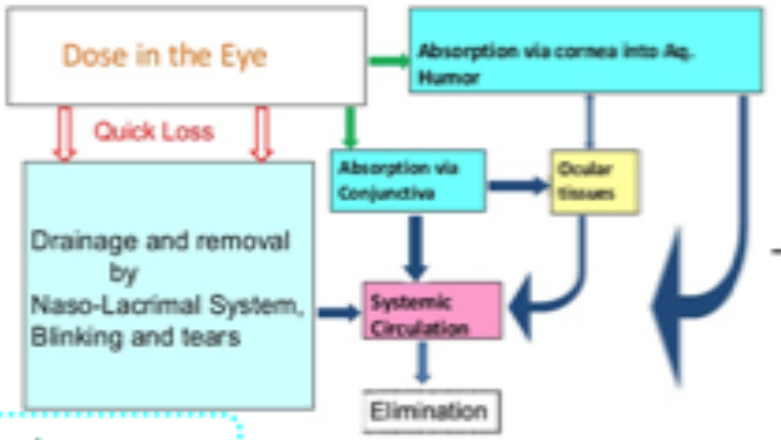
Pharmacokinetics of topical (local) drugs

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) او ممكن تقول أبي أدرنالين

2-Systemically: Oral, IV

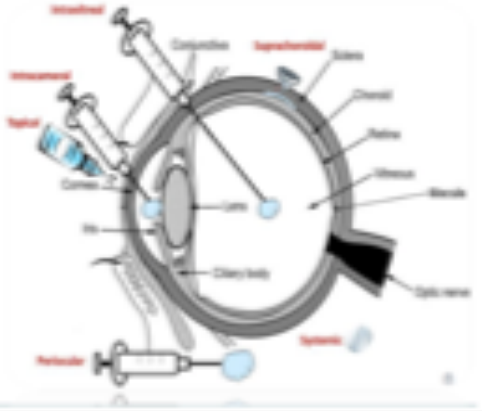
Oral or IV

- 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)** هنا بيكك 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

(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(6)

Drugs acting on parasympathetic system:
cholinergic agonists, cholinergic antagonists

Cholinergic agonists

Drug

Direct agonists

Acetycholine
M receptor
Methacholine
M+N receptor
Carbachol

من كثرة الكرب (Carb) صار شخص اكول (achol)

Pilocarpine
M receptor

just a phase= for short time

Indirect agonists (anticholinesterases)

Reversible Bind for short time with Ach esterase then leave it

Physostigmine
Demecarium

Deme carries the baby for shot time

Irreversible

Echothiophate
Isoflurophate

Phate = fate, your fate is to be stuck with this forever

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)

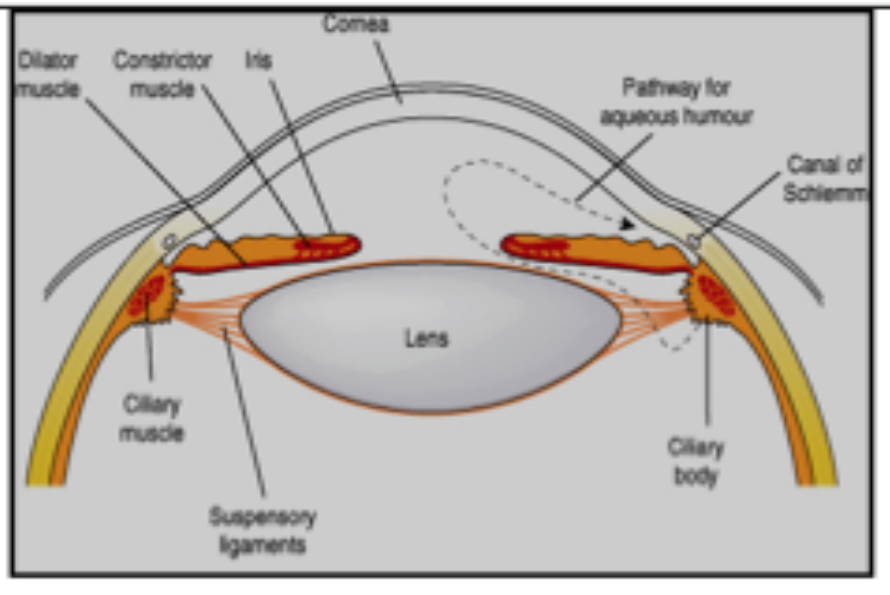
0Mech. Of action

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



(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(7)

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 مريض بالعين بسبب كربة وهم التشخص **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 β2 receptors leads to smooth muscle relaxation

(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(8)

Drugs acting on sympathetic nervous system

Adrenergic agonists

Drug	Non-selective agonists (α1 , α2 , β1 , β2)	Selective α1 agonists	Selective α2 agonists
	1- Epinephrine **2- Dipivefrin (pro-drug of epinephrine)** Dipivefrin = Epinephrine	**Phenylephrine** أبو فنيلة يرفع الضغط	**Apraclonidine (eye drop)** تذكرنا بمعجزة عيسى (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.		

(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(9)

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** .	

(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(10)

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) التي سيارة (Alpha(1+1=2)) فيه ألف وحدة ووحدة blockers)

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

(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(11)

Carbonic anhydrase inhibitors & prostaglandin analogues

	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.

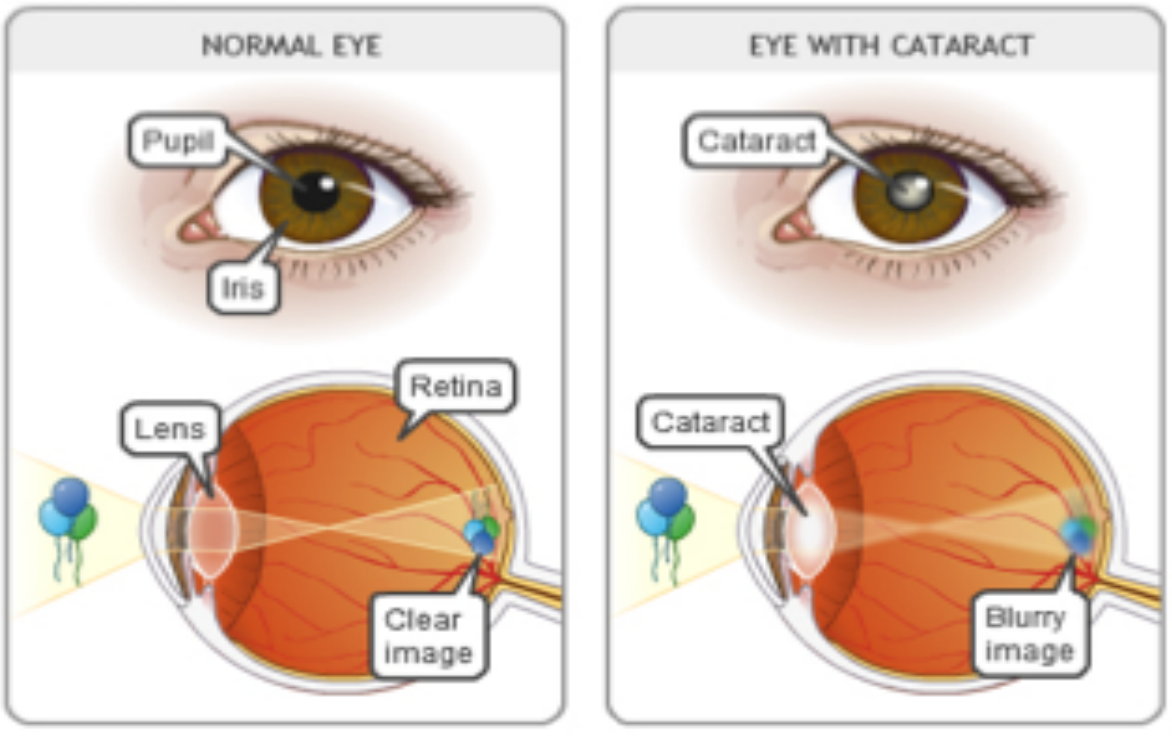
(1) Pharmacology of drugs acting on the eye

Lecture(1) slide(14)

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. تقرا اسم الدرق (كانو ذا 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

Cataracts



436

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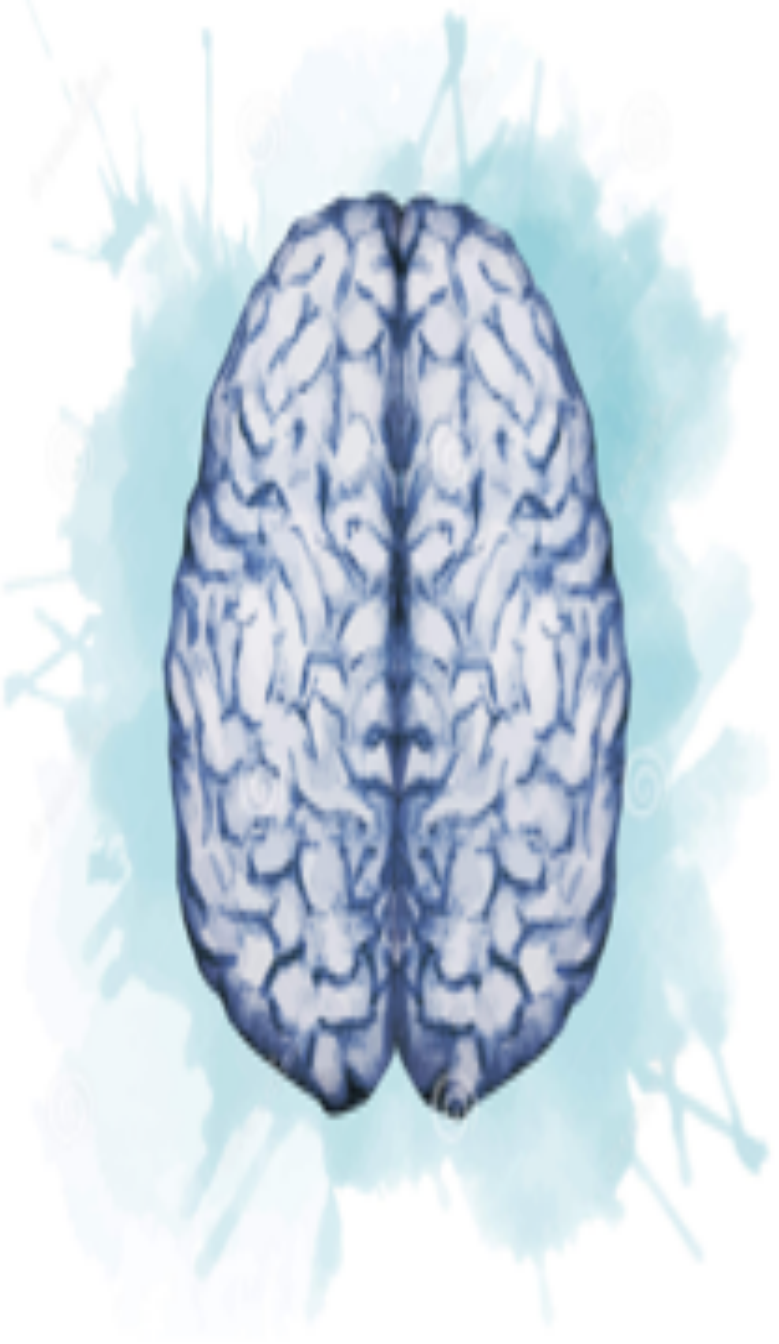

Medication affecting the balance system

(2) Medication affecting the balance system

Lecture(2) slide(3)

Overview

Drugs related to balance system

Specific treatment

Involves targeting the ***underlying cause*** of the Vertigo (e.g., ear infection).

Symptomatic treatment

Involves controlling the ***acute symptoms*** and ***autonomic complaints*** (e.g., vertigo and vomiting)

Vestibular suppressants

Reduce the intensity of vertigo and nystagmus evoked by a vestibular imbalance.

لما قلنا له)هيو السكين=هذا هو السكين (خاف وأغمى عليه

1- *Anti-cholinergics*

hyoscine

2-*Benzodiazepines.*

ممكن نحرف اخر مقطع من اسم الدرقز ونقراه)لما الزين بان أغمى علينا من جماله(

Lorazepam

Clonzepam

Diazepam

3- *Betahistine*

نقرأ اسم الدرق)بتحس الدنيا تدور(

Antiemetics

used to control vomiting & nausea

1- *Antihistamines.*

Dimenhydrinate

2- *Phenothiazines.*

prochlorperazine

نقرأ اسم الدرق)فينو ذا الزين(

نقرأ اسم الدرق)بروكلي اللي برا زين(

3- *Dopamine antagonists.*

metoclopramide

domperidone

Metoclopramide/ Prochlorperazine

كلهم فيهم مقطع ممكن نقراه)اللي ببطنك كلو برا =يعني رجع اللي ببطنه(

Dimenhydrinate = Dehydrate(the vomiting lead to dehydration)

Prophylactic treatment

Aims to ***reduce the recurrence*** of specific vertiginous conditions.

