MED 443
King Saud University

PHARMACOLOGY
TEAM 443

List of the drugs

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Table of content

click on the lecture title

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L1: Drugs Acting on the Eye

How can drugs be delivered to ocular tissue?

Locally "Topically" (*more common*)					Systemically	
Eye Drops	Ointments	Injections			Orally	IV
		Periocular	Intraocular			
- **most common** - contact time is low.	- ↑ contact time (better effect). - the drug has to be high lipid soluble to have max effect.	- **Sub conjunctival, Retrobulbar, Peribulbar.** - for infection of ant segment and inflammation of uvea. - good for drugs with low lipid solubility (penicillin). - steroids and local anesthetics	**Intracameral:** acetylcholine or lidocaine during cataract surgery.	**Intravitreal:** antibiotics in cases of endophthalmitis, steroid in macular edema.	Factors that can control systemic drug penetration: 1. Lipid solubility: ↑ penetration with ↑ lipid solubility 2. Protein binding (PB): more effect with ↓ PB 3. Eye inflammation: ↑ penetration with	

Treatment of Glaucoma

Open-angle (Chronic)		Narrow-angle (Acute)	
↑ Outflow of aqueous humor	• **Prostaglandins** (1st line) • Non-selective adrenergic agonists • Parasympathomimetics	↓ IOP before iridectomy (*emergency*)	• Oral Acetazolamide • Pilocarpine (cholinomimetic) • Osmotic agents (mannitol&glycerol)
↓ Production of aqueous humor	• **β blockers** (2nd line) • **α2** agonists • CA inhibitors	Analgesics (for pain)	• Morphine • Pethidine

Drugs Causing Eye Deposits

Corneal							Iris
Digitalis	Phenothiazines	Sildenafil	Amiodarone	Chloroquine	Ethambutol	Steroids	Prostaglandins
1- Chromatopsia (objects appear yellow) 2- Ocular disturbances	**Brown** deposits in Cornea, eyelid, & conjunctiva	1- **Bluish** haze 2- Light sensitivity	Optic neuropathy Pigmented deposits of cornea		With gradual progressive vision loss	1- **Cataract** 2- ↑ IOP	Pigmentation of iris (*heterochromia iridis*)

Autonomic drugs: parasympathetics

Group		Agent	Uses		CI	ADRs	Action(s)
Cholinergic Antagonists	*Natural alkaloids*	**Scopolamine (Hyoscine)**	1- Fundoscopic examination of eye 2- To prevent adhesion in uveitis & iritis 3- Measure refractive error		Glaucoma	1- Cycloplegia 2- Loss of light reflex 3- Sandy eye	1- ↑ IOP 2- ↓ Lacrimation → sandy eye 3- Passive mydriasis 4- Cycloplegia 5- Loss of light reflex
		Atropine					
	Synthetic	**Tropicamide**					
		Cyclopentolate					
		Homatropine					
Cholinergic Agonists	*Direct*	**Methacholine**	Induction of miosis in surgery	1- Glaucoma (open& closed) 2- Counteract mydriatics 3- To break iris-lens adhesions	-	1- Myopia 2- Headache	1- ↓ IOP 2- ↑ Lacrimation 3- Miosis 4- Accommodation 5- ↑ Aqueous outflow 6- Conjunctival vasodilation
		Carbachol					
		Pilocarpine	-				
	Indirect Reversible	**Physostigmine**					
		Demecarium					
		Isoflurophate					
	Indirect Irreversible	**Echothiophate**	Accommodative esotropia				

L1: Drugs Acting on the Eye

Adrenergic	*Non-selective*	α & β Agonists	**Epinephrine**	**Open-angle glaucoma**	**Pts with closed angle (may precipitate closed-angle glaucoma)**	**1- ↑ BP 2- Arrhythmia 3- Headache**	**↑ Uveoscleral outflow of aqueous humor**
			Dipivefrin (pro-drug)				
		β blockers	**Timolol**	1- Can be used in pts with hypertension 2- open angle glaucoma	Asthma	Ocular irritation	↓ Aqueous humor production
			Carteolol				
	Selective	β_1	**Betaxolol**				
		α_1 Agonists	**Phenylephrine**	1- Funduscopic examination of eye 2- To prevent adhesion in uveitis & iritis 3- Decongestant in minor allergic hyperemia of eye	Pts with closed angle glaucoma	1- significant ↑ BP 2- Rebound congestion	Active mydriasis without cycloplegia
		α_2 Agonists	**Apraclonidine** *Sympatholytic*	1- Open-angle glaucoma 2- Prophylaxis against IOP spiking after glaucoma laser procedures	CVS patients	1- ↓ BP 2- Bradycardia 3- Headache	1- ↑ Uveoscleral outflow of aqueous humor 2- ↓ Aqueous humor production
Carbonic Anhydrase Inhibitors			**Acetazolamide**	open angle glaucoma		1- Myopia 2- Malaise 3- Anorexia & GI upset 4- Renal stone 5- Metabolic acidosis 6- Headache	**Block CA enzyme required for production of bicarbonate → ↓ aqueous humor production**
			Dorzolamide		1- Pregnancy 2- Sulfa allergy		
Prostaglandin Analogues			**Latanoprost**		replaced β-blocker	Preferred due to lesser ADRs	**Pigmentation of iris (*heterochromia iridis*)**	**↑ Uveoscleral outflow of aqueous humor**
			Travoprost				
Osmotic Agents			**Mannitol**	Given as IV infusion for acute cases to temporarily reduce ↑ IOP until definitive treatment is given	CI: Heart failure	1- Diuresis 2- circulatory overload 3- Pulmonary edema 4- Heart failure 5- CNS effects (seizures & cerebral hemorrhage)	**Rapidly** lower IOP by decreasing vitreous volume prior to anterior surgical procedures
			Glycerol		ADRs: 1- Hyperglycemia 2- Nausea		
Corticosteroids	*Topical*		**Hydrocortisone**	1- Anterior uveitis 2- Severe allergic conjunctivitis or scleritis 3- Prevention / suppression of corneal graft rejection		1- Glaucoma (↑ IOP) 2- Cataract 3- Skin atrophy 4- Secondary infection 5- Delayed wound healing	Inhibit phospholipase A2 → inhibition of arachidonic acid release from phospholipids
			Dexamethasone				
			Prednisolone				
	Systemic		**Cortisone**	1- Posterior uveitis 2- Optic neuritis			
NSAIDS			**Flurbiprofen**	Preoperatively to prevent miosis during cataract surgery		Stinging	Inhibit COX
			Diclofenac	1- Postoperative inflammation 2- Mild allergic conjunctivitis & uveitis			
			Ketorolac	Cystoid macular edema occurring after cataract surgery			