1- *Diuretics*[1] : Except Loop diuretics[2]. (Loss of Na & H2O ↓ H2O in the endolymph)

2- *Corticosteroids*[3]

3- *L- type Ca Channel Blockers*[4]

Cinnarizine

نقرأ اسم الدرق)سناء رزينة(

Verapamile

نقرأ اسم الدرق)فيه رابر اسمها أمل(

ونتخيل إن)سناء و أمل (صاروا كبار بالسن وجتهم هشاشة عظام لان)قل الكالسيوم =تقفلت قنوات الكالسيوم(

(2) Medication affecting the balance system

Lecture(2)
slide(4)

Vestibular suppressants

Drug	Anticholinergics	Benzodiazepines	Betahistine
	Hyoscine (scopolamine)	• **Lorazepam** • **Clonzepam** • **Diazepam**	
Action/Mech. of action	**1-inhibit firing in vestibular nucleus** neurons. **2-Reduce the velocity of vestibular nystagmus** - Acts by interfering with the transmission of nerve impulses by ACh in the parasympathetic nervous system (specifically the vomiting center)	ممكن نقول ريلاكس بلا قلق احنا ماسكين زمام الأمور (Zepam=Zemam) - **Minimize anxiety** and **panic** associated with **vertigo** by binding adjacent to **GABAA** receptors enhance the effects of GABA by **increasing GABA affinity** for the GABA receptor open **Cl ion channel** **hyperpolarize** cell membrane.	**It is a structural *analog* of histamine with:** **1- *Weak histamine H1 receptor* agonist** **By stimulating H1 receptors located on Blood Vessels in the inner ear→ local vasodilation and ↑ permeability helps to reverse the underlying problem of endolymphatic hydrops.** (accumulation of endolymph) → Reduce pressure in endolymph. **2- *More potent histamine H3 receptor antagonist* properties** **By *blocking H3* receptors in presynaptic nerve end → prevent reuptake of Histamine by H3 Receptor ↑ the local concentration of histamine in the inner ear** → ↑the direct H1-agonist activity. **- increases the level of serotonin in the *brainstem* → ↓ the activity of *vestibular nuclei*.**
P.K	نتخيل عندنا شخص عنده دوار الحركة وشوي وبيدوخ علينا، فعشان ننسيه الموضوع نقول له شوف(هيو مشهد البحر قدامك ما اجمله) (Hyo-scine=Hyo-scene)		- **Tablet or oral solution** - Rapidly and completely absorbed **(Lipid soluble)** - **t½= 3-4 h.** - **excreted in urine within 24h.** - **Low protein binding.**
Indications	Management of ***vertigo***, ***sedation*** & **motion sickness**	In ***small dosages*** useful for the ***management of acute vertigo***.	Meniere's Disease
ADRs	**- dry mouth** **- blurred vision** **- sedation**	**- Dependence** (addiction) **- impaired memory** **- increased risk of falling** (***it inhibits*** the ***coordination*** of skeletal muscle)	**- Headache** **- Nausea** **- GIT side effects.** (***H1 Receptor*** is found in ***smooth muscles of GIT*** ↑ contractility by the effect of histamine) **- Hypersensitivity reactions.**
C.I	نتخيل عندنا شفرة سرية بين مروجين المخدرات (Dependence) بينهم وبين بعض لما يشوفونها يقولون(الزين بان)=Zepam		**- *Pheochromocytoma*** **- Bronchial asthma.** **-History of peptic ulcer.**

(2) Medication affecting the balance system

Lecture(2)
slide(5)

Anti-emetics

drugs used to control vomiting and nausea.

Drug	Anti-histamines	Phenothiazines	Dopamine antagonists
	Diminhydrinate	**Prochlorperazine**	**Metoclopramide**
Action/Mech. of action	=Dimin-hydrate دايم هيدريت • Block H1 receptors in CRTZ. • Sedative effects. • Weak anticholinergic effects. • ↓ Excitability in the labyrinth & blocking conduction in vestibular-cerebellar pathways.	Pro = professional = total block Meto = only partial antagonist • Blocks dopamine receptors (D2) at CRTZ. • Antipsychotic , some sedation + antiemetic. • Some vestibular suppressant	• A potent central antiemetic acting on CRTZ. • Has some sedative action. • Has potent gastroprokinetic effect.
Indications	• **Vertigo.** • **Motion sickness.**	وحدة قالت فيني غثيان والحل؟ ردت الثانية خذي لك فينو ذي أزين حبة Phenothiazine One of the best antiemetics in vertigo	
ADRs	• Sedation. • Diziness. • Anticholinergic side effects.		• Restlessness or drowsiness. • Extrapyramidal manifestations (on prolonged use.) Meta u close il pyramids Metoclopramide = extrapyramidal
Contraindications	• **Glaucoma.** (anticholinergic effect increase IOP) • **Prostatic enlargement.** (Anticholinergic causes urinary retention)		

(2) Medication affecting the balance system

Lecture(2)
slide(6)

Ca^{2+} channel blockers (Prophylactic)

سناء رزينة دايم تاخذ احتياطاتها

Drug	Cinnarizine
Action/Mech. of action	- Selective K+ channel blocker. - Selective Ca2+ channel blocker - Anti-Histamine, Anti-Serotonin, Anti-Dopamine - As physiological condition, ↑ hydrostatic pressure on hair cells activates K+ currents, Cinnarizine inhibits K+ currents lead to 1- lessen vertigo 2- motion induced nausea by dampening the over-reactivity of the vestibular hair cells. - It promotes cerebral blood flow (by the effect of ↓ viscosity) to improve memory especially in elderly .
P.K	- orally in tablet form. - - Rapidly absorbed. - Low oral bioavailability due to hepatic first pass metabolism. - - If administered IV in lipid emulsion, it has better bioavailability.
Indi-cations	- Nausea and vomiting associated with motion sickness - vertigo - Meniere's disease.
ADRs	- Sweating. - Headache. - Drowsiness. - Muscle rigidity and tremor due to D2 blocking effect.
Contra-indications	- Parkinsonism due to bc they suffer from shortage of dopamine. - Car drivers Due to bc of anti-histaminic effect sedation.
Notes	The cinnarine is one of Ca2+ channel blokers - Rapidly absorbed. - Low oral bioavailability due to hepatic first pass metabolism.

سناء رزينة دايم تاخذ احتياطاتها وتقفل الأبواب

سناء الرزينة على إنها كبيرة بالسن بس ذاكرتها ممتازة

سناء الرزينة ما عندها ضغط دم مرتفع ولا مشاكل دم غيرها

سناء الرزينة تسأل أول باص متى؟

سناء الرزينة اسم زوجها (منير)

سناء الرزينة ما تحب تروح للبارك ولا تسوق سيارة

436

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pharmacology

Alcohol and the brain

(4) Alcohol and the brain

Lecture(4)
slide(7)

Organ/ system			Complications
Hematology			1. **Iron deficiency anemia** (microcytic anemia) due to inadequate dietary intake and GIT blood loss. 2. **Megaloblastic anemia** due to **folate deficiency**, malnutrition and impaired folate absorption. 3. **Hemolytic anemia.** (Destruction of red blood cells) 4. **Bone marrow suppression.** 5. **Thrombocytopenia** (suppressing platelet formation and prolong bleeding time). 6. **Impaired production of vitamin-K dependent clotting factors** leading to prolonged prothrombin time. **(Vit K is an important precursor to clot if there were deficiency thrombocytopenia will happen)**
Endocrine	Hypogonadism	In women	ovarian dysfunction, amenorrhea (abnormal absence of menstruation) , anovulation, hyperprolactinemia (high prolactin) associated with low estrogen →infertility.
		In men	Gynecomastia, decreased muscle and bone mass, testicular atrophy and sexual impotence due to inhibition of luteinizing hormone (LH), decreased in testosterone, estradiol and progesterone.
	Hypoglycemia & ketoacidosis		due to impaired **hepatic gluconeogenesis** & excessive lipolytic factors, especially increased **cortisol** and **growth hormone**. **Ketoacidosis can be seen in 2 condition if the glucose is :** - **Low : alcoholism patient (fatty liver)** - **High : diabetic patient**
CNS			1. **Tolerance.** 2. **Physiological and psychological dependence.** • Physiological dependence: Changes in physiological action according to the substance the patient's addicted to it. • Psychological dependence: No changes in the physiology but the person just want to show off. 3. **Addiction: dopamine, serotonin and opioids are involved** 4. **Neurological disturbances.** 5. **Wernicke-Korsakoff syndrome.** Vitamins deficiency→ A,D,B"B1"→ Wernicke encephalopathy or Korsakoff psychosis may occur

ترى موب رجولة إنك تشرب الكحول !

(4) Alcohol and the brain

Lecture(4)
slide(9)

Alcoholism withdrawal symptoms

There symptoms result from ***high sympathetic activity & upregulation of the receptors***

- Autonomic hyperactivity & craving for alcohol
- Vomiting, thirst
- Profuse sweating, severe tachycardia
- Vasodilatation, fever
- Delirium, tremors, anxiety, agitation, insomnia (CNS effects and need to be controlled)
- transient visual/ auditory illusions, violent behavior, hallucinations.
- Grand mal seizures (after 7-48 hours of alcohol cessation) Due to super-sensitivity of glutamate receptors & hypo-activity of GABA receptors are possibly involved.

Management of alcoholism withdrawal

Substituting alcohol with a long-acting sedative hypnotic drug (depressant drug) then tapering the dose

Benzodiazepines	as (**Chlordiazepoxide**, **diazepam**) →long acting drug. Or **lorazepam** that is ***preferable*** (***shorter*** duration of action)
	Dose of benzodiazepines should be carefully adjusted To provide Efficacy: (**IV/ po**) &Manage **withdrawal symptoms** & prevent irritability, insomnia, agitation & seizures. & avoid **excessive dose** that causes respiratory depression & hypotension.
Fluoxetine	• Serotonin reuptake inhibitor (anti-depressant drug). • Affect dopamine levels.
Clonidine & Propranolol	**Clonidine** is a2 agonist **inhibits** the action of exaggerated **sympathetic activity.**
Acamprosate	a weak **NMDA receptor antagonist & GABA activator**, reduce psychic craving (reduce risk of relapse)

To prevent alcohol relapse

Disulfiram therapy: 250 mg daily → Inhibits hepatic aldehyde dehydrogenase → increase blood level of acetaldehyde → **Disulfiram** induced symptoms render alcoholics afraid from drinking alcohol → Acetaldehyde produces extreme discomfort, vomiting, diarrhea, flushing, hotness, cyanosis, tachycardia, dyspnea, palpitations & headache

Alcohol and drug interactions

Acute alcohol use (large dose)	causes **inhibition** of liver microsomal enzyme, decreases metabolism of some drugs and increases their toxicities e.g. **bleeding** with **warfarin**
Chronic alcoholuse(continuous dose)	**induces** liver microsomal enzymes and increases metabolism of drugs such as **warfarin, propranolol** and etc
other	• **Acetaminophen** + alcohol (chronic use)= risk of **hepatotoxicity**. →due to increased production of free radical metabolite of acetaminophen→High metabolism of high doses of acetaminophen →high free radicals (result from metabolismby microsomal enzymes) →hepatotoxicity • **NSAIDs + alcohol:** Increase in the risk of developing a major GI bleeding or an ulcer. Because [illegible] eeding, so the combination increases the ri[illegible] • Narcotic drugs (**codeine** and **methahdone**) + alcohol= risk of **respiratory and CNS depression** • Alcohol suppresses gluconeogenesis, which may increase risk for hypoglycemia in diabetic patients.

ميثا تحط كود وتهد السمباثتيك والريسبايرتوري

436

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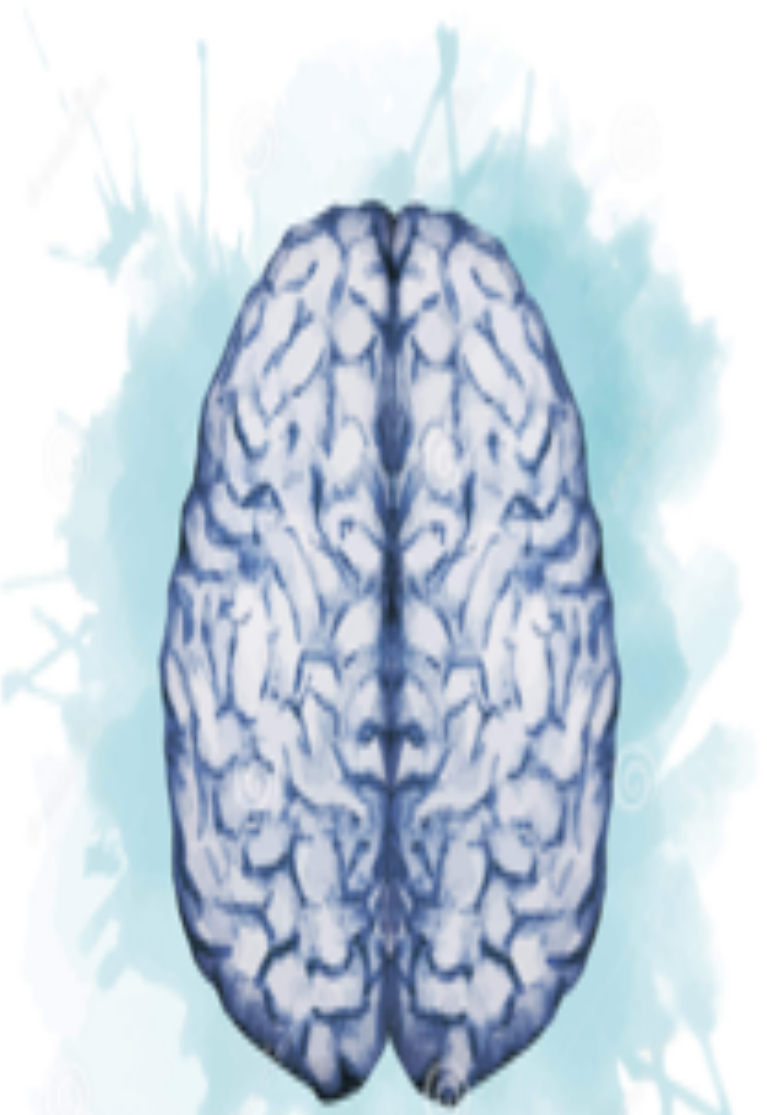


Drugs used in Parkinsonism

(5) Drugs used in Parkinsonism

Lecture(5)
slide(3)

Overview on the treatment of Parkinson's disease

- Parkinson's disease treatment of par
  - Mild cases → selegiline, amantadine or anticholinergics
  - Main cases → Levodopa and carbidopa
    - نقرأ اسم الدرق بالمعكوس، يوصل (L-dopa)للمخ (Centrally)بالسيارة (Bi car)
  - Adjuncts to levodopa → Other medications
    - عيدوا برومو (Promo = Bromo)الكريب (crip=crepe)تاني مره (tine)
    - Dopamine agonist →Bromocriptine
    - موب (MAO-B)هذا (selective= Selegiline)السيليق (Seleg)لنا (iline)؟
    - MAO-B inhibitors →Selegiline
  - Other useful drugs
    - ممكن نقرأ اسم الدرق أمنته بالدين أوأمانة تديّن
    - Enhance dopamine release →Amantadine
    - Muscarinic receptor antagonist →Benztropine and trihexyphenidyl
    - كم (COMT)عندك أنت كوبون (Enta-capone)؟
    - COMT inhibitors entacapaone
    - عندك أنت قبعة وحدة بس (Enta-cap-one)!؟

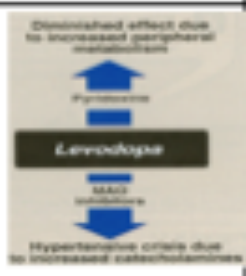
Benzo is from benzene so it is lipid soluble → cross BBB. It is a minor treatment if the patient can't take dopamine → give him anti-muscarinic drugs.