L2: Alcohol & the Brain

Pharmacokinetics

- Small lipophilic molecule
- crosses all biological membrane including placenta & CNS
- Has large Vd (distributed to all body tissues).
- Rapidly & completely absorbed from GIT
- Rate of elimination is zero-order kinetic

●Acute acetaldehyde toxicity
- Common in Asian populations (bc: genetic variation in AD)
- Characterized by: nausea,vomiting, dizziness, headache, vasodilatation, facial flushing hotness ,

Metabolism

1- Oxidation of ethanol to acetaldehyde via **alcohol dehydrogenase (AD) or CYP450 (CYP2E1).**
● **low ethanol conc:** mainly by Alcohol dehydrogenase and minor metabolism by MEOS CYP-450 (CYP2E1).
● **significant conc:** mainly by microsomal CYP-450 (CYP2E1). Upon continuous alcohol use this enzyme is stimulated and contribute significantly to alcohol metabolism & tolerance.
- Acetaldehyde is more toxic than alcohol.
2- Acetaldehyde is converted to acetate by **aldehyde dehydrogenase** which also reduces NAD+ to NADH.
3- Acetate ultimately is converted to CO_2 + water.

MOA of alcohol (Alcohol is a CNS depressant)

Acute alcohol:
●↑**effect of GABA** on its GABA receptors in brain leading to CNS depression.
●↓glutamate action on NMDA receptors leading to disruption in memory,consciousness, and alertness.

Chronic alcohol:
- Up-regulation Of NMDA receptors & voltage sensitive Ca2+ channels (Ca2+ influx to nerve cells) leading to alcohol tolerance & withdrawal symptoms (tremors, exaggerated response & seizures)
- Down-regulation of GABA receptors

Actions of Acute Alcohol

A) In mild-moderate amounts
***CNS depression:**
● Relieves anxiety, euphoria, Nystagmus, slurred speech, impaired judgment, ataxia, Sedation, hypnosis, loss of consciousness,

***CVS depression:**
● Myocardial contractility depression
●Vasodilatation due to :
-Vasomotor center depression
-Direct smooth muscle relaxation caused by acetaldehyde

B) In severe amounts
● CNS depression
● Respiratory depression & acidosis
● Nausea, vomiting,aspiration of vomitus
● CVS depression
● Volume Depletion ,Hypotension ,Hypothermia.
● Coma, death.

Actions of Chronic Alcohol

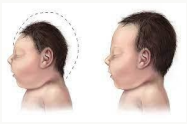
Tolerance ,Dependence Addiction,Behavioral Changes

●**Liver** :Hepatic cirrhosis -Liver Failure
●**CVS** : Hypertension -Myocardial infarction
●**CNS** :Cerebral atrophy -Cerebellar degeneration -Peripheral neuropathy -**Wernicke encephalopathy or Korsakoff psychosis may occur .**
Addiction to : **Dopamine** , serotonin and opioids

- Hematological disorders, neoplasia.
- **Endocrine**: Gynecomastia-Testicular atrophy "lack of testosterone"
- **GIT**: Irritation-Inflammation-Bleeding - Nutritional deficiencies → Anemia

Chronic alcoholism associated syndromes:

Fetal Alcohol Syndrome : Irreversible Prenatal exposure to alcohol causes congenital malformation
● **Microcephaly**
● Impaired facial development
● Physical and mental retardation
Congenital Defects



Wernicke-Korsakoff Syndrome: It's a combined manifestation of 2 disorders:
1. Wernicke's Encephalopathy
2. Korsakoff's psychosis
- Cause: Thiamine **(vit. B1) deficiency**
-**TREATMENT: Thiamine + dextrose-containing IV fluids**

Drugs Used in case of:

Management of Alcoholism Withdrawal:
●Benzodiazepines(**Diazepam**** more effective, lorazepam) is the best choice .
-Induces GABA , ↓**symptoms of withdrawal**
●Acamprosate ●Fluoxetine ●Clonidine and Propranolol

Prevent alcohol relapse:
●**Disulfiram****: inhibits hepatic aldehyde dehydrogenase →↑ blood level of acetaldehyde, this induces the symptoms of Acute acetaldehyde toxicity
Acamprosate

Alcohol and drug interactions

●**Acute Alcohol use :** inhibition CYP450 2E1 → ↓ metabolism of other drugs taken concurrently as warfarin , increases their toxicities e.g. bleeding with warfarin
●**Chronic Alcohol use :**induces CYP450 2E1 → significant increases in ethanol metabolism (Tolerance) → ↑ metabolism of drugs such as warfarin, propranolol.
●**Acetaminophen + alcohol (chronic use):** risk of hepatotoxicity due to increased production of free radical metabolite of acetaminophen.
● **NSAIDs + alcohol:** Increase in the risk of developing a major GIT bleeding or ulcers.
● **Narcotic drugs (codeine and methadone)** + alcohol: risk of respiratory and CNS depression.
● Alcohol **suppresses gluconeogenesis,** which may increase risk for hypoglycemia in diabetic patients.

L3: drugs related to balance

Class	Drug name	MOA	Indication	ADRs	#
Vestibular Suppressant					
Anticholinergics	Hyoscine aka Scopolamine	1- Inhibits firing in vestibular nucleus neurons 2- ↓ the velocity of vestibular nystagmus	- Motion sickness - Sedation	- Dry mouth. -Blurred vision. -Sedation	-
Benzodiazepines	Lorazepam, Clonazepam, Diazepam.	Enhances GABA action on the brain -> reduces anxiety associated with vertigo	- Acute vertigo (small doses) -Minimize anxiety & panic associated with vertigo	- dependence -Impaired memory. - increased risk of falling	-
Betahistine	betahistine	1- Weak H1 agonist (vasodilation) 2- Potent H3 antagonist (increases histamine) 3- Increases serotonin	-Ménière's syndrome	- Headache - Nausea - GIT disturbance (inc HCL)	-Pheochromocytoma - bronchial asthma - History of peptic ulcer -hypersensitivity
Antiemetics					
Antihistamines	Dimenhydrinate	1- Blocks H1 receptor in CRTZ. 2- Sedative effect. 3- Weak anticholinergic effect. 4- ↓ excitability in the labyrinth & blocks conduction in the vestibular-cerebellar pathways.	-Vertigo -Prevention of nausea & vomiting associated with motion sickness	- sedation - dizziness - anticholinergic side effects	- Glaucoma - prostatic enlargement
Phenothiazines	Prochlorperazine	1-Blocks Dopamine receptors at CRTZ. 2-Antiemetic. 3-Antipsychotic + some sedation. 4-Some vestibular suppression.	Best antiemetic drug used in vertigo	-	-
Dopamine Antagonists	Domperidone, Metoclopramide	1- Blocks DOPAMINE D2 receptors in CRTZ 2- Sedative effect. 3- potent gastroprokinetic	-GERD	-restlessness -drowsiness -extrapyramidal manifestation (like Parkinson)	-
Prophylactic					
Ca^+ & K^+ channel blocker & Antihistamine	Cinnarizine	1- Selective Ca2+ channels blocker 2-Antihistamine, Antiserotonin, Anti dopamine 3-Promotes cerebral blood flow 4-inhibit K+ currents	-treatment of nausea & vomiting associated with : motion sickness, vertigo, Meniere's Disease	-sweating -headache -drowsiness -muscle rigidity & tremors	- Parkinsonism - car drivers
Diuretics	-	-	-	-	Except loop diuretics
Corticosteroids	-	-	-	--	-

L3: drugs related to balance

Drugs inducing vertigo

<table>
<tr><td rowspan="2">Vestibular toxin</td><td colspan="2">Altering function</td></tr>
<tr><td>1- Drugs altering fluid & electrolyte balance:
Diuretics (especially loop diuretics, other Diuretics are prescribed for emergency) (Furosemide)</td><td>2. Drugs altering vestibular firing:
• Anticonvulsants
• Antidepressants
• Sedative hypnotics
• Alcohol & cocaine</td></tr>
<tr><td rowspan="2">Mixed ototoxins</td><td>Altering structure</td><td>Altering Function: ↓ local blood flow -> biochemical changes ->↓ electromechanical transduction ->↑ firing of impulse.</td></tr>
<tr><td>Aminoglycoside antibiotics :
1. GENTAMICIN: mitochondrial pathway
Induces apoptosis by evoking free radicals.
2. NEOMYCIN: death receptor pathway
Induces apoptosis by activating caspases.
3-Kanamycin
4-streptomycin</td><td>• Quinine, chloroquine, quinidine
• Nitrogen mustard
• Loop diuretics (Furosemide)
• NSAIDs
• Tobacco</td></tr>
</table>

L4: Pharmacology of NTs

NT	Its role	Associated diseases
Norepinephrine (NE)	Many, based on the receptor	↑ in : Mania ↓ in : depression
Serotonin (5HT)	• feeling of well-being & happiness. • Mood. • Sleep. • Appetite. • Pain perception.	•Depression. ↓ 5-HT •Social phobia. •Obsessive Compulsive Disorders(OCD) •Generalized Anxiety. •Schizophrenia. •Vomiting.
Dopamine	Based on the pathway: Mesolimbic: Cognitive ,emotional. Mesocortical:Memory, motivation & emotions. Nigrostriatal: Controls Movement. Tuberoinfundibular:Regulation of prolactin secretion. CTZ: Nausea & vomiting.	• Parkinson's disease. ↓ DA • Attention Deficit Hyperactivity disorder(ADHD) • Schizophrenia.↑ DA • Depression. • Drug addiction.
AcetylCholine	• Memory. • Arousal. • Attention.	• Damage to cholinergic receptors (muscarinic) is associated with memory deficits as in **Alzheimer's disease.** • Muscarinic antagonists as hyoscine cause **amnesia**. • ↑ brain level of ACh predispose to **Parkinson's disease.** • **Schizophrenia** may be due to imbalance between ACh & dopamine brain levels. • **Depression** may be a manifestation of a central cholinergic predominance.
Glutamic acid (Glutamate)	Excitatory NT	• ↑ in epilepsy
GABA	Inhibitory NT	↓ in : • Epilepsy • Anxiety • Convulsions • Insomnia

L5: Drugs used in Parkinsonism

Class	1-Dopamine Precursor		2-Dopamine receptor agonist	
Drug	**Levodopa** (L-Dopa) First line	**DC inhibitors:** **Carbidopa** ,Benserazide	**Bromocriptine** ergot derivative	**Pramipexole** non-ergot derivative
P.K	1-Given orally (should be taken on empty stomach) 2-High protein meal interferes with its absorption **Short duration of action (t1/2 =2 h) (fluctuation of plasma concentration).**		• D2 agonist • given orally Half life=6-8 h	• D3 agonist. • given orally. • **Has the advantage of being free radicals scavenger**.
MOA	1-Is **converted** into **dopamine peripherally** and **centrally** by the action of an enzyme called **dopa decarboxylase (DC).** 2-Dopamine acts on dopaminergic receptors D1-D5 (G-protein linked receptors): - D1, D5 → Excitatory - D2, D3, D4 → inhibitory	They **inhibit peripheral** conversion of L-dopa to dopamine in GIT and other peripheral tissues, thus increasing T1\2.	-	-
Uses	• **the most efficacious** • The best results in the first years. • L-dopa improve all signs of parkinsonism but doesn't cure it. • **Shouldn't** be used in parkinsonism associated with **antipsychotic drug therapy.**	**Benefits of L-dopa+carbidopa combination:** 1. Increases the availability of levodopa to the CNS. 2. Lowers the effective L-dopa dose 3. Reduce dose of L-dopa and side effects	• **Parkinson's** disease. •**Hyperprolactinemia** (Galactorrhea) • **Infertility** in women.	• Used alone as Initial therapy or in combination with L-dopa
			• As **monotherapy**, the dopamine agonists are less effective than levodopa. • In **advanced stages**, dopamine agonists are used as an **adjunct** to levodopa, they may contribute to clinical improvement and reduce levodopa dosage needs. • Have longer duration of action than L-dopa (less likely to cause dyskinesia than levodopa).	
ADRs	• **Peripheral effects:** - Anorexia ,nausea, vomiting, (due to stimulation of CTZ.) - arrhythmias. - Mydriasis - orthostatic hypotension •**CNS effects (Psychological):** depression, delusions, hallucinations, confusion ,insomnia.	-	Similar to L-dopa: • Nausea, vomiting, cardiac arrhythmias. • Confusions, hallucination, delusions. • Dyskinesias (less prominent).	
Limitations	• Dyskinesia, due to fluctuating plasma levels of levodopa. can be reduced by lowering the dosage. • Wearing-off effect • On-off phenomenon • Wearing off effect and on-off phenomena occur due to progression of the disease and the loss of striatal dopamine nerve terminals.	-		
#	• **Psychotic** patient. • **Glaucoma** • **melanoma** (L-dopa is a precursor of melanin)	-	•**Psychosis**. • Patients with peripheral **vascular disease** (Ergot derivatives only). • Recent **myocardial infarction.**	
Drug Interactions	• High proteins meals. • Pyridoxine (Vitamin B6). • Non Selective MAO inhibitors (phenelzine)	-		