(5) Drugs used in Parkinsonism

Lecture(5)
slide(6)

Drugs that increase dopaminergic activities (DA precursors)

Drug	**Levodopa (L-dopa) cont.**
Indications / Uses	- The most efficacious therapy. → 1 st line treatment. - The best results of **levodopa** are obtained in the first few years of treatment. - **L-dopa** ameliorates all signs of parkinsonism particularly **bradykinesia & rigidity** but does not cure the disease. - Should **not** be used in parkinsonism associated with antipsychotic drug therapy.
Drug interaction	- **High proteins meals.** (compensate on the same receptors) - **Pyridoxine** (Vitamin B6). → 6 (L-dopa) عدد حروف الدرق o ↑ peripheral metabolism by Vit.B6. - Adrenomimetic aminees - **Nonselective MAO inhibitors (phenelzine, tranylcypromine).** → Hypersensitivity crisis due to ↑ catecholamines, MAO inhibitors are 3 types A (metabolize catechol amines: 5-TH + NE) & B (metabolize DA)& non-selective
ADRs	**Peripheral**: - Anorexia, nausea, vomiting (due to stimulation of chemoreceptor trigger zone CTZ). →They are more common with combination of DC inhibitors. - Cardiac arrhythmias. → because of increased catecholamines peripherally. - **Mydriasis** → May occur and participate in acute glaucoma. - orthostatic (postural) hypotension →with higher doses
	CNS: Mainly depression, delusions, confusion, sleep disturbances(insomnia), hallucinations, vivid dreams
CI	- Psychotic patient. →because it may exacerbate the mental disturbance. (Effective against all types of parkinsonism except those associated with antipsychotic drug therapy.) - **Glaucoma** (due to mydriatic effect). - Patients with history of melanoma. Why? →**L-dopa** is a precursor of melanin → so it may activate malignant melanoma



Dopamine Receptor Agonists

Overview:

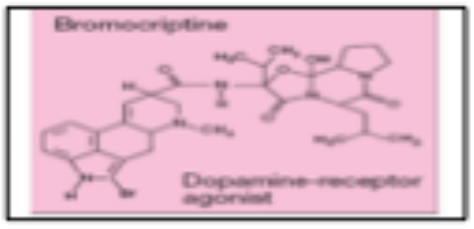
- Have longer duration of action than **L-dopa** (less likely to cause dyskinesias than **levodopa**) but more likely to cause psychotic side effects
- They are divided into ergot derivatives and non ergot depending on the density .
- **Ergot derivatives: bromocriptine, pergolide**
- **Non ergot derivatives: pramipexole, ropinirole**

ممكن نقرأ اسم الدرق)سووا برومو للكريب تاني(

Clinical use:

ممكن نقرأ اسم الدرق)برا مابي يا زول(

- As monotherapy, the dopamine agonists are less effective than levodopa. Thus can only be used as initial therapy for early stages of the disease, and it has longer duration of action.
- In advanced stages, dopamine agonists are used as an adjunct to levodopa, they may contribute to clinical improvement and reduce levodopa dosage needs.
- Lippincott: Dopamine agonists may delay the need to use levodopa therapy in early Parkinson disease and may decrease the dose of levodopa in advanced Parkinson disease.



(5) Drugs used in Parkinsonism

Lecture(5)
slide(7)

Dopamine Receptor Agonists

Drug	Ergot derivatives: e.g:Bromocriptine, pergolide	Non ergot derivatives:
	Bromocriptine	**Pramipexole**
Mech. of action	• **D2 agonist,** and a partial D1-antagonist • T½ = 6-8 h. • Longer than Levodopa (t½ =2 h) • But L-dopa more effective.	• D3 agonist • Used alone as initial therapy or in combination with Ldopa.
Route of admin.	**Orally** Absorbed to a variable extent from the GIT ; peak plasma levels are reached within 1–2 hours after an oral dose. Excreted in the bile and feces.	**Orally** Rapidly absorbed, reaching peak plasma concentrations in approximately 2 hours, excreted largely unchanged in the urine **excreted unchanged in urine.** Renal insufficiency may necessitate dosage adjustment
Indications	Used for the treatment of: 1. Parkinson's disease 2. Hyperprolactinemia (galactorrhea) G…evated s…fertility i…is under inhibitory control by dopamine. 3. Infertility in women.	Has the advantage of being free radicals scavenger. For example, cimetidine, which inhibits renal tubular secretion of organic bases, increases the halflife of pramipexole by 40%
ADRs	• Confusion, hallucinations, delusions • Dyskinesias (less prominent). • Somnolence	
Contraindications	• Psychosis • Peripheral vascular disease (only ergot derivatives, which cause severe vasoconstriction and may cause gangrene with high dosage) • Recent myocardial infarction. • Active peptic ulceration (with Bromocriptine)	

HyperPROlactinemia = BROmocriptine
من نفس تشبيه الكريب ←الكريب يقدم مع حليب ساخن عادة

My bro (bromocriptine) is an earl (ergot). he married twice (D2). because his ex-wife is infertile. His 2nd wife has Hyperprolactinemia so she can fed all his children.
أخوي شخص نبيل .متزوج ثنتين، لأن زوجته الأولى ما تجيب أطفال، وزوجته الثانية عندها كمية فائضة من الحليب تقدر ترضع أطفاله كلهم .

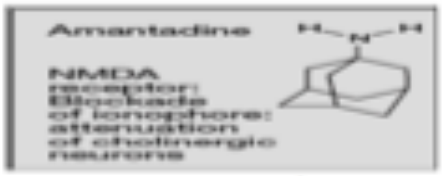
(5) Drugs used in Parkinsonism

Lecture(5)
slide(8)

Amantadine

action

- originally introduced as an **antiviral**. Anti-parkinsonism.
1. inhibits the reuptake of DA→ Increases dopamine release
2. Acts as an antagonist at **muscarinic receptors**
3. Antagonist at NMDA receptors (N-methyl-D-aspartate) (glutamate receptors)



Route of admin.

- Given **orally** with short half life = 2-4 h
- Most of the drug is excreted unchanged in the **urine**

Efficacy

- Less efficacious than L-dopa (Modest effectiveness)
- **Tolerance** (decrease of response) develops to its therapeutic effect after 6-8 months. (tolerance is after 3-5 years for levodopa)
- Its benefits last only for short period and only used for L-dopa resistance. (which is caused by variation in response among patients)
- Amantadine and the anticholinergics may exert additive effects on mental functioning. (Amantadine) أمانة (Anticholinergic) قبلي أنتي كُلي ffect and atropine like effect)

Uses

- Useful in the **early stages** of parkinsonism or as an adjunct to levodopa therapy.

C.I

-Anticholinergics. -In patients with a history of seizures or heart failure

ADRs

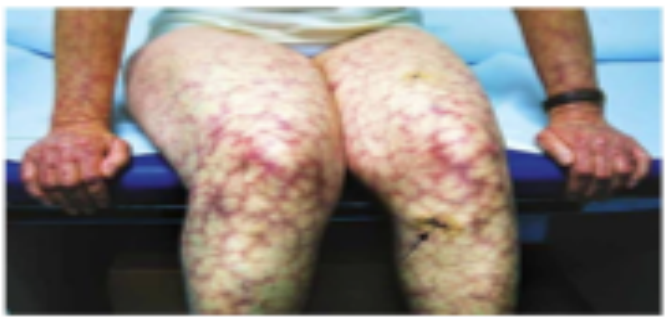
Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects).
- Dry mouth, urinary retention , constipation (anticholinergic effects).
- Restlessness and hallucinations (NMDA antagonist). →

NMDA is a type of glutamate receptors & glutamate is an excitatory

(Amantadine) لا تعلم أحد باللي شفته فيني وقال لك أمنتك بالدين (Livedo reticularis) نتخيل جاك مريض بنفس هذي الحالة llucinations.

- Ankle edema, and **livedo reticularis***.(rare)

*Discoloration of skin due to accumulation Of blood inside veins.



Amantadine is contraindicated with heart failure patients because it causes fluid retention.

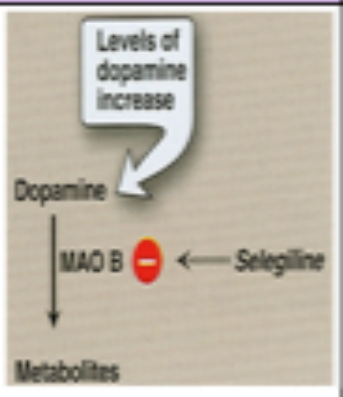
Notes

Lippincott: It was accidentally discovered that the antiviral drug amantadine [a-MAN-ta-deen], which is effective in the treatment of influenza has an antiparkinsonism action.
-Amantadine has several effects on a number of neurotransmitters implicated in causing parkinsonism, including increasing the release of dopamine, blockading cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors.
-The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. Amantadine is less efficacious than levodopa, and tolerance develops more readily. However, amantadine has fewer side effects. The drug has little effect on tremor, but it is more effective than the anticholinergics against rigidity and bradykinesia.

(5) Drugs used in Parkinsonism

Lecture(5)
slide(9)

Monoamine oxidase-B (MAO-B) inhibitors

Drug	Selective = Sele — **Selegiline**
Mech. of action	It is a **selective** irreversible inhibitor of **MAO-B**, an important enzyme for **dopamine** metabolism. * MAO-A →metabolize NE, 5-HT, DA - The blockade of **dopamine** metabolism makes more **dopamine** available for stimulation Mech. of its receptors. **Selegiline may have neuroprotective effects due to:** - Metabolized to **desmethylselegiline**, which is anti-apoptotic. - Has anti-oxidant activity against toxic free radicals produced during **dopamine** Metabolism so it slows the progression of the disease 
Indications	Adjunctive to **levodopa/carbidopa** in later-stage parkinsonism to: - Reduce the required dose of **levodopa.** - As monotherapy may be effective in newly diagnosed patients - Delay the onset of dyskinesia and motor fluctuations that usually accompany long-term treatment with **levodopa.**(the main goal is to prolong the effect of L-dopa without increase the dose and within the therapeutic range and that happens when we combine L-dopa with MAO & COMT inhibitors)
ADRs	At high doses: - It may inhibit MAO-A →**(hypertensive crises)** →as a result, do not prescribe selegiline with drugs that increase the level of catecholamines. - May ↑the adverse effects of levodopa. - May cause insomnia when taking later during the day.
Contra-indications	**Co-administered with:** 1. **Meperidine** 2. **Tricyclic antidepressants.** 3. Selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma).due to increase in catecholamine →Serotonin toxicity 4. Food restriction "low **tyramine** diet" is required. (cheese effect)(cheese and banana are rich in tyramine which increase noradrenaline. So, taking this type of food with MAO B inhibitor (which indirectly increase noradrenaline) will increase the catecholamine level epically noradrenaline and causes hypertension)

(Tyra-رايقه لك طير مني= MAO/MOA-B) تراني)مو /موب BP mine)

COMT (Catechol-O-Methyl transferase) Inhibitors

Only in girl slides!

	Entacapone	Tolecapone
Drug		
Action/Mech. of action	- Acts peripherally to inhibit COMT enzyme required for L-dopa degradation. - Usually given in combination with L-dopa and carbidopa to diminish peripheral metabolism of L-dopa. - Can't cross BBB	- Peripheral and central COMT inhibitor - More lipid soluble than entacapone. - More penetration into CNS. - Tole = Total = Central & peripheral Not all patients respond to anti-cholinergic drugs
Indications	**Used as adjuvant to L-dopa + carbidopa to:** - Decrease fluctuations - Improve response - Prolong the ON-TIME	
ADRs	**L-dopa side effects**	
	Orange discoloration of urine.	-

436

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Drugs used in management of pain

(6) Drugs used in management of pain

- Opioids
  - Receptors (g protein coupled r)
    - 1.Mu (μ).
    - 2. Kappa (κ)
    - 3. Delta (δ)
    - 4. ORL-1.
  - classification according to
    - their source
      - 1. Natural → Morphine,Codeine
      - 2. Semisynthetic → Heroin
      - 3. Synthetic → Pethidine, Methadone
    - agonistic/antagonistic action
      - Agonists Morphine, Codeine, Pethidine, Methadone
      - Mixed agonist\antagonist Pentazocine
      - Pure antagonist Nalaxone, Naltraxone
    - their specificity of action on receptors
      - μ receptor. agonists → Morphine, codeine, heroin
      - agonist at k receptor. & antagonist at μ receptor. → Pentazocine

Co-deine مزدوج
الديانة

ممكن نقرأ اسم الدرق كذا
متأكد بتهدّيني هالمسكنات ؟
أصلاً متى هدّوني هالمسكنات؟

ممكن نقرأ اسم الدرق بطريقة ثانية)متحدون(

بنتك تايه ما تدري على ايش تشتغل

لما الشباب يلعبون كورة بلاستيشن يقول يله نعلب واحد ضد واحد (one X one)

436

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Drugs used in schizophrenia

Antipsychotic drugs

What are they ?

are group of drugs used in the treatment of schizophrenia.
-Old name (neuroleptic drugs)

Classification:

Drugs used in schizophrenia are classified according to chemical structures Into	
Typical	Atypical Better!
discovered first, non selective, many side effects, rarely used nowadays.	more selective, less side effects, 1st line treatment for schizophrenia.

Classification of antipsychotic drugs

كل شيء قديم زين (ZINE)

Typical Antipsychotic Drugs→ affect D2 mainly Except Cariprazine on D3 → treat the +ve symptoms

Phenothiazine derivatives فينو ذا الزين ؟ Its chemical structure similarto TCAs →similar ADRs	Such as: Chlorpromazine(Protype very old),Thioridazine Chlorpromazine لا أبدا ما زين ؟ Thioridazine دا زين ؟
Butyrophenones	Such as: Haloperidol
Thioxanthene	Such as: Thiothixene ذي أو ذي زين ؟

Atypical Antipsychotic Drugs better than typical → Affect both DA & 5-HT receptors →treat +ve & -ve symptmos.