L5: Drugs used in Parkinsonism

Class	Drug	P.K	MOA	Uses	ADRs	#
3-Dopamine releaser	Amantadine	• Given orally with **short half life.** • Most of the drugs is excreted unchanged in urine. • Less efficacious than L-dopa. • **Tolerance** develops to its therapeutic effect **after 6-8 months.**	• Originally introduced as an **antiviral**. • **Inhibits dopamine reuptake,** and increases its release. • Acts as an antagonist at **muscarini**c & **NMDA** receptors.	• It's benefits last only for short period and only used for L-dopa resistance. • Useful in the **early** stages of Parkinsonism or as an adjunct to levodopa therapy. •Amantadine and the **anticholinergics** may exert additive effect on mental functioning.	• **Dopamine like side effects**:Nausea, hallucinations, anxiety, insomnia, confusion. • **Anticholinergic effects:** Dry mouth, urinary retention. • Ankle edema ★ livedo reticularis "Reduction of blood flow to the skin (harmless/rare)"	-
4-COMT inhibitors	**Entacapone**	• Usually given in combination with L-dopa and carbidopa to diminishes **peripheral** metabolism	Acts **peripherally** to inhibit COMT enzyme required for L-dopa degradation.	Used as adjuvant to L-dopa + carbidopa to: • Decrease fluctuations, Improve response and Prolong the ON-Time	•L-dopa side effects •Brownish Orange discoloration of urine	-
	Tolcapone	• More lipid soluble than entacapone • More penetration into CNS	**Peripheral** and **central** COMT inhibitor		-	-
5-MAO-B inhibitor	**Selegiline**	• It is a selective irreversible inhibitor of MAO-B an important enzyme for dopamine metabolism. • The blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors.	Selegiline may have neuroprotective effect due to: •Antioxidant activity against toxic free radicals produced during dopamine metabolism. •Metabolized to desmethyl-selegiline, which is Anti-apoptotic.	Adjunctive to levodopa/carbidopa in later-stage Parkinsonism to: • Reduce the required dose of levodopa. • Delay the onset of dyskinesia and motor fluctuations that usually accompany long-term treatment with levodopa.	• At high doses, It may inhibit MAO-A → (Hypertensive crises) • May cause insomnia when taken later during the day.	Co-administered with: • Tricyclic Antidepressants. • Selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma) • Food restriction "low tyramine diet" is required.
6-Anticholinergic Drugs	**Benztropine** **Trihexyphenidyl**	–	Central muscarinic antagonist, has modest anti-Parkinsonian actions.	• Improves tremor & rigidity but have little effect on bradykinesia. • Provide benefit in drug-induced Parkinsonism (due to antipsychotics). • Used during the early stages of the disease or as adjunct to levodopa therapy.	• Cycloplegia, mydriasis, dry mouth, urinary retention, constipation. • At high doses: confusion, delirium, hallucinations.	• Prostatic hypertrophy • Glaucoma • Intestinal obstruction.

L6&7: Drugs used in epilepsy

drug	Barbiturates (CNS depressant): Phenobarbital mephobarbital pentobarbital	Benzodiazepines (CNS depressant): Midazolam diazepam Lorazepam clobazam clorazepate clonazepam	Phenytoin: *Oral Fosphenytoin: *Parenteral IV,IM	Carbamazepine Oxcarbazepine (prodrug)
MOA	↑ GABA(A) receptor activity by increasing duration of GABA-A receptor opening time	↑ GABA(A) receptor activity by increasing frequency of GABA-A receptor opening	-Block Na+ & Ca2+ influx into neuronal axon -Inhibit the release of excitatory transmitters (glutamate & aspartate) -Potentiate GABA action	-Block Na+ & Ca2+ influx into neuronal axon -Inhibit the release of excitatory transmitters (glutamate & aspartate) -Potentiate GABA action
P.K	-Metabolised by CYP2C9, -Induce CYP2C &CYP3A subfamilies	-	-Enzyme Inducer -Phenytoin should NEVER be given IM because it can cause tissue damage and necrosis.	-Strong enzyme inducer including its own metabolism (كسرني خليني أتوب)
Clinical use	-Generalized tonic-clonic -focal seizures	-Clonazepam use for absence seizures and myoclonic seizures in children . -focal seizures -status epilepticus	-Partial and generalized tonic-clonic seizures -In status epilepticus,IV -C.I for absence seizure	-Drug of Choice in complex partial seizures -Trigeminal Neuralgia -Tonic-clonic seizures (1ry&2ry generalized) -C.I for absence seizure
ADRs	-Sedation -Nystagmus ,Ataxia (high dose). -Tolerance, addiction. -Respiratory depression	-Drowsiness,lethargy -Hypotonia,dizziness -Seizures if the drug is discontinued abruptly -tolerance addiction. -reversible memory loss	-headache,vertigo,ataxia ,diplopia, nystagmus, sedation -Gum hyperplasia (Gingival hyperplasia) -VitD deficiency (**osteomalacia**) -Hirsutism ,acne -Folic acid deficiency (**megaloblastic anemia**) -Fetal Hydantoin Syndrome : growth retardation ,microencephaly, craniofacial abnormalities cleft possibly due to an epoxide .	**Carbamazepine:** -GIT upset Drowsiness , ataxia , headache ,diplopia -Water intoxication Hyponatremia. -Idiosyncratic blood dyscrasias and severe rashes -Teratogenicity **Oxcarbazepine:** Fewer ADRs than CBZ,Phenytoin

Broad spectrum antiepileptic

drug	Sodium Valproate (VPA: valproic acid)	Lamotrigine Male's Dr: may cause cardiac problems
MOA	- Blocks activated Na+ channels -↑ GABA synthesis & ↓ degradation - Suppress Glutamate Action -Blocks T-type Ca2+ channels	-Blocks Na+channels -Inhibits excitatory amino acid release (glutamate & aspartate) -Does not induce or inhibit CYP-450 isozymes
P.K	Enzyme inhibitor	-
Clinical use	-Effective for all forms of epilepsy (for status epileptic not as 1st choice) -Bipolar disorder & mania -Migraine prophylaxis - Lennox-Gastaut syndrome	-Partial seizures: as add-on therapy or as monotherapy -Lennox-Gastaut syndrome -pregnancy safe
ADRs	-Weight gain (↑ appetite) -Transient hair loss with re-growth of curly hair -Thrombocytopenia -Hepatotoxicity. -Bone loss -Teratogenicity(most dangerous)	-Influenza-like symptoms -Skin rash → may progress to Steven–Johnson Syndrome -Somnolence (drowsiness), Blurred Vision,Diplopia ,Ataxia

L6&7: Drugs used in epilepsy

Broad spectrum antiepileptic Cont…

drug	Topiramate	Zonisamide Sulfonamide derivative	Felbamate
MOA	-Blocks Na+ channels → membrane stabilization -Potentiates the inhibitory effect of GABA	•Na+ channel inhibitor • Inhibits T-type Ca2+ currents • Binds to GABA receptors • Facilitates dopaminergic & serotonergic neurotransmission	•Blocks voltage-dependent Na+ channels (weak). • Competes with the glycine-coagonist binding site on the NMDA receptor. • Block Ca2+channels. • Potentiates GABA actions. • Has a broad spectrum of anticonvulsant action
Clinical use	•Can be used alone for partial, generalized tonic-clonic, & absence seizures • Lennox-Gastaut syndrome (or Lamotrigine, or Valproate) • Adjunct therapy	Approved for adjunct treatment of partial seizures in adults.	Refractory epilepsies (particularly Lennox-Gastaut syndrome) -Important : Temporal lobe is the most common type of epilepsy and 30% of them are refractory
ADRs	•Psychological or cognitive dysfunction (nervousness) • Weight loss (can be a desirable effect) • Sedation, dizziness & fatigue • Urolithiasis (renal stones) • Paresthesias (abnormal sensation) • Teratogenicity (in animal but not in human) •C.I in Glaucoma	• Weight loss • Abnormal thinking • Nervousness, agitation & irritability	• Aplastic anemia • Hepatic failure

Calcium Channel Blockers

drug	Ethosuximide (ETSM)	Gabapentin (Neurontin) Pregabalin (Lyrica)
MOA	Inhibit T-type Ca2+ channels in thalamocortical neurons	Initially designed as an analogue of GABA, then found out to bind to P/Q type Ca channels instead of GABA receptors
P.K	• Absorption is complete • Syrup & capsule forms. • Not bound to plasma proteins or tissues. • Metabolized in liver • t1/2 = 52-56 h. • 10-20% of a dose is excreted unchanged in urine	Pregabalin: • A pro-drug of Gabapentin • More potent than gabapentin
Clinical use	Absence seizures	Gabapentin: adjunct therapy in adults and children with partial & secondarily generalized seizures and as monotherapy. • Neuropathic pain ,Fibromyalgia: a syndrome characterized by chronic pain in muscles of soft tissues surrounding joints, fatigue, & tenderness at specific sites in the body
ADRs	• Gastric distress • Hiccups • Drowsiness, fatigue & headaches	• Weight gain with ankle edema • Irritability • Behavioral problems in children • Movement disorders

L6&7: Drugs used in epilepsy

Other Mechanisms

drug	Levetiracetam "Keppra"	Brivaracetam	Cannabidiol "CBD" (Epidiolex)	Fenfluramine (Fintepla)
MOA	-Act on synaptic vesicle protein 2A (SV2A) → slow synaptic vesicle mobilization -Brivaracetam more potent		It is the first FDA-approved drug that contains a purified drug substance derived from marijuana. M.O.A.: Activation of CB1 receptors → inhibition of glutamate release	-amphetamine In is an derivative. M.O.A : Stimulate 5-HT1D and 5-HT2C → Inc GABA release Antagonize σ1 R → modulate NMDA responses
Clinical use	• Adjunct therapy for adults with partial seizures. • Some patients have success with monotherapy. -C.I in Renal dysfunction	Adjunctive therapy for partial seizures with or without secondary generalization in patients aged 4 years or older. -C.I in Hypersensitivity	• The first FDA approval of a drug for the treatment of Dravet syndrome(Genetic disorder cause epilepsy that not responding to medication) • Lennox-Gastaut syndrome	Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.
ADRs	• Asthenia (physical weakness) • Infection • Behavioral problems in children	• Somnolence & dizziness • Infection (influenza) • Convulsion • Suicidal ideation & psychotic disorder	• Somnolence • ↑ Hepatic enzymes *CBD does NOT cause intoxication or euphoria that comes from tetrahydrocannabinol (THC). It is THC (and not Cannabidiol) that is the primary psychoactive component of marijuana.	ADRs: Decreased appetite, diarrhoea, pyrexia, fatigue, upper respiratory tract infection, lethargy, somnolence, and bronchitis. C.I: -Aortic or mitral valvular heart disease. -Pulmonary arterial hypertension -Within 14 days of the administration of MAOIs due to an increased risk of serotonin syndrome.

Summary for specific cases

Case	Management
Status Epilepticus	All are given I.V. :Lorazepam (drug of choice), Diazepam ,Phenobarbital, ,Midazolam, Fosphenytoin.
Pregnancy & AntiEpileptic Drugs	• Patient has to continue therapy. • NO antiepileptic drug is safe in pregnancy. The safest (Category C) are:Lamotrigine (best) & Levetiracetam • Monotherapy is usually better than drug combination. • Valproate & Phenytoin are contraindicated during pregnancy.
withdrawal	When is withdrawal considered: -Normal IQ. -Seizure–free period of 2-5 years or longer -No juvenile myoclonic epilepsy (life-long treatment) - Normal EEG prior to withdrawal
Non-pharmacological Treatment of Epilepsy	• Vagal nerve stimulation • Surgery • Ketogenic diet

L8: General anesthetics

Pre-anesthetic medication

Drugs	Uses	Examples
Opiates	induce analgesia.	-
Anticholinergics	prevent secretion of fluids into the respiratory tract.	-
Sedatives & anxiolytics	relieve anxiety	diazepam
Antihistaminics	Postoperative allergic reactions	diphenhydramine
Antiemetics	Post or pre surgical nausea & vomiting.	Metoclopramide & prochlorperazine
H2-receptor blockers	Postoperative To Reduce gastric acidity	Ranitidine
Barbiturates	Smooth induction	Thiopental

Adjuncts to general anesthesia

Neuromuscular blockers	Facilitate intubation, Suppress muscle tone	Succinylcholine, vecuronium, atracurium

General Anesthesia

MOA	• **Enhance the action of GABA & glycine on receptors** → opening Cl- channel → Hyperpolarized neuronal cell→ **thus↓neuronal excitability.** • **Blocking NMDA receptors (Ketamine):** ◦ **Reduce Ca2+ influx** ◦ **Reduce neural excitability**

Inhalational anaesthetic

Pharmacological action

*CNS
- ↓ metabolic rate. - ↑ ICP (due to cerebral vasodilatation). - Dose dependent EEG changes (**Enflurane**).

*CVS
- Hypotension - Bradycardia EXCEPT (**Isoflurane** & **Desflurane**).
- Myocardial depression (Halothane – Enflurane).
-Sensitize **heart** to catecholamines (**H**alothane)

*Respiratory
- All respiratory depressants(bronchodilation) EXCEPT: Desflurane -Airway irritation (Desflurane-Enflurane).