الزباين غير عاديين صراحة (ZEPINE)

Dibenzodiazepines	المحل امتلأ كلو زباين	Such as: Clozapine
Benzisoxazoles	يا ريس خلصت (ris-per-i-done)	Such as: Risperidone
Thienobenzodiazepines	زباين علا (Ola-n-zepine)	Such as: Olanzapine
Dibenzothiazepines	الملابس كويتيها باين	Such as: Quetiapine
Benzisothiazoles	زيبرا سيد رقم واحد بلا منافس	Such as: Ziprasidone
piperazine/piperidine derivatives	السيارة اللي برا زينة ؟	h as: Cariprazine (approved in 2015 by the FDA)

(7) Drugs used in Schizophrenia

Lecture(7)
slide(8)

Atypical Antipsychotics

*very important

Raspberry has 2 colors

Zebra has 2 colors

Remember it's Atypical

Drug	Risperidone	Ziprasidone	Clozapine	Olanzapine	Quetiapine	Cariprazine
Mech. of action	Blocks D2 & 5HT2 receptors.	Blocks D2 & 5HT2 receptors	Blocks both D4 & 5HT2 receptors.	Blocks D1 - D4 & 5HT2 receptors.	Blocks D1 -D2 & 5HT2 receptors	approved in 2015 by the FDA - has higher affinity at D3 receptor
Indications		Drug interactions: - Should not be used with any drug that prolongs the QT interval. - Activity decreased by carbamazepine (inducer of CYP3A4) - Activity increased by ketoconazole (antifungal) (inhibitor of CYP3A4)		When you eat all in, you gain weight and get big stomach (Flatulence)	Doctor is boring, student 1&2 got sleepy (sedation and sluggishness), so they started talking and stopped being Quite	has a positive impact on the cognitive symptoms of schizophrenia
ADRs	- Postural hypotension - QT prolongation - Weight gain	- Drowsiness, Akathisia (cant keep still) ,Headache ,Dizziness, Weight gain.	Agranulocytosis - Seizures - Myocarditis - Excessive salivation (during sleep)	- Weight gain - -Sedation Flatulence, increased salivation & thirst. - Postural hypotension.	- Sedation Hypotension Sluggishness - Dry mouth - Increased appetite (weight gain) - Abdominal pain - Constipation	
Contra-indications	Patients with long QT interval.	It increases mortality in elderly patients with dementia-related psychosis.	it contraindicated in patient with epilepsy			

idone = QT prolongation

مقلم(Ziprasidone = Zebra) حيوان الحمار الوحشي
أبيض وأسود واذا الواحد نظر إليه كثير يدوخ ويصدع راسه

zebra can't stand still

Quetiapine
= Quiet
= Sluggishness

Ziprasidone = alzheimer = dementia

436

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Drugs used in anxiety & panic disorder

(8) Drugs used in anxiety & panic disorder

Lecture(2)
slide(3)

SUMMARY

Classes of anxiolytics	Uses	Adverse effects
Benzodiazepines (2nd line treatment)	Generalized anxiety disorders, OCD, phobia, panic attack.	Ataxia, confusion, dependence, tolerance, withdrawal symptoms.
In severe case — **SSRIs (fluoxetine)** (1st line treatment)	Generalized anxiety disorders, Obsessive-compulsive disorder, phobia, panic attack.	Sexual dysfunction, atropine like actions.
Tricyclic Antidepressants (doxepin, imipramine)	Anxiety with depression & panic attacks.	Weight gain, sexual dysfunction, atropine like actions, arrythmia.
In Mild case — **5HT1A agonists (buspirone)**	Mild anxiety(only) Not effective in panic attack.	Minimal adverse effects.
Beta adrenergic blockers (propranolol, atenolol)	Phobia (social Phobia). Control the somatic symptoms	Hypotension.

Benzodiazepines

Suffix "zolam" or "zepam"

classifications according to duration of action

Short acting
(3-8hrs) TO
(Average 4h)

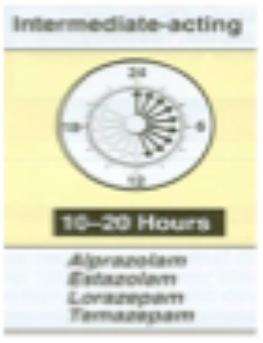
جرب لعبة او اكس ما تاخذ وقت معك (try O,X)

- Triazolam
- Oxazepam

intermediate
(10-20hrs (a day) "late"

لورا وتيما أصدقاء من أبريل

- Lorazepam (antiepileptic)
- Alprazolam
- Temazepam
- Estazolam



Long acting
(24-72hrs)

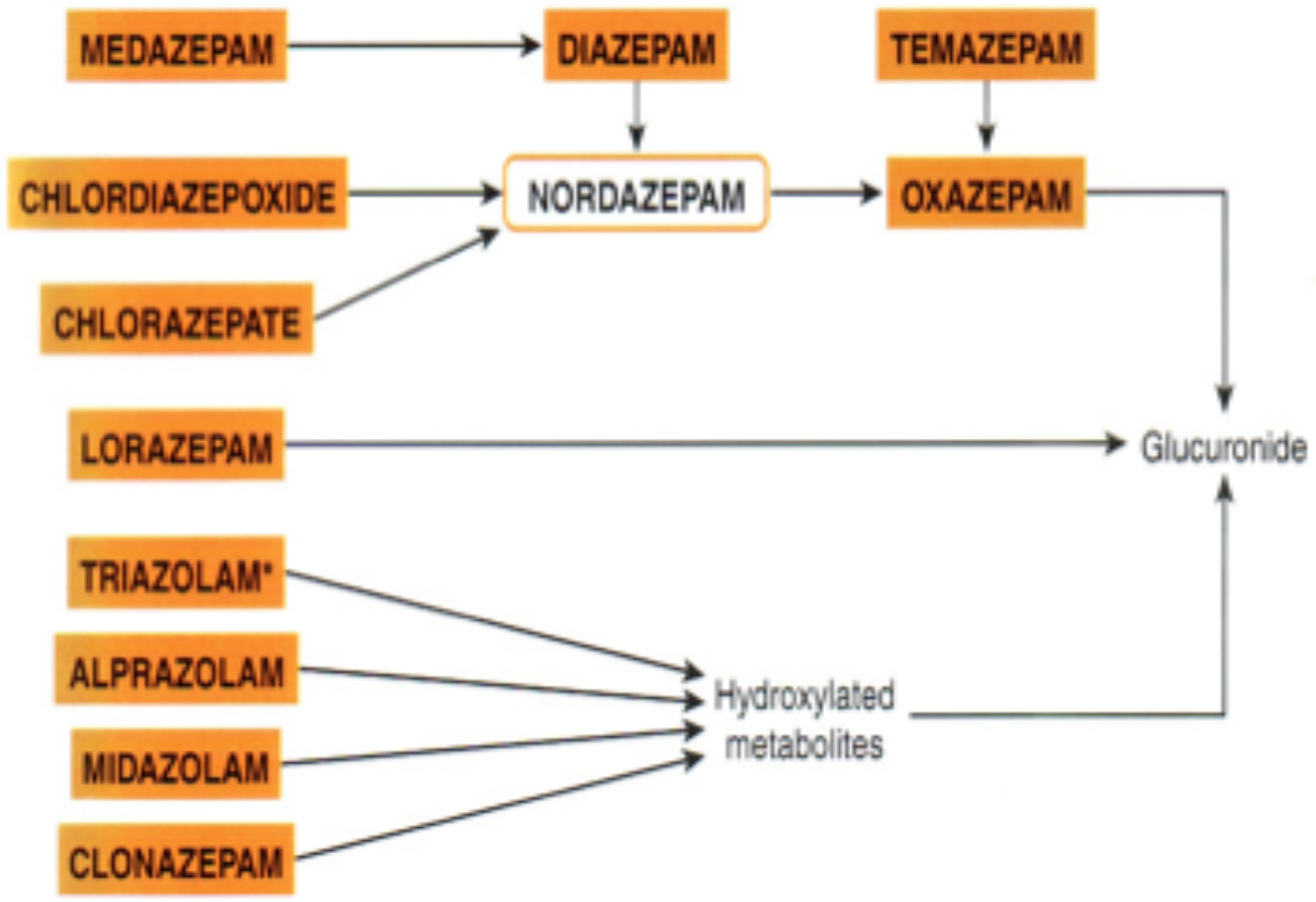
مات عشانه تسمم بالكلور والفلور لمدة طويلة فيهم

- Diazepam
- Chlordiazepoxide
- Flurazepam
- Clorazepate
- Quazepam

(8) Drugs used in anxiety & panic disorder

Lecture(2)
slide(3)

Benzodiazepines



*Triazolam withdrawn in UK

Fig. 36.4 The metabolism of benzodiazepines. The N-demethylated metabolite nordazepam is formed from a number of benzodiazepines and is important because it is biologically active and has a very long half-life. Compounds with pharmacological activity are shown in blue. Drugs available for clinical use are shown in shaded boxes.

explanation :

- Big form of **benzodiazepines** metabolize in the liver and transfer into intermediate metabolize called Nordazepam which also has CNS depressant and then it will transfer to another metabolize which is called Oxazepam (short duration action) which enter glucuronide conjugation to be easily execrated in urine.

- Glucuronic acid is a phase 2 (phase 1 : oxidation , reduction , hydrolysis) studied in foundation block ☺

- So we won't give the elderly patient long duration drugs due to :

1- They have low metabolize function + increasing in age will decrease phase 1 enzyme function so → they will have what's called : CNS super sensitivity = respond more than young patient to drugs

2- Accumulation of the diazepam will cause → sever CNS depression eg : delirium (patient can open the house door and go out without consciousness)

- **Lorazepam** go directly to phase 2 → **that's why it is preferred in elderly patient + it is an intermediate in action**

لورا عندها واسطة تروح دايركت ويحبونها كل العجز

(8) Drugs used in anxiety & panic disorder

Lecture(2)
slide(6)

Benzodiazepines

Therapeutic uses

1. Anxiety disorders:

Short term relief of severe anxiety, General anxiety disorder, OCD (Obsessive- Compulsive Disorder) , Panic disorder with depression Alprazolam (antidepressant + anxiolytic effect)

الشخص البار لأهله لا يجيه اكتئاب ولا قلق بهالحياة

- Benzodiazepines are fast acting typically bringing relief with[illegible]

lora had flu and she tried to sleep but she can not.

2. Sleep disorders (Insomnia): Triazolam, Lorazepam, Flurazepam. (Triazolam not used as sleeping pills anymore due to short action) They tend to decrease the latency to sleep onset and increase Stage II of NREM sleep.

3. Treatment of epilepsy: Diazepam – Lorazepam. (given in emergency as IV)

لورا ماتت من الصرع

4. In anesthesia:

- Pre-anesthetic medication (diazepam). Before surgery

كل مريض قبل ما يدخل عمليته يراوده شعور إنه ممكن يموت

- Induction & maintenance of anesthesia (Midazolam, IV)

نخدره وسط العملية (MID)

5. Alcohol withdrawal syndrome: (diazepam)

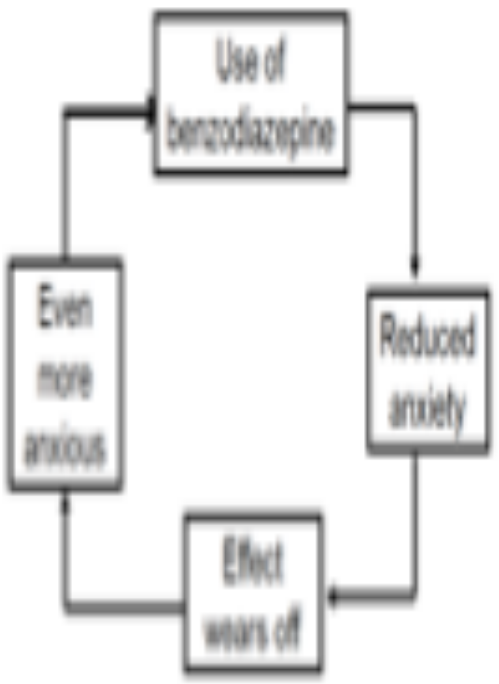
ترى إذا ما تركت الكحول ترى احتمال إنك تموت عالي

ADRs

- Cognitive impairment.
- Ataxia (motor incoordination) with ↑ dose
- Impairment of driving ability.
- Anterograde amnesia.
- Hangover: (excess sedation,drowsiness, confusion)
- Tolerance and dependence.
- Psychological & physical dependence with continuous use.
- Risk of withdrawal symptoms:

Rebound (exaggerated) insomnia, anorexia, anxiety,agitation, tremors & convulsion).

- Respiratory & cardiovascular depression in large doses only (toxic effects).



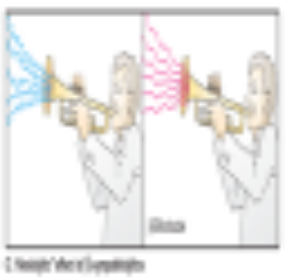
Drug

الفلو ما زين لي أبداً

Flumazenil (Benzodiazepine antagonist)

(8) Drugs used in anxiety & panic disorder

Lecture(8) slide(7)

class	$5HT_{1A}$ agonists (5-hydroxytryptamine)	SSRIs	Tricyclic Antidepressants	Beta Blockers
Drug	***Buspirone*** Bus-per-One Bus-Air-One	***Fluoxetine*** فلوسي	Doxepin , Imipramine , Desipramine	Propranolol (non selective), Atenolol
Action/Mech. of action	• **Acts as a partial agonist at brain $5HT_{1A}$ receptors, presynaptic inhibiting 5HT release.** • Weak dopamine D2 action , but not antipsychotic • Rapidly absorbed orally • Slow onset of action (delayed effect) • T½ : (2 – 4 h). • Undergoes extensive hepatic metabolism, some of the metabolites are active • Its **clearance is reduced by liver dysfunction** • Adaptive changes after chronic treatment , reduction in 5HT2 receptors in cortex	• (SSRIs) : Selective serotonin reuptake inhibitors by blocking uptake of 5-HT • Given orally • has long half life	• act by reducing uptake of 5HT & NA • Delayed onset of action (weeks).	↓ by blocking peripheral sympathetic system ↓ Reduce somatic (not psychological) symptoms of anxiety.
Indication	Used As anxiolytic in (mild) generalized anxiety disorders cause : 1. It's only anxiolytic 2. No hypnotic effect. 3. No muscle relaxant effect. 4. No anticonvulsant action. 5. No alcohol additive effect. 6. Doesn't impair memory and coordination. (can use in elderly patients) 7. Does not affect driving skills. 8. Minimal risk of dependence. 9. No withdrawal symptoms. 10. No potentiation of other CNS depressants 11. Minimal psychomotor & Cognitive dysfunctions	First line of treatment for anxiety disorders c disorder, OCD, PTSD, phobia) use they are : **ll tolerated,** **v risk for** **ndency and abuse** **v potential for overdose.** (CVS& spiration depression)	1. Used for anxiety especially associated with **depression** 2. Effective for panic attacks	• Decrease BP & slow heart rate → so Used in performance or social anxiety. • Are less effective for other forms of anxiety
ADRs + Contraindication	• Slow onset of action (delayed effect) • GIT upset, dizziness, drowsiness • Not effective in severe anxiety/panic disorders • Drug Interactions with CYT P450 inducers and inhibitors • Increase blood pressure in people taking MAOI. **Should be used with precaution :** • Pregnant women or breast-feeding. • People over 65 (old people) • Dose reduction is recommended in liver disease & old people	-Delayed onset of action (weeks). -Nausea, diarrhea , GIT upset -Weight gain or loss Fluoxetine cause weight Loss. -Sexual dysfunction -Dry mouth -Sleep disturbance or insomnia -Seizures	-Atropine like actions : (dry mouth-blurred vision, urinary retention Tachycardia) -α-blocking activity (Postural hypotension) -Sexual dysfunction -Weight gain	Should be used with caution in asthma, cardiac failure, peripheral vascular disorders 

Bus Driver usually are elderly and help them to use their brain effectively

Bus Driver

DRUG interaction

عزام وأمل ركبو ال Air-Bus-One وطاروا

Buspirone	CYP450 3A4 Inhibitors : (verapamil, diltiazem Ca+2 blocker)	↑ buspirone level.
	CYP450 3A4 Inducers : (Rifampin)	Causes 10 fold ↓ buspirone level.