*Uterus & Skeletal Muscles
-Skeletal muscle relaxants. -Uterine relaxation [**nitrous oxide** has minimal relaxant effect may delay (labor)].
**Malignant Hyperthermia: genetic condition of skeletal muscle metabolism triggered by inhalation anesthetics.
★ Treatment:**Dantrolene**

Drug	Properties	ADRs
Methoxyflurane	-For veterinary (animal) use only -**Low MAC** value (**Most** potent anesthetic)	-Slow induction -Nephrotoxicity
Halothane	-Potent anesthetic, Weak analgesic -Non irritant (Pleasant smell"used in children")	-Slow induction and recovery - Hepatotoxicity -Malignant Hyperthermia -Sensitization of Heart to catecholamines
Enflurane	-Metabolized to fluoride (8%)	-Airway irritation (Pungent Smell "not for pediatrics") -Not for pediatrics -less induction -CNS stimulation (Epilepsy-like seizure, abnormal EEG) -**Contraindicated in:** *Patients with seizure disorders *Patients with renal failure (release fluoride)
Isoflurane	Stable compound -No nephrotoxicity -No hepatotoxicity	-
Sevoflurane	-No airway irritation (Better smell "in children") -Little effect on HR	-

L8: General anesthetics

Inhalational anaesthetic

Desflurane	-Less metabolized (0.05 %) -Low boiling point (special equipment)	-Airway irritation (Pungent odor) ★(C.I in patient with asthma)
Nitrous oxide (Gas)	-Potent analgesic, **Least** potent anesthetic -Minimal CVS adverse effects	-Weak anesthetic -Diffusion hypoxia -Nausea & vomiting -Inactivation of B12 → Megaloblastic anaemia, congenital anomalies -**Contraindicated** in pregnancy (uterine relaxant)

Intravenous anaesthetic

Features	*Rapid induction & recovery EXCEPT benzodiazepines anesthesia. *Injected slowly (rapid induction), NO need for special equipments. *Recovery is due to redistribution from CNS.	-Can be used alone in short operation & Outpatients Analgesic activity: Opioids, Ketamines Amnesic action: Benzodiazepines, Ketamines

Drug	Onset&D.O.A	Uses/ Action	ADRs	C.I
Barbiturates (Ultrashort acting) Thiopental	Fast onset(1min),slowly metabolized by the liver,, slow recovery, hangover, Ultra short D.O.A (15-20 min), High lipid solubility	- Induction in major surgery and alone in minor surgery. - Potent anesthetic. - ★↓**ICP** (used in head injury)	- CVS collapse & respiratory depression (Laryngospasm, bronchospasm) - Precipitate porphyria attack symptoms: severe abdominal pain, numbness, anxiety & confusion - Hypersensitivity reaction. -Chronic obstructive lung disease -Local tissue necrosis & ulceration if injected SC or IM (highly alkaline)	- Severe hypotension (hypovolemic & shock patient) - COPD
Etomidate Ultrashort acting hypnotic (Non Barbiturates)	Rapid onset & short D.O.A, Rapidly in liver, fairly fast recovery→ less hangover	-	- Minimal CVS & respiratory depressant effects. -Involuntary movements /Excitatory effects during induction. -Postoperative NV -Pain at injection site. - ★**Adrenal**/Adrenocortical suppression	-
Propofol Hypnotic (Non Barbiturate)	Rapid onset & short D.O.A, rapidly metabolized, Faster recovery than thiopental.	-↓ICP	- Hypotension (↓PVR) - CVS & respiratory depression - Excitation (involuntary movements). - Pain at site of injection. Propofol infusion syndrome	-
Benzodiazepines (anxiolytic drugs) Midazolam Diazepam & Lorazepam	-	- No pain, have anxiolytic & amnesic action. - Induction of general anesthesia - **Alone** in minor procedure (endoscopy). - In balanced anesthesia& has amnesic effect (GABA effect) (Midazolam).	- Minimal CVS & respiratory depressant effects.	- Respiratory Patients
Ketamine I.M (can be used in children)	-	- Dissociative anesthesia: (analgesic activity, amnesic action, immobility, complete separation from the surrounding environment). - ★Potent bronchodilator (asthmatics). - Used in (hypovolemic, shock & elderly patients.	- ↑ Central sympathetic activity (↑ BP & CO) - ↑ Plasma catecholamine levels (↑ ICP) -Postoperative/Psychotomimetic effects: hallucination, vivid dreams, disorientation & illusions - Risk of hypertension and cerebral hemorrhage ↑ ICP - Post operative NV, salivation	-CV diseases: (hypertension, stroke) -Head injuries.
Opiate drugs Fentanyl, Alfentanil, Sufentanil, Remifentanil	-	- ★Potent analgesia. - ★**Cardiac surgery** (morphine + nitrous oxide)	- Nausea & vomiting, Urinary Retention - ↑ICP - Prolongation of Labor & fetal distress - Respiratory depression, bronchospasm (wooden rigidity)	- Head injuries. - Pregnancy - Bronchial asthma, -COPD - Hypovolemic shock (In Large dose

L9: Anti Anxiety drugs

Benzodiazepines

Drug	Diazepam	Midazolam	Lorazepam	Triazolam, Flurazepam	Alprazolam
Uses	**-Anxiety disorders:** -Benzodiazepines are **fast-acting**, typically bringing relief within 30 min to an hour. **-Short term** relief of severe anxiety (NOT for long term because it leads to dependence) **-GAD (general anxiety disorder)** **-OCD (obsessive compulsive disorder)**				
	-Treatment of **epilepsy** -Preanesthetic medication **-Alcohol withdrawal** syndrome	**IV, Induction** of anesthesia	-Treatment of **epilepsy** **-Sleep disorders** (insomnia)	**Sleep disorders** (insomnia)	**Panic disorder with depression (antidepressant effect)**
ADRs	-Cognitive impairment -Ataxia (motor incoordination) -Impairment of driving ability -Anterograde amnesia -Hangover (excess sedation, drowsiness, confusion) -Tolerance Stop gradually -Psychological & physical dependence with continuous use -Risk of **withdrawal symptoms**: rebound insomnia, anorexia, anxiety, agitation, tremors & convulsion -Respiratory & CVS depression in large doses only (toxic effects)				
Drug-interaction (for all)	**BDZ + CNS depressant** (e.g alcohol, antihistamine) = ↑ effect of BDZ (additive effect)		BDZ + CYT P450 inhibitors (Cimetidine,, Erythromycin) = ↑ t 1/2 of BDZ	BDZ + CYT P450 inducers (e.g Phenytoin, Rifampicin) = ↓ t 1/2 of BDZ	
Precaution	• Pregnant or breastfeeding women. BDZ are considered D category in pregnancy, which is dangerous • Dose reduction is recommended in: 1-Liver disease 2-Old people				

BDZ Antagonist

	Flumazenil
M.O.A.	Selective benzodiazepine receptor antagonist.
P.K.	given by injection, Short half-life → repeated dosing is required
Uses	**Benzodiazepines overdose (antidote)**
ADRs	Can precipitate withdrawal symptoms in benzodiazepine addicts.

L9: Anti Anxiety drugs

Selective serotonin reuptake inhibitors (SSRIs) (Fluoxetine)

MOA	• **acts by blocking uptake of 5-HT.**
Uses	• Considered the **first line of treatment** for most anxiety disorders (panic disorder, OCD, GAD, PTSD, phobia) because they're well tolerated, have low risk for dependency and abuse and low potential for overdose.
ADRs	•Delayed onset of action (weeks). Increase in anxiety symptoms, insomnia or headache in the first days treatment may↓ compliance • Nausea, diarrhea • Sleep disturbance or insomnia • Weight gain • Sexual dysfunction • Dry mouth (Atropine like actions) • Seizures

Tricyclic antidepressants (Doxepin- imipramine – desipramine)

MOA	• **act by reducing uptake of 5HT & NA.**
Uses	•Used for anxiety especially associated with depression. • Effective for panic attacks.
ADRs	• Atropine like actions (muscarinic blocking actions)(dry mouth-blurred vision, tachycardia, urinary retention). • α-blocking activity (Postural hypotension). • Sexual dysfunction. • **Weight gain.**

5HT1A agonists (Buspirone) M.O.A: partial agonist at brain 5HT1A receptors

Actions	•**Only anxiolytic.** •**It doesn't impair memory and coordination.** •**Doesn't affect driving skills.** •**Minimal risk of dependence.** •Less interference with motor function which is particularly important in elderly patients. •**No hypnotic effect** •**No muscle relaxant effect.** •**No anticonvulsant action.** •**No alcohol additive effect.** •**No withdrawal symptoms.**
Uses	**As anxiolytic in mild anxiety & generalized anxiety disorders.** First line
Disadvantages	•Slow onset of action (delayed effect) •**Not effective in severe anxiety/panic disorders** •GIT upset, dizziness, drowsiness •Drug interactions with CYT P450 inducers & inhibitors
Interactions	•CYP450 3A4 Inhibitors (verapamil, diltiazem)→↑ buspirone level •CYP450 3A4 Inducers (Rifampin) → ↓ buspirone level
precautions	•Pregnant women or breast-feeding •People over 65 •Dose reduction is recommended in liver disease and old people. (Undergoes extensive hepatic metabolism, its clearance is reduced by liver dysfunction.)

Monoamine oxidase inhibitors (MAOIs) -Phenelzine

M.O.A	Acts by blocking the action of MAO enzymes
Uses	○ Used for **panic attacks** & **phobias** ○ Reserved for patients who have not responded to, or proved intolerant of, other treatments
P.K	Require dietary restriction: avoid wine, beer, fermented foods as old cheese that contain tyramine ↑ NA release (Sympathomimetic) → hypertensive crisis
ADRs	•Dry mouth, constipation, diarrhea, restlessness, dizziness.

Beta blockers *peripheral*(Propranolol – Atenolol)

M.O.A	○ Act by blocking peripheral sympathetic system don't act on CNS ○ Reduce **somatic symptoms** of anxiety (physical NOT mental,) ○ Decrease BP & slow heart rate
Uses	• Used in performance or social anxiety. • are less effective for other forms of anxiety
precautions	should be used with caution in asthma, cardiac failure, peripheral vascular disorders

L9: Anti Anxiety drugs

Pregabalin

MOA	●Modulates calcium channels in CNS, ↓Ca++ influx & modulates release of neurotransmitters.
P.K.	○ Onset occurs in first days of treatment ○ Excreted unchanged in urine
Uses	● Effective in treatment & prevention of relapse of GAD (**1st line as SSRIs**). ●**Used in epilepsy & neuropathic pain**
ADRs	●dizziness and somnolence ● Withdrawal symptoms may occur but less severe than benzodiazepines

L10: Drugs used in management of pain

Opioid Agonists

M.O.A.	• **Presynaptic inhibition:** Gi-coupled opioid receptors →↓ AC → ↓cAMP → ↓ **voltage-gated Ca^{2+} channels** → ↓ release of excitatory transmitters • **Postsynaptic inhibition:** ↑ opening of K^{+} channels → ↓ neuronal excitability
μ Agonist	
Morphine	
Source	Natural
P.K.	○ t1/2 = 2 h → disadvantage : frequent dosing for sustained analgesia. ○ Slowly & erratically absorbed orally→ medically given SC, IM, or IV ○ Metabolized by conjugation with glucuronic acid ○ Undergoes enterohepatic recycling → ↓ amount of active drug + longer t1/2 & DOA.
P.D. Effects ★	**1) Analgesia** in acute and chronic pain **2) Euphoria & sedation** **3) Respiratory depression** **4) Depression of cough** **5) Nausea & vomiting** (↑ CRTZ) **6) Pin-point pupil** **7) Histamine release** → flushing & warming. 8) Effects on **GIT**: ○ **Severe constipation** ○ **↑ pressure in biliary tract & Biliary colic** ○ **Contraction of gallbladder.** 9) Depresses renal function.
Uses	○ Control pain: cancer pain, severe burns, trauma, severe visceral pain (thoracic, pelvic, abdominal), but ★NOT in renal/biliary colics or acute pancreatitis because of constriction. ○ Acute pulmonary edema ○ Myocardial ischemia ○ Non-painful conditions (to relieve distress) e.g. heart failure ○ Pre-anesthetic medication
Tolerance	Rapidly (12-24 h)
Dependence	**Physical dependence** : ↑ body ache, insomnia, diarrhea, goose flesh, lacrimation. (withdrawal manifestation upon stoppage) **Psychological dependence:** craving.
ADRs	○ **Constipation** ○ **Respiratory depression** ○ **Constricted pupil** ○ Hypotension on long-term use. ○ Itching ○ Nausea & vomiting (+ CRTZ) ○ Sedation
CI ★	○ **Head injury** ★ **Bronchial asthma** ○ **Biliary colic & pancreatic pain** ○ Elderly: more sensitive ○ Infants, neonates or during childbirth. ○ With MAOIs due to CYP450 enzyme inhibition by the MAOI.

L10: Drugs used in management of pain

Opioid Agonists

	μ Agonists				K Agonist
Drug	**Codeine**	**Tramadol**	**Fentanyl**	**Methadone**	**Pethidine(Meperidine)**
Source	Natural	Synthetic			
P.D.		• Inhibits **NE** & **5HT** reuptake • **Less** potent than Morphine • **P.K.** : Can be given orally; has more oral bioavailability than Morphine.	**More** potent than Pethidine & Morphine	• Weaker synthetic μ agonist. • t 1/2 = 55 h (long-acting) disadvantage: dose difficult to titrate.	• No cough suppressant effect • **Atropine-like action** (smooth muscle relaxant) • **Less** analgesic, constipating, depressant on fetal respiration than Morphine
Uses	• **Mild & moderate pain** • Cough • Diarrhea	• Mild, moderate acute & chronic **visceral pain** • **During labor**	• Analgesic supplement during **anesthesia (I.V)** • Induce & maintain anesthesia in poor-risk pts (stabilizing heart) • **Neuroleptanalgesia** (with droperidol) • **Cancer** pain • Severe **postoperative** pain	To treat **opioid withdrawal**	• As in Morphine, but not in cough & diarrhea • **Preanaesthetic** medication (better) ★ Used in **obstetric analgesia** (no ↓ respiration) ★ Severe visceral pain; **renal & biliary colics**
ADRs	**Less** dependence than Morphine	• **# Seizures not used in epileptics** • Nausea, Dry mouth,Dizziness, Sedation • **Less** adverse effects on respiratory & C.V.S.	• **Respiratory depression** (more serious than Morphine) • **Bradycardia** may occur.	★ In non addicts, it causes **tolerance & dependence** but not as severe as that of Morphine	• Tremors, convulsions • Hyperthermia • Hypotension • Atropine-like effects: blurred vision, dry mouth, urine retention • Tolerance & addiction