436

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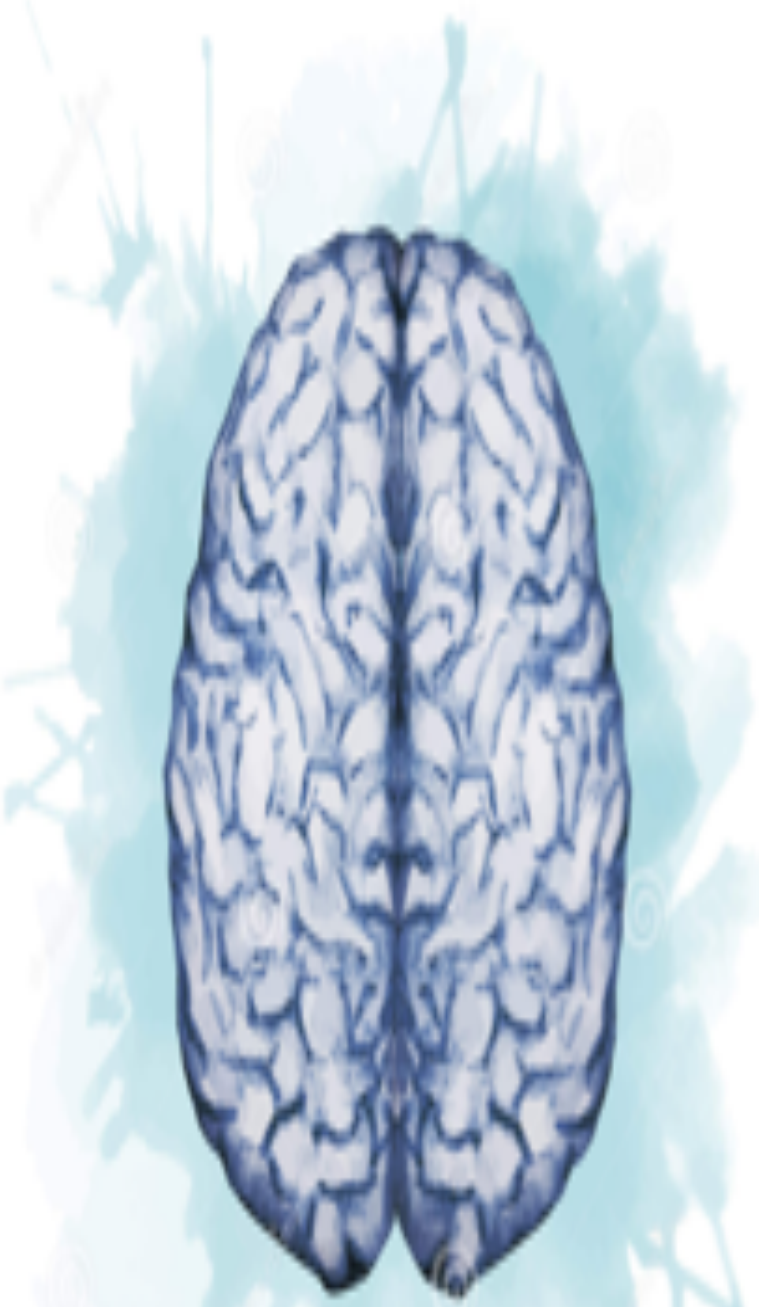

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Drugs used in Depression Old &new

(9 &10) Drugs used in Depression old & new

Lecture(9)
slide(2)

Introduction

Depression

- Depression is a very common psychiatric disorder that is related to the Mood (affective disorder)
- Disorders of mood like: depression and mania are associated with changes in mood, it causes symptoms that affect feelings. .
Clinical depression: the symptoms comes every day for two weeks at least, and here we need the treatment.
- Disorders of mood rather than disturbance in thought or cognitions.

Incidence:

- Depression is a chronic and recurrent illness that can affect at least 20% of the population at some period in their lifetime.
- Estimated: 35-40 million Americans will suffer from major Depressive Illness . costing 15-35 billion dollars/ year.

Symptoms of depression:

Symptoms of depressive illness are highly recognizable, both to those affected and to those closest to them, once they are told what to look for.

Here is a checklist of symptoms of Depressive illness:

- Loss of energy and interest
- Diminished ability to enjoy oneself
- Decreased or increased sleeping or appetite
- Difficulty in concentrating
- indecisiveness, slowed thinking
- Exaggerated feelings of sadness, hopelessness, or anxiety.
- Feelings of worthlessness
- recurring thoughts about death and suicide

If most of these symptoms last for two weeks or more, the person probably has Depressive illness.

Symptoms of mania:

causes mood swings creating periods with the following symptoms:

- a high energy level with Decreased need for sleep.
- Unwarranted or exaggerated belief in one's own ability.
- Extreme irritability.
- Rapid unpredictable emotional changes.
- Impulsive, thoughtless activity, with a high risk of damaging consequences (i.e., stock speculations, sudden love affairs, etc.).

Pathophysiology:

Neurotransmitter Imbalances & Dysregulation creates a state of deficiency in monoamines creates a state of deficiency in monoamines such as NTs (serotonin (5-HT), Dopamine, NE)

قالوا لنورا سيري بالدب فجاها اكتئاب

Classification of depression

Classification

- According to severity of symptoms:
  - 1. Mild depression self-limiting
  - 2. Moderate depression difficulties at home and work
  - 3. Severe depression serious, associated with suicidal thoughts in this case we need to make sure that the patient takes his medications
- According to type:
  - 1- Bipolar depression (manic-depressive):
    - in which depression alternates with mania.
    - It is mainly hereditary and appears in early adult life
  - 2- Unipolar depression (major depression):
    - mood swings are always in the same direction (depression)
    - about 75% of cases are non-familial
    - accompanied by symptoms of anxiety and agitation
    - Associated with stressful life events.
    - 25% familial unrelated to external stresses(endogenous depression)
- Other forms of depression:
  - 1.Psychotic depression caused by genetic factors
  - 2.Postpartum depression such as pregnant women
  - 3.Atypical depression

(9 &10) Drugs used in Depression old & new

Lecture(9)
slide(4)

Very very very useful video explains each class with their mechanism of action. watch from (1:40)

Classification :

Classification of antidepressants based on site of action:

*Mechanism of action very important

Drugs that block the reuptake of NE and 5-HT and this will trigger the nerve to synthesis more NE&5-HT

ترى السيكل قديم

e.g. Most tricyclics (old Antidepressants)

Drugs that Inhibit MonoAmino Oxidase

فين الزين، من زمان عنه

ترانى لس برا أنتظرك لي فترة طويلة

MAOIs, Phenelzine, Tranylcypraine, Moclobemide)

ترانى لك من زمان

ترى مو كلو بالميد داخل)فيه محاضرات من الدفع القديمة محذوفة)

(old Antidepressants)

Drugs that selectively block 5-Ht reuptake(SSRIs)

فلوسى Fluxetneسر SSRIسعادتي

Fluoxetine, Paroxetine, Sertraline, Citalopram

(New Antidepressants)

Drugs that Block Presynaptic α2 adrenoceptors

سيروا على مرت عزيز الثانية

هذي مرت عزيز باين عليها متزوجة جديد

(e.g.: Mirtazapine, Mianserin).

مرته عزيزة نفس باين عليها، تو تو الف ما شاء الله عليها وحواليها

(9 &10) Drugs used in Depression old & new

Lecture(9)
slide(5)

Antidepressants Available in the Market (Worldwide)

Class	Drugs
Tricyclics (TCAs) and Tetracyclics	Imipramine, Amoxapine, Maprotiline, Nortriptyline, Trimipramine, Clomipramine, Protriptyline, Desipramine, Amitriptylin , Doxepin
Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Fluvoxamine, Citalopram, Sertraline, Paroxetine, Escitralopram
Monoamine Oxidase Inhibitors (MAOIs)	Tranylcypramine, Phenelzine, Moclobemide
Serotonin And Noradrenaline and Reuptake Inhibitors (SNRIs)	Venlafaxine, Duloxetine
Serotonin-2 Antagonist and Reuptake Inhibitors (SARIs)	Nefazodone , Trazodone
Noradrenergic and Specific Serotonergic Antidepressant (NaSSAs)	Mirtazapine
Serotonin Reuptake Enhancer	Tianeptine
Noradrenaline Reuptake Inhibitor (NRI)	Reboxetine
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)	Bupropion

نورا NAسيري Serotoninجيبي لنا فانيلا مع ديو

نتخيل فيه واحد اسمه نايف يستهبل ولبس لبس الهنود اللي هو الساري SARIفنقول له نايف ترى زودتها

مرت عزيز باين جاها عرق النسا NaSSAمره ثانية alpha2

نورا Noraعيدي تغليف Re box itالهدية ما عجبتني

ربي صديقة نورا المتشائمة

ندري NDRIصار دب Dopamineلأنه كثر من البوب كورن أو البيبروني

Old Anti-depressant

You have to know the classification of each drug (tricyclic or tetracyclic)

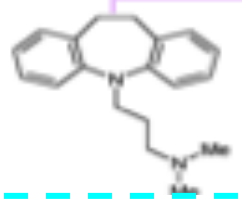
Old antidepressants

What is the common mechanism of TCAs&MAOIs on NTs?
Increasing monoamines.
Monoamine: serotnin&dopamine.
and they're endogenous products, synthesized in your body.

TRICYCLIC ANTIDEPRESSANTS* (TCAs)

the oldest one

أمي نورا من زمن أول الطيبين



أمي نورا تجرب تحط آيلاينر
Ami try to put eyeliner

- Imipramine
- Desipramine
- Clomipramine
- Amitriptyline
- Nortriptyline
- Doxepin
- Trimipramine

أمي يا بر الأمان، دسي السر بالبئر

Transformation BY Demethylation From active form to other active form

TETRACYCLIC ANTIDEPRESSANTS

- Maprotiline
- Amoxapine

*TCAs have characteristic three-ring nucleus

Note: depression also comes in mild forms that do not require treatment with antidepressants. Treatment is only required to suffer from severe forms of depression mentioned above.

Mechanism of action of tricyclic antidepressants

(9 &10) Drugs used in Depression old & new

Lecture(9)
slide(7)

Old Anti-depressant

Drug	Tricyclics (TCAs) Cont.
Drug interaction	➢ **TCA** are strongly bound to plasma protein, therefore their effect can be potentiated by drugs that compete for their plasma protein binding site (**Aspirin and Phenylbutazone**). increase their effect. ➢ **TCAs** are metabolized by **liver microsomal enzymes**, therefore their effect can be reduced by inducers of liver microsomal enzymes (**Barbiturates**) ↓ of TCA, or potentiated by inhibitors of liver microsomal enzymes (**Oral contraceptives, Antipsychotics,** and **SSRIs**) increased effect of TCA . ➢ **TCAs** (inhibitors of monoamine reuptake) should not be given with **MAOIs** (monoamine oxidase inhibitors, which are inhibitors of monoamine degradation) →cause **hypertensive crisis.** Because the both increase NE -> lead to hypertension ➢ **Additive to anti-psychotics and anti-parkinsonism** (which have anticholinergic effect) → increase anti-cholinergic effects.
C.I مره مهم	➢ TCAs should not be used in patients with **Glaucoma or with enlarged prostate** because of their atropine-like action. Because of anticholinergic effects ➢ TCAs (given **alone**) are contraindicated in **manic-depressive illness** (Bipolar disease), because they tend to "switch" the depressed patient to the "manic" phase, therefore, they should be combined with "**lithium salts**". Give 2 together ➢ **Seizure disorders** →because they decrease its threshold. ➢ **Cardiovascular** (IHD "ischemic heart disease" and arrhythmias)

باربي كعادتها متحمسة

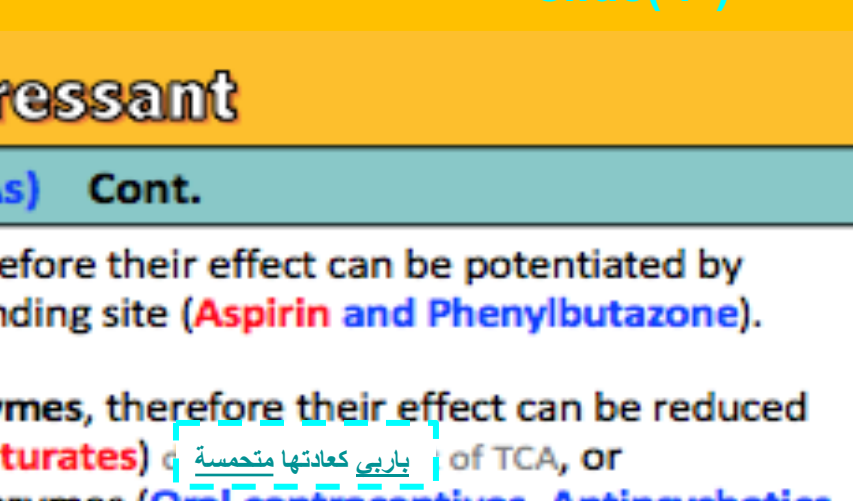
Monoamine oxidase

MAO is a mitochondrial enzyme found in nearly all tissues, and they exist in **two forms:**

MAO-A: responsible for **NE, 5-HT** catabolism. It also metabolizes **tyramine** of ingested food.

MAO-B: is more selective for dopamine metabolism .

They play role in Parkinson's disease.



Monoamine oxidase inhibitors (MAOIs)

فين الزين؟ طول الغيبة راح ولا رجع

- Monoamine oxidase inhibitors (MAOIs)
  - non-selective (MAO-A & MAO-B)
    - phenelzine (irreversible, long acting))
    - tranylcypromine (reversible)
  - selective
    - moclobemide (MAO-A) → (antidepressant action, Short acting)
    - selegiline (MAO-B) → (used in the treatment of Parkinsonism)

→ The effect of irreversible MAOIs persists for a period of **2-3 weeks** after stopping treatment, time needed by the body to synthesize new enzyme.

The best drug in it is group for depression, because it is selective & reversible

تكفى قول مو كلو معنا بالميد، عندي أمل أجيب اي، وإلا بيجيني اكتئاب

رايح للبارك Parkinsonism أكيد موب MAO-B جايب سيليق Selegiline معك يا دب Dopamine !

(9 &10) Drugs used in Depression old & new

Lecture(9)
slide(8)

Monoamine oxidase inhibitors (MAOIs)

Drug	Phenelzine	Tranylcypromine	Moclobemide	Selegiline
Type	Non- selective mostly in labs not for patients		Selective and Reversible. * better !	
	Irreversible (phenelzine) long acting (2-3 weeks) Non-selective = act on MAO A & B		Act on MAO-A - Anti depressant action. - Short acting	Act on MAO-B - Used in the treatment of Parkinsonism. *better !
Clinical uses	Only used for refractory cases and in atypical depression where phobia and anxiety are prominent symptoms., and have a limited uses because: ➢ ADRs ➢ food and drug interactions ➢ low antidepressant efficacy } =Low benefit/risk ratio.			
ADRs	Anti-muscarinic effects , Postural hypotension, Sedation, sleep disturbance, Weight gain			
	Specific ADRs for (Phenelzine) ➢ Sexual dysfunction ➢ Hepatotoxicity		the side effects is stronger than TCAs.	
Drugs interaction	1- Pethidine pain killer: MAOIs interact with the opioid receptor agonist (pethidine) which may cause severe hyperpyrexia, restlessness, coma, hypotension. The mechanism still unclear – but it is likely that an abnormal pethidine metabolite is produced because of inhibition of normal demethylation pathway. 2- Levodopa for parkinsonism: Precursor of dopamine can interact with MAOIs leading to hypertensive crisis. 3- Amphetamine and Ephedrine with allergic conditions: Indirectly acting sympathomimetic can interact with MAOIs causing the liberation of accumulated monoamines (NE) in neuronal terminals leading to hypertensive crisis 4- TCAs: (inhibitors of monoamine reuptake) can interact with MAOIs (inhibitors of monoamine degradation) leading to accumulation of monoamines (NE) which will cause hypertensive crisis. 5- MAOIs & SSRIs: Serotonin syndrome. (give 1-2 weeks gap before initiating SSRIs)			

Type	Drug	Sedation	Anti- cholinergic	Hypotension
Non-selective irreversible	Isocarboxazid	+	++	+
	Phenelzine	+	++	+
	Tranylcypromine	-	+	+
Selective reversible	Moclobemide	-	-	-

- Very important : Moclobemide is selective + reversible
- With less side effects

Cheese Reaction

Cheese reaction طاير مني MOAI مو Tyramine، لاحقين على الأكل

This occurs when Tyramine rich foods (Old cheese, Concentrated yeast products, Pickled or smoked fish, Red beans, Red Wine, Chicken liver, Sausages) are taken with MAOIs.

- Tyramine in food is normally degraded in the in the gut by MAO-A.
- Since the **enzyme is inhibited by MAOIs**, tyramine from ingested food is absorbed, and then taken up into adrenergic neurons where it is converted into **octopamine** - a **false transmitter** which causes **massive release of** (NE) and may result in **hypertensive crisis,** severe hypertension, severe headache and fatal intracranial hemorrhage.

➢ **Important Note: Moclobemide has No cheese reaction occurs with its use** → It can be displaced from MAO-A by tyramine, and this mitigates the risk of food interactions . And this is a unique thing for it !

(9 &10) Drugs used in Depression old & new

Lecture(10)
slide(11)

Side effects of SSRIs

Only in boys' sllides

Drug	Cardiotoxicity	Nausea	Anti-cholinergic	Sedation
Citalopram	?	++	–	–
Fluoxetine	–	++	–	–
Fluvoxamine	–	+++	–	+
Paroxetine	–	++	+	+
Sertraline	–	++	–	–

Remember Have mentioned in previous slide

Fluoxetine differs from others members of this class in:

1- It has a **longer** $t_{1/2}$ **(50hrs)**.
2- Available as **sustained release preparations** once weekly.
3- Its metabolite **norfluoxetine** = **potent** as parent drug $t_{1/2}$ =**10** days.

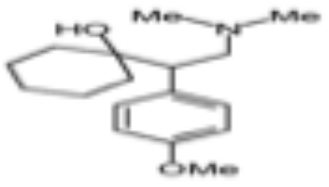
2. Noradrenergic and specific Serotonergic Antidepressant (NaSSA)

Noradrenergic and specific Serotonergic Antidepressant (NaSSA)	
Drug	**Mirtazapine** * very important
Action/Mech. of action	سيروا على مرت عزيز الثانية ▪ α2 receptor antagonist it increase sympathetic outflow because it do negative feedback Increase NE and 5HT levels ▪ Blocks 5HT2A, 5HT3 and thus reduces side effects of anxiety, and sexual dysfunction ▪ Blocking 5HT2C, and H1 receptors.
Indications	**Preferred in cancer patients because: it's so important to know these points and compare it with other drugs.** المرض عذابين صدق خاصة السرطان 1. Improves appetite 2- ↓ nausea & vomiting (5-HT_3 blocking) 3- ↑ **body weight** (appetite stimulant) 4- **Sedation** (potent antihistaminic) 5- **Less sexual dysfunction (5-HT_2 blocking)** 6- Has no anti-muscarinic effect 7- anti-depressant effect **Because of these reasons we use it for cancer patients**
ADRs	▪ Sedation (H1 blocking effect) ▪ weight gain (5-HT2C blocking effect)
Notes	Mirtazapine acts as an antagonist at central pre-synaptic alpha(2)-receptors, inhibiting negative feedback to the presynaptic nerve and causing an increase in NE release. Blockade of heteroreceptors, alpha(2)-receptors contained in serotenergic neurons, enhances the release of 5-HT, increasing the interactions between 5-HT and 5-HT1 receptors and contributing to the anxiolytic effects of mirtazapine. Mirtazapine also acts as a weak antagonist at 5-HT1 receptors and as a potent antagonist at 5-HT2 (particularly subtypes 2A and 2C) and 5-HT3 receptors. Blockade of these receptors may explain the lower incidence of adverse effects such as anxiety, insomnia, and nausea. Mirtazapine also exhibits significant antagonism at H1-receptors, resulting in sedation. Mirtazapine has no effects on the reuptake of either NE or 5-HT and has only minimal activity at dopaminergic and muscarinic receptors

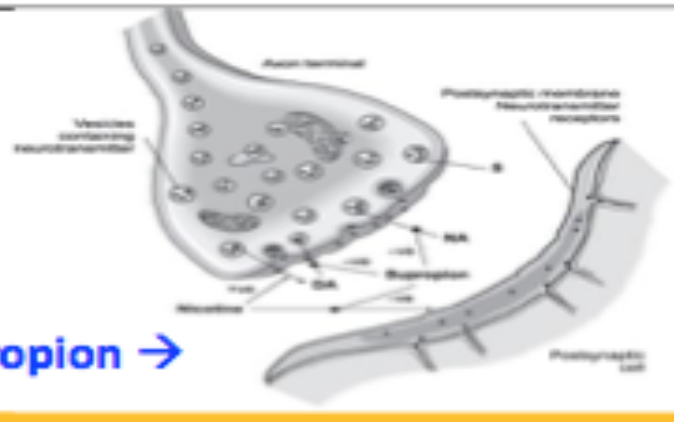
(9 &10) Drugs used in Depression old & new

Lecture(10) slide(13)

Antidepressants drugs (new group) cont

Drug	Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)	Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)
	Venlafaxine (effexor)	**Bupropion *very important**
Action/Mech. of action	Selective 5HT and NE uptake blockers combines the action of SSRI and NRI. But without α1, M1 cholinergic or H receptor blocking properties.	Stop(Bup) smoking Is unique in possessing significant potency as NE and dopamine reuptake inhibitor, with no direct action on 5HT.
uses	It is used primarily for the treatment of depression, generalized anxiety disorder, and social anxiety disorder in adults. Venlafaxine is first and most commonly used SNRI. (more tolerable)	• Treatment of **major depression and bipolar depression** • Can be used for smoking cessation Pop(Bup) corn with Cheese(smoking cessation) the severity of nicotine craving & withdrawal symptoms
ADRs	-	Seizures; it decrease threshold of neuronal firing (increases the stimulating NT, Similar toTCAs)
Notes	Desvenlafaxine is a metabolite of Venlafaxine (Similar to TCAs, but they have better tolerability.) Venlafaxine → 	Advantages: • No sexual dysfunction (because no 5-HT blocking effect) → given in young (combination with SSRIs to avoid sexual dysfunction) • No weight gait [No 5HT effect] • No orthostatic hypotension.

Bupropion selectively inhibits the neuronal reuptake of dopamine, norepinephrine, and serotonin; actions on dopaminergic systems are more significant than imipramine or amitriptyline whereas the blockade of norepinephrine and serotonin reuptake at the neuronal membrane is weaker for bupropion than for tricyclic antidepressants. The increase in norepinephrine may attenuate nicotine withdrawal symptoms and the increase in dopamine at neuronal sites may reduce nicotine cravings and the urge to smoke. Bupropion exhibits moderate anticholinergic effects

Bupropion → 

Side effects of atypical antidepressants

Drug	Toxicity	Sedation	Hypotension	Anticholinergic effects
Mirtazepine	-	++	_	+
Nefazodone	-	+	+	-
Trazodone	+	+++	+++	-
Venlafaxine	+	++	+	+

(9 &10) Drugs used in Depression old & new

Lecture(10)
slide(14)

Clinical Uses of Antidepressants

Be smart focus on red!

- Endogenous Depression : SSRIs (first Choice), New generation and Tricyclics can be used
- Panic Disorders (Imipramine or SSRIs)
- Obsessive Compulsive Disorders (SSRIs or Clomipramine) and Chronic pain (Amitriptyline)
- فلوسي تعرف كيف تفتح شهيتي للأكل وكيف تقفلها
  Anorexia nervosa and Bulemia (SSRIs) → Fluoxetine
- Schizo-Affective Disorders (Amoxapine or SSRI + Haloperidol) name of these 2 drugs are important
- هذا سري SSRIما ينقال لأي أحد
  Premature ejaculation (SSRI)
- Anxiety disorders (Amitriptyline)
- Migraine and Anxiety & IBS irritable bowl syndrome (Amitriptyline)
- نتخيل طفل صغير يقول :أمي يا بر الأمان، ترى سويتها على نفسي وأنا نايم
  Nocturnal Enuresis in children e.g. Imipramine (strong anti-cholinergic effect) name of this drug is important
- Neuropathic Pain (Dual NE and 5-HT reuptake Blocker)

436

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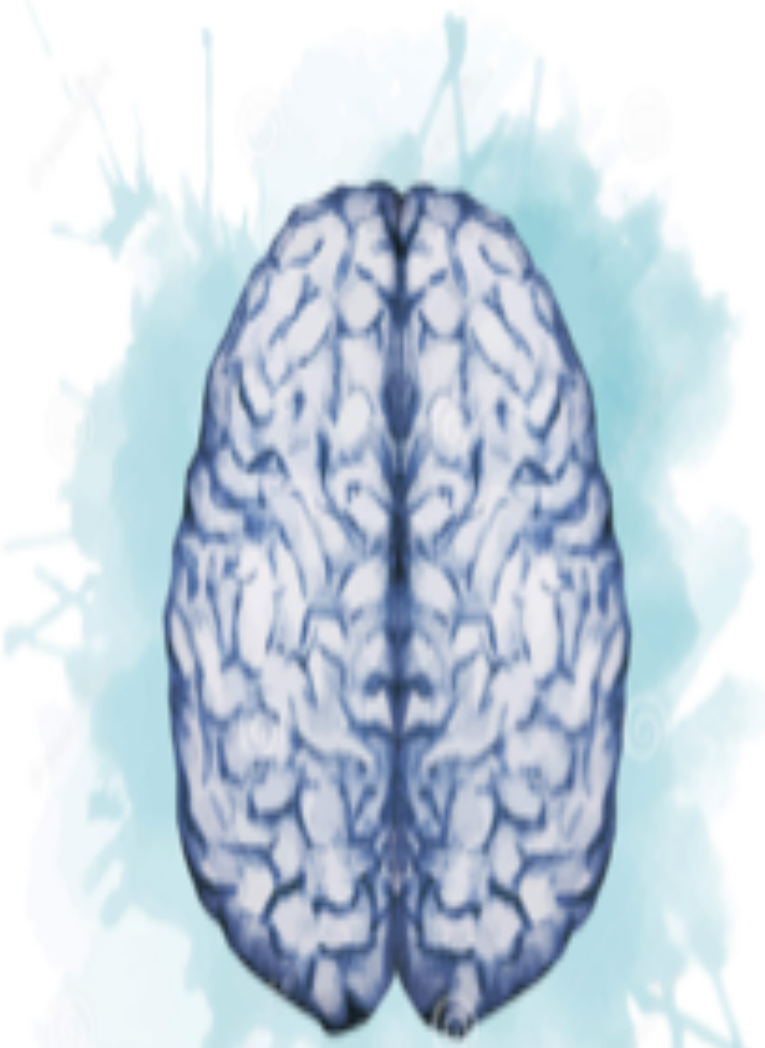

Drugs Used In Meningitis

(11) Drugs used in meningitis

Lecture(11) slide(4)

Penicillins

Aminopenicillins = Minus(-) & Positive(+)

Spectrum	**Narrow Spectrum**	**Extended or wide (active against gram +ve and –ve)**
Drug	Penicillins (G) = Positive(+) & موجب **Penicillin G (benzyl penicillin)** natural penicillin	**Aminopenicillins** synthetic penicillin **Amoxicillin** | **Ampicillin**
MOA	Inhibit bacterial cell wall synthesis by inhibiting the peptidoglycan layer of bacterial cell wall (bactericidal)	
Pharmacokinetics	• Poor oral absorption • destroyed by gastric acidity. • Given IV never orally because it can't cope with gastric acidity • Short acting (4-6 hrs.) → the half-life of penicillin G can be increased to 10 hours in the presence of renal dysfunction. Probenecid inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels • β- lactamase sensitive(penicillinase sensitive)= they are susceptible to hydrolysis by β-lactamases • Half- life 30-60 min.	• Broad spectrum of activity than penicillin G • They are acid stable (effective orally) • Can also be given parenterally (I.V or I.M) • Amoxicillin is better absorbed from the gut and not affected by food. • Ampicillin is better to take it on empty stomach because of food drug interaction • *Not active against pseudomonas aeruginosa* → because Pseudomonas aeruginosa has restrictive porins (proteins inserted in the lipopolysaccharide layer), making this organism intrinsically resistant to many antimicrobial agents
β-lactamase	-	• Inactivated by β-lactamase enzyme. (now a days combination with B-lactamase inhibitors are available e.g. 1- Amoxicillin + Clavulanic acid = Augmentin (given orally). 2- Ampicillin + salbactum = Unasyn. (Injection). • This combination is intended to: 1. Prevent enzymatic hydrolysis by β-lactamase. 2. Extend antimicrobial activity.
ADRs	• **Hypersensitivity** (anaphylactic reaction) → make sure that patient doesn't have allergy from the beta-lavtam antibiotics before giving him the treatment. Mild→ such as skin rash ,release of histamine and hypotension or sever →anaphylactic reaction • **Antibiotic-associated diarrhea** (only if taken orally) → the normal flora dies → Super infection mainly by clostridium difficile in colon. • **Nephritis** (with high doses). → beta lactam antibiotics (such as penicillin's) excreted mainly by kidney. • **Super-infections or secondary infections** (candidiasis, oral thrush). oral thrush happen especially in children after long term broad spectrum antibiotic course(normal flora died) and it is a fungal infection • **High dose in renal failure (seizure).** → high toxicity caused by renal failure → may cause seizure.	
Extra	• Ampicillin (with or without the addition of gentamicin) is the drug of choice for the gram-positive bacillus Listeria monocytogenes.	

B with P

(11) Drugs used in meningitis

Lecture(11)
slide(5)

Drugs	Cephalosporins (3rd generation)	Carbapenems
	Ceftazidime + Ceftriaxone	Imipenem (امي بنام)
MOA	Inhibits bacterial cell wall synthesis (Bactericidal)	
Pharmacokinetics	Both of them are given by intravenous infusion.	• Not absorbed orally (because it is NOT lipophylic instead it is hydrophilic BUT can cross BBB) given by I.V. • Penetrates body tissues and fluids including CSF. • Excreted primarily by the kidney. • *Doses must be reduced in renal failure.* • Short Half- life about 1 hr. • Inactivated by dehydropeptidase in renal tubules to a nephrotoxic metabolites, so it is given with a dehydropeptidase inhibitor *Cilastatin* for clinical use it given by combination of *(Imipenem/cilastatin).* Imipenem + Cilastatin = Last pen • Meropenem is one of carbapenems but doesn't cause renal toxicity s
Bacterial spectrum	عندنا انطباع سلبي (Negative)عن كلمة زفت (Ceft) • Highly effective against Gm –ve bacilli. • Anaerobic microbes Ceftazidime= عن اللي قبلي (أزيد) كأنه يقول أنا • Ceftazidime → against pseudomonas aeruginosa. • Highly resistant to β- lactamases→ Ceftriaxone and cefotaxime are approved for treatment of meningitis. • Used for treatment of bacterial meningitis caused by(gram –ve organisms) *pneumococci*, *meningococci*, and *Haemophilus influenzae*.	Bape Car نقرا اسم المجموعة بالمعكوس has everything inside it • Has a wide spectrum of activity (aerobic & anaerobic gram negative and gram positive bacteria, including pseudomonads). • *Resistant to most β-lactamases.* Bape Car has everything نقرا اسم المجموعة بالمعكوس inside it (Pseudomonas) يرد أحد عليه ويقول له كذاب
ADRs	• Allergy if the patient is allergic to penicillin he will be allergic to Cephalosporins. • Thrombophlebitis at site of injection. • Renal toxicity. • Super-infection. • GIT Upset & diarrhea. (not characteristic)	• Nausea, vomiting, diarrhea. • Skin rash and reaction at the site of infusion. • High doses may cause seizure in patients with renal failure. • Patients allergic to Penicillins may be allergic to Carbapenems.

(11) Drugs used in meningitis

Lecture(11)
slide(6)

Drug	Other inhibitor of cell wall synthesis	AMINOGLYCOSIDES
	Vancomycin	**Gentamicin**
MOA	Inhibits bacterial cell wall synthesis **(Bactericidal)** it is **not beta lactam**	**Inhibit protein synthesis (30s subunit) (Bactericidal)**
Pharmacokinetics	• **Poorly** absorbed **orally.** • Used **orally only** to treat **GIT infections** caused by **clostridium difficile** e.g. **pseudomembranous colitis** because it will stay in GIT and wont move anywhere else and **excreted in feces.** • Given **intravenously** for the treatment of **meningitis.**	• **Not absorbed orally** • **Given by injection I.V** **Remember:** all antibiotics affects the protein synthesis are considered as bacteriostatic EXCEPT **aminoglycosides** are **bactericidal.**
Indications	• Used against Methicillin resistant S. aureus **(MRSA).** • Used when the patient is allergic or resistant to penicillin's. because it is against the same type of bacteria which is gram +ve	
ADRs	• **Ototoxicity** rare, but the administration with another ototoxic or nephrotoxic dru… aminoglycoside, increases t… • **Nephrotoxicity** • **Phlebitis** (inflammation of a vein) at site of injection. • **Histamine** release Causes **Red man (red neck) syndrome** →not IgA mediated reaction. →you might administered anti-histamine to prevent histamine effects such as diphenhydramine. • **Hypotension** (minimized if injected slowly over 60 minutes) usually infusion of the drug takes 20 min. and this is the cause of hypotension.	• **Ototoxicity** • **Nephrotoxicity (direct related to serum concentration).** • **Neuromuscular blockade *(in very high dose).*** **Contraindicated in patient with myasthenia gravis.**
Spectrum	• **Active only against Gram +ve bacteria** • (narrow spectrum) • With the exception of Flavobacterium.	• Antibacterial spectrum. • Bacterial exclusive for aerobic G-bacteria.
Combinations	• Used in combination with **3rd generation Cephalosporins** for treatment of meningitis caused by **penicillin resistant pneumococci.**	
	• May be combined with **Ampicillin or Ceftazidime** as an **initial therapy (empiric therapy)** of meningitis in infant, elderly and immunocompromised patients. • **Ceftazidime is better than Ciftriaxone in child.**	
Note	• **S. pneumoniae is the main cause of community acquired pneumonia and meningitis in children and the elderly and immunocompromised patients**	

ركبنا باص (Vancomycin) كان سائقه معصب ووجه أحمر (Red man)

Aminoglycosides = Minus(-)

436

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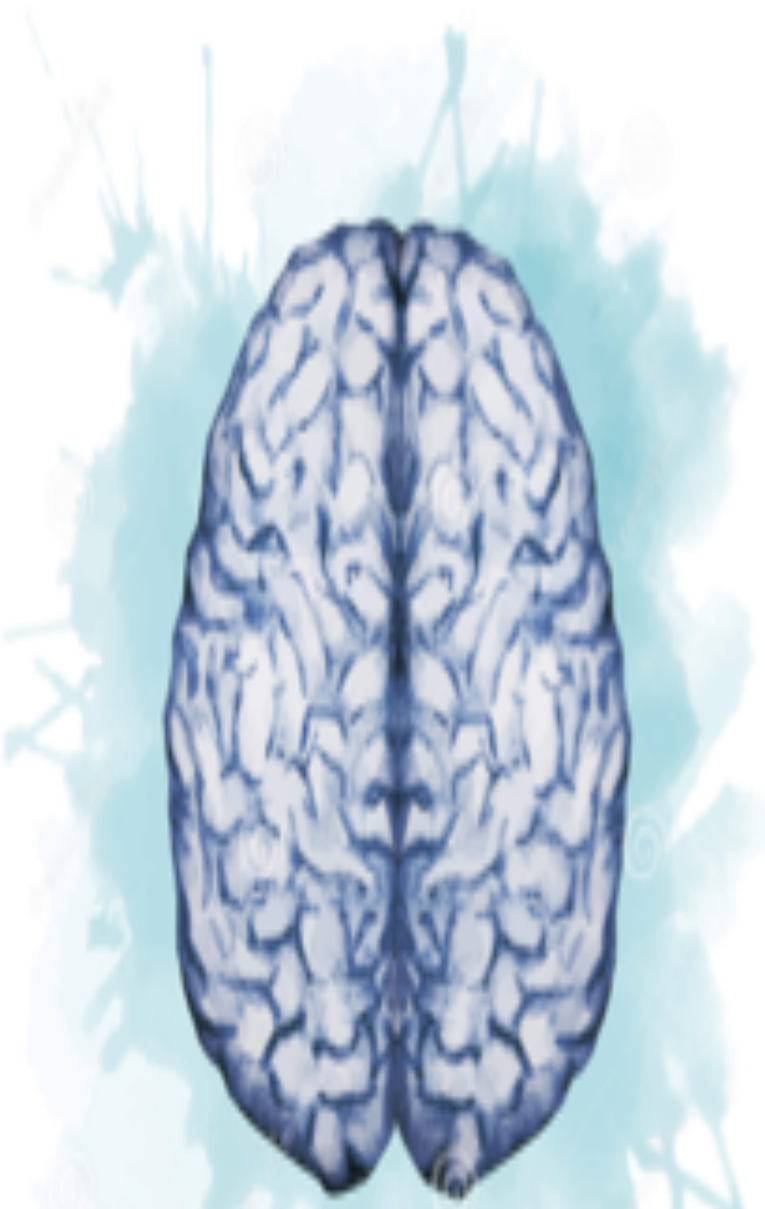

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Drugs used in epilepsy 1&2

(12&13) Drugs used in epilepsy

Lecture(12&13)
slide(4)

considered Withdrawal

- Seizure–free period of 2-5 years or longer.
- Normal IQ.
- Normal EEG (Electroencephalography (EEG) is an electrophysiological monitoring method to record electrical activity of the brain) prior to withdrawal.
- No juvenile myoclonic epilepsy. Sever type begin in young age

❖ **Relapse rate when antiepileptic's are withdrawn is 20-40%.** *(20% in young patients and 40% in elderly)*

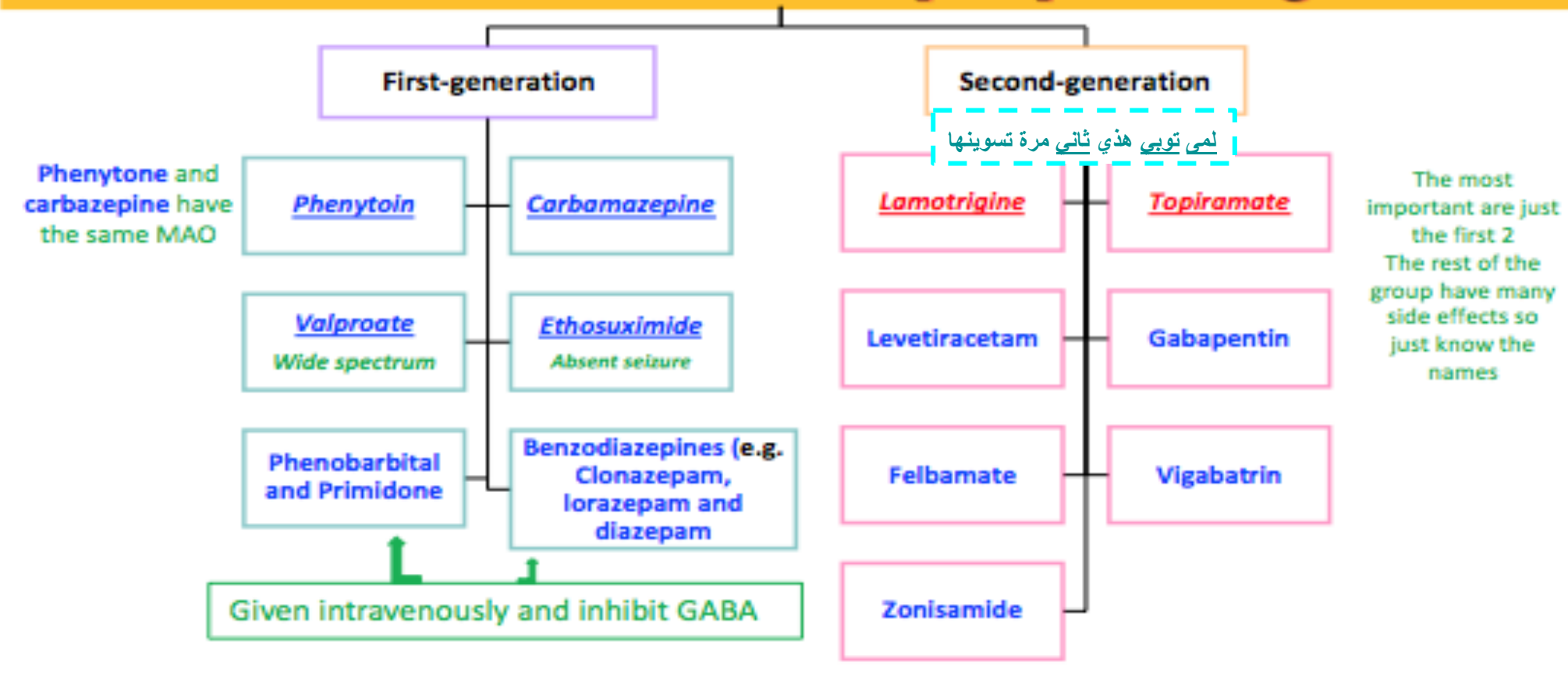
Mechanism of Anti-Epileptic Drugs:

Antiepileptic drugs inhibit depolarization of neurons by following mechanisms:

- Inhibition of excitatory neurotransmission (Glutamate).
- Enhancement of inhibitory neurotransmission (GABA). Main inhibitory neurotransmitter in the brain
- Blockage of voltage-gated positive current (Na^+) (Ca^{2+}).
- Increase outward positive current (K^+).

***mechanism of action and side effects are very important in this lecture**

Classification of antiepileptic drugs

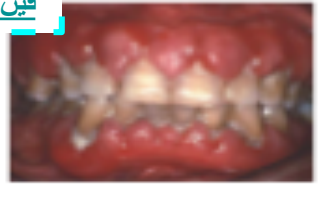


Difference between 1st and 2nd generation: the 1st generation do have effect on microsomal enzymes and most of the 2nd generation drugs don't have this effect.

(12&13) Drugs used in epilepsy

Lecture(12&13)
slide(5)

Anti-Epileptic Drugs 1st Generation

Drug	Phenytoin (the oldest one)	Fosphenytoin (Parenteral form of phenytoin)	Carbamazepine
Mech. of action	*important • Blockade of Na^+ & Ca^{2+} influx into neuronal axon. • Inhibit the release of excitatory transmitters. • Potentiate the action of GABA.		
Pharmacokinetics	• Given orally, well absorbed from GIT. • Also available as capsules, IV and IM →called (fosphenytoin) • Enzyme inducer. (increase its metabolism → the duration of action decreases)drug-drug interaction • Metabolized by the liver to inactive metabolites. • Half life approximately 20 hr. • Excreted in urine.	• Parenteral form of phenytoin. • Prodrug. • Rapidly converted into Phenytoin in the body. ❖ Advantages over Phenytoin: • More Rapid IV administration. (Suitable in ER use) • May be IM administered. • Lower local tissue and cardiac toxicity. • Less pain and phlebitis (inflammation of the vein) at injection site.	• Available as capsule or syrup orally only. can not be used in Status epilepticus *very important • Well absorbed. • Strong enzyme inducer. (including its own metabolism). Needs Plasma level monitoring • Metabolized by the liver to active & inactive metabolites. o T1\2=18-35 hr. • Excreted in urine.
Indications	أفكر أروح الحفلة بالسيارةParty= partial seizures Carbamazepine • Partial and generalized tonic-clonic seizures. • Not in absence seizure. • In status epilepticus as *IV SLOW infusion of Phenytoin* to prevent cardiac side effects but we can use *Fosphenytoin as RAPID IV infusion*.		Drug of choice in partial seizures. *very important • Tonic-clonic seizures (1ry & 2ry generalized)grand mal • Not in absence seizures. →because it may cause an increase in seizures. ❖ Other uses: ○ Bipolar depression. ○ Trigeminal neuralgia
ADRs	• Nausea or vomiting. • Neurological like headache, vertigo, ataxia, diplopia and nystagmus. • Sedation. • Gum (gingival) hyperplasia. (very important side effect) • Hirsutism. (abnormal hair growth) • Acne. • Folic acid deficiency (megaloblastic anemia=large red blood cells). • Vitamin D deficiency →(osteomalcia). • Teratogenic effects. (very common side effect and prohibited during pregnancy)	فين Phenytoin أسنانك ما أشوفها، لثتك مغطية عليها ! 	• GIT upset. • Hypersensitivity reactions. • Drowziness , ataxia, headache & diplopia. • Hyponatremia and water intoxication *very important (anti-diuretic Na= No for Carb لا نقول الكرب not patients) • Teratogenicity. (prohibited during pregnancy)

(12&13) Drugs used in epilepsy

Lecture(12&13)
slide(6)

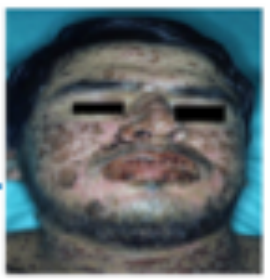
Anti-Epileptic Drugs 1st Generation

Drug	Sodium Valproate (صوديوم بالبارود)	Ethosuximide
Mech. of action	• Blocks activated Na^+ channels. • Enhances GABA synthesis & reduces degradation. • Suppress glutamate action. • Blocks T-type Ca^{2+} channels. (that's why it can be used for absence seizures)	Selectively Inhibits T- type Ca2+ channels in thalamo-cortical neurons. which of the following used for absence seizure ? *very important The best is Ethosuximide because it is selective Then sodium Valproate (choose this if the first one is not in the choices)
P.K	• Broad spectrum antiepileptic. • Available as capsules, Syrup and I.V. can be used in status epilepticus • Metabolized by the liver into inactive form. • Enzyme inhibitor. • T1\2= 12-16 hr. • Excreted in urine.	• Absorption is complete. • Syrup & capsule forms (to be easily taken for children) • Not bound to plasma proteins or tissues. • Metabolized in liver. • *T1\2 = 52-56 hr.* • 10-20% of a dose is excreted *unchanged* the urine.
Indications	It is effective for all forms of epilepsy: → wide broad spectrum • Generalized Tonic-Clonic seizures (1ry or 2ry). • Absence seizures. • Complex partial seizures • Myoclonic • Atonic • Photosensitive epilepsy. **Other uses** • Bipolar disorder and mania. (as a mood stabilizer) • Prophylaxis of migraine. • Lennox-Gastaut syndrome. The Lennox-Gastaut syndrome (LGS) is a type of epilepsy with multiple different types of seizures& affect children, particularly tonic (stiffening) and atonic (drop) seizures. Intellectual development is usually, but not always, impaired. (not very important but you should read it)	Absence seizures. (mainly given to children)
ADRs	• GIT (nausea, vomiting, heart burn) • Weight gain (↑appetite). • Transient hair loss, with re-growth of curly hair. • Thrombocytopenia (not used with aspirin or Coumadin) • Transient increase in liver enzymes &Hepatotoxicity (we do periodic assessment) • Teratogenicity (neural tube defect) • *very important • (prohibited during pregnancy) It happen in the brain or spinal cord Like spina bifida OR anencephaly  مرره صدم زوجي Sodium لما عرف ان طفلنا عنده تشوه خلقي Nural tube defect	➢ Gastric distress: • Nausea. • Vomiting. ➢ Drowsiness, fatigue, hiccups, headaches. It is not teratogenic because of that it is given to children

(12&13) Drugs used in epilepsy

Lecture(12&13)
slide(5)

Anti-Epileptic Drugs 2ed Generation

Drug	Topiramate دوبني رميت	Lamotrigine لمى حاولي تجين
Action/Mech. of action	*very important • Blocks **sodium channels** (membrane stabilization). • potentiates the inhibitory effect of GABA.	*very important • Blockade of **Na+** channels. • Inhibits excitatory amino acid release (glutamate & aspartate).
P.K	• Well absorbed orally (80 %). • Food has no effect on absorption. • **Has no effect on microsomal enzymes** (most important difference from the first generation) • **9-17 % protein bound** (minimal). • Mostly excreted unchanged in urine. • Plasma t½ 18-24 hr.	• Available as oral tablets. • Well absorbed from GIT. • Metabolized primarily by **glucuronidation.** • **Does not induce or inhibit CP-450 isozymes** (most important difference from the first generation and that's why it has no Drug-Drugs interactions). • T1\2= approximately 24 hr.
Indications	• Can be used alone for **partial, generalized Tonic-Clonic, and absence seizures.** don't confuse stick to Ethosuximide (specific) and sodium Valproate (wide spectrum) for absence seizure • Lennox-Gastaut syndrome (or **lamotrigine**, or **valproate**).	• As **add-on** therapy or as **monotherapy** in **partial seizures**. **And generalized tonic-clonic seizure** • **Lennox-Gastaut syndrome.** • **Bipolar depression**
ADRs	دوبني رميته Topi-ramate ايش فيني نسيت بسرعة !! • Psychological or cognitive dysfunction. • **Weight loss** (can be desirable side effect). • Sedation. • Dizziness. • Fatigue. • Urolithiasis. • Paresthesias (abnormal sensation). • Teratogenecity (in animal but not in human).	• **Influenza-like symptoms.** • **Skin rashes** (may progress to **Steven-Johnson syndrome**). لمى عندها Skin rashes ومعجبة مرره بستيف جوبز S… , serious … membranes. It's usually a reaction to a medication or an infection. Often, it begins with flu-like symptoms, followed by a **painful** red or purplish rash that spreads and blisters • Somnolence (**drowsiness**). • Blurred vision. • Diplopia. • Ataxia (**can be teratogenic**). 

436

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Drugs used in headache and migraine

(14) Drugs used in headache and migraine

Lecture(14)
slide(5)

Treatment strategy

Prevent recurrence Prophylactic	Acute attack (Controls attack)	
	ABORTIVE therapy (severe-disabling) Treat the cause	**RESCUE therapy** (mild to moderate) Treat **Symptoms**
↓ Recurrence frequency, severity, duration & / or disability. ↑Responsive to abortive therapy (drugs stops migraine)	- They specifically target pathways of migraine by ↓ meningeal dilatation & ↓ neural activation via 5HT1 agonism (serotonin constrict blood vessels) i.e. Stopping headache as it is evolving. - Abortive medications effective if taken early, just before the pain starts (before vasodilatation), losing effectiveness once the attack has begin (may prevent further attacks only) So they must be rapidly acting	Non-specifically target individual symptoms. i.e. Alleviating Pain, emesis and associated symptoms

N.B. Full effect of therapy needs several weeks to manifest & should continue for 6 months & can be repeated

ACUTE ATTACK (RESCUE THERAPY)

Drug

Mech. of action

Analgesics

NSAIDs:

- **Acetaminophen (=paracetamol)** it is stronger than the others.
  - **If we combine acetaminophen with:**
    1. **Caffeine (Panadol extra) this will cause wakefulness.**
    2. **1st generation Anti-Histamine this will cause sedation and it's good in migraine.**
- **Aspirin** (weaker).

أبو إبراهيم تعب واخذ غفوة

Ibuprofen, Naproxen → Drug of choice **for mild to moderate attack with no nausea & vomiting.**

Opioid like drugs : μ agonist e.g.: tramadol Central Strong analgesic used in **severe attack** of migraine and is causes tolerance.

Anti-emetics (prevent nausea and vomiting)

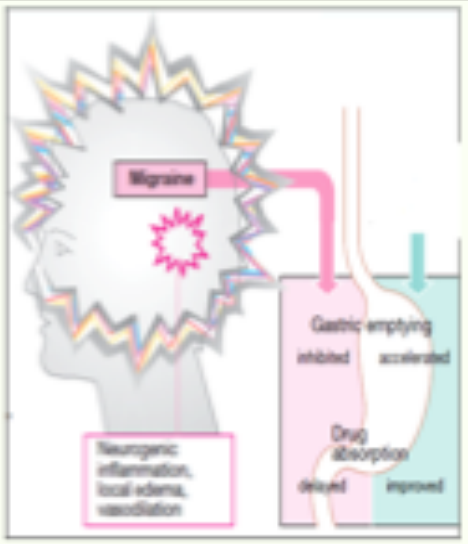
1. **Dopamine Antagonists**

Dom-done دوم دن دوم دن
كأنه صوت شيء يتحرك
Gastro-prokinetic

A- **Domperidone**

- Drug of choice to avoid sedation and sleeping (not *sedative*).
- **Gastro-prokinetic effect** (gastric empting) (increase gastric motility → Increase absorption of drug & → reduce vomiting) →

↑ **Absorption & bioavailability of abortive therapy.**



B- **Phenothiazines** (**Promethazine**): **it is dopamine antagonist &** Has a **sedative** effect.

فين ذا الزين ؟ شكله نايم

2. **5HT3 antagonists:**

Ondanseteron, Granisetron (the best drugs for vomiting): For severe **nausea** and **vomiting.**

آخر مقطع من اسم الدرق نقدر نقراه بالمصري ، الست الحديدة Set-iron يعني يستخدم للحالات الشديدة

3. **H1 antagonist:**

Meclizine, diphenhydramine: Has **anti-histaminic +sedative + Anti-cholinergic** effect. → **Safe for pregnancy.**

Messi is a good Defender

(14) Drugs used in headache and migraine

Lecture(14)
slide(8)

ACUTE ATTACK (ABORTIVE THERPY) cont.

2-Triptanes

- **Selective** Agonist at 5-HT1 (5-HT1D/1B) receptors→ better than ergots.
- Similar to ergotamine except that triptans are more selective as serotonergic agonist.
- No α1, α2, β –adrenergic, dopamine or muscarinic receptors.

Summer (Suma) is Hot (Nar) in Sudan (Zol)

Drug	Sumatriptan Super fast	Zolmitriptan	Naratriptan
	oral, nasal spray, and injectable	nasal spray, and injectable	Oral preparations
MOA	• Same as ergot's MAO • **Triptans** inhibit the release of **vasoactive peptides,** promote vasoconstriction, and **block pain pathways in the brainstem .** • **Triptans** inhibit transmission in the **trigeminal nucleus caudalis.**		
pharmacokinetics	- Oral Bioavailability→ low - **Subcutaneous → 97%,** peaks after 2 min & T1/2 nearly 2 hours (fast action with SC, **subcutaneous, good for patient with vomiting)**	- **Oral** bioavailability **40%,** peaks after 2 hrs & T1/2 nearly 3 hours.	-**Oral** bioavailability **70%,** peaks after 2 hrs & T1/2 nearly 6 hours **(slower onset, less side effects)**
Indications	• To **abort** attacks in patients with frequent, moderate or infrequent but severe attacks. • In **cluster headache** generalized headache including head and neck. • Sumatriptan → first-line therapy for acute severe migraine attacks.		
ADRs	• Most of ADRs are the same as with **ergot** but **triptans** are **better tolerated.** • Mild pain and burning sensation at the site of injection. • Vasospasm, **Ischemic heart; Angina** and Arrhythmias. • **Zolmitriptan causes** Chest & neck tightness, **Coronary vasospasm** and Somnolence. هذا زول كبير تعبان قلبه كتير		
Contraindications	• Peripheral vasospastic diseases. • Uncontrolled hypertension. • **Coronary artery disease.** • History of ischemia. • Cerebrovascular disorders. • In concurrent use with **ergots** or others inducing vasospasm. • In concurrent use with MAOIs, lithium, SSRIs, → (5HT increased to toxic level). • Renal or hepatic impairment. Because these drugs also increase serotonin and norepinephrine and it will cause sever vasoconstriction and arrhythmia or even death		

(14) Drugs used in headache and migraine

Lecture(14)
slide(8)

Deciding whether better with a triyptan or with DHE

Patients

- migraines a day or less → **Triptans** (they give rapid relief of pain)
- pregnant women → **Paracetamol** or **intranasal Sumitriptan** and or **Diphenhydramin**, **Meclizine** are **safe.**
- headache episodes lasting 2 or 3 days at a time → **DHE** is often the optimal choice because it has longer $t_{1/2}$

Factors when Choosing a Triptans:

remember : always start with analgesic and Never use Ergotamine tartarate.

Medication	T-max (h) Give rapped effect	T 1\2 (h) Reduce pain and prevent recurrence for longer time
DHE	2 1	10
Sumatriptan SQ	1 0.25	2
Rizatriptan	3 1-1.5	2-3
Zolmitriptan	2.5	3
Naratriptan	2-3	2 6
Eletriptan	2.8	3 4
Frovatriptan	2-3	1 26

- **Advantages of fast T-max: fast release of pain.**
- **Advantages of longer T1/2: less doses needed.**
- Differences in the time to peak blood concentration T_{max}, equates with faster relief of pain.
- Differences in t ½ → a clinical effect in terms of recurrence of headache.
- The form of drug preparation could influence the choice, Injectable **Sumatriptan** reaches T_{max} the fastest followed by **DHE** nasal spray and **Rizatriptan.**
- **For extremely fast relief within 15 min**. injectable **Sumatriptan** is the only choice.
- **If expected re-dosing is needed and/or recurrence of headache** → **Naratriptan, frovatriptan,** have slower onset, fewer side effects,
- and a lower recurrence rate.
- **Menstraul migraine**: **Frovatriptan (longer T 1\2 = 26hrs)**
- per day beginning two **days before the anticipated onset of menstrual migraine and continuing for six days.**

Forever = Frovatriptan

Female cycle = Frovatriptan