Opioid Antagonists (Antidotes)

	Naloxone (Pure)	**Naltrexone** (longer DOA)
P.K.	Effects lasts only for 2-4 h	Longer duration of action (t1/2 = 10 h)
Uses	• **Treat respiratory depression caused by opioid overdose.** • **Reverse the effect of analgesia on the respiration of the newborn baby.**	
ADRS	★ Precipitate **withdrawal syndrome in addicts**	

L11/ Drugs used in schizophrenia

Class	M.O.A	Drugs
Typical non-selective	Blocks many receptors including dopamine, serotonin, adrenergic, cholinergic, and histaminergic receptors.	Phenothiazine derivatives. ➢ Chlorpromazine ➢ Thioridazine Butyrophenones. ➢ Haloperidol (common) Thioxanthene. ➢ Thiothixene
Atypical selective 2nd generation	Block both dopaminergic & serotonergic (5HT-2) receptors.	-Clozapine -Risperidone -Olanzapine -Quetiapine -Ziprasidone -Cariprazine

Therapeutic Uses

Psychiatric :	Non-psychiatric
➢ Schizophrenia (primary indication). ➢ Acute mania. ➢ Manic-depressive illness (bipolar affective disorder) during the manic phase.	➢Nausea and vomiting (Prochlorperazine, chlorpromazine and Benzquinamide) are only used as antiemetics. ➢Pruritus. severe itching (Why? because they block Histamine receptors) ➢Preoperative sedation (rare use).

Pharmacological Actions

Action on	Mechanism	Effect
CNS	Blockade of **dopamine** receptors in the **mesolimbic system**.	**-Antipsychotic effect:** •Produce emotional quieting and psychomotor slowing. •Decrease hallucinations, delusions and agitation.
	Blockade of **dopamine** receptors in the **nigrostriatal system**	**-Extrapyramidal Symptoms:** Abnormal involuntary movements : tremors, parkinsonism like syndrome& **tardive dyskinesia**.
	Prevent **dopamine** inhibition action of prolactin release from pituitary→ **Hyperprolactinemia**	**Endocrine effects:** -Galactorrhea (Excessive production of milk) -amenorrhea(Missing one or more periods) -gynecomastia (Enlarged breast in men) -impotence.
	Blockade of **dopamine** receptors in medullary **periventricular pathway**	Changes in eating behavior and weight gain.
	Blockade of **dopamine** receptors in the **CTZ** of the medulla	Effective against drug & diseases induced vomiting (But not motion sickness).
	Block H1 receptor	**Antihistamine effect:** • Sedation,drowsiness,fatigue Haloperidol (typical) Risperidone(atypical)
ANS Autonomic	Block Muscarinic receptors	**Anticholinergic effect:** • Blurred vision • Dry mouth • Urinary retention • Constipation Chlorpromazine (Typical) Clozapine(Atypical)
	Blockade of **α- adrenergic** receptors	**Antiadrenergic Effects:** • Postural hypotension. • Impotence. • Failure of ejaculation. Chlorpromazine (Typical) Thioridazine(Typical)

L11/ Drugs used in schizophrenia

Miscellaneous Effects

- Temperature regulation: May decrease body temperature, due to vasodilation (α-blocking) or central effect
- ECG changes: Prolongation of QT intervals, Abnormal configuration of ST-segment and T wave ,Quinidine-like actions
- Antihistamine effect: Sedation due to H1 receptor blockade
- Obstructive Jaundice, Weight gain,
- Granular Deposits in cornea
- Thioridazine: Retinal deposits
- Clozapine: Seizures, Agranulocytosis (an acute condition involving severe and dangerous ↓WBC)

Atypical Antipsychotics (2nd Generation antipsychotics)

Characteristics

- Now considered to be **first line** treatments for schizophrenia.
- Effective in treatment of **resistant schizophrenia**.
- Block both **dopaminergic & serotonergic receptors**.
- **Little or no extrapyramidal side effects.**
- Are effective on both positive & negative symptoms.

Uses

- **Refractory** cases of schizophrenia.
- To reduce the risk of recurrent **suicidal behavior** in patients with schizophrenia.

Drug	Receptor blockage	ADRs
Clozapine	D2 / D4 **& 5HT2a receptor.**	➢ Agranulocytosis. ➢ Seizures ➢ Myocarditis. ➢ Excessive salivation (during sleep).
Risperidone	**D2 & 5HT2 receptors.**	➢ Postural hypotension. ➢ QT prolongation —> **C.I** in patients with **long QT interval.** ➢ Weight gain.
Olanzapine first line treatment for schizophrenia	**D1- D4 & 5HT2 receptors.**	Weight gain, Sedation, Flatulence, increased salivation & thirst, Postural hypotension
Quetiapine	**D1-D2 & 5HT2 receptors.**	Sedation , Hypotension ,Sluggishness ,Dry mouth ,Increase appetite (weight gain) ,Abdominal pain. Constipation.
Ziprasidone	D2 & 5HT2 receptors.	➢ Drowsiness. . ➢ Dizziness ➢ Akathisia. ➢ Headache. ➢ Weight gain.
	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 (inhibitor of CYP3A4).** -**Warning** : Increase mortality in elderly patients with Dementia-related psychosis.	
Cariprazine	• Has higher affinity at **D3 receptor.** • **Has a positive impact on the cognitive symptoms of schizophrenia.**	

L12&13 Antidepressants

Old Group

TriCyclic Antidepressants (TCAs)

Drugs	Tricyclic Antidepressants: **Imipramine**, **Desipramine**, **Clomipramine**, **Amitriptyline**, **Nortriptyline** ,Tetracyclic Antidepressants: **Amoxapine Maprotiline**	
M.O.A	**5-HT** and **NE** reuptake inhibitors. Imipramine, Amitriptyline, Clomipramine (more potent for inhibiting 5HT reuptake) Desipramine, Nortriptyline (more potent for inhibiting NE reuptake)	
Actions	**Elevate mood , Improve mental alertness ,Increase physical activity** In **non-depressed patients**: They cause sedation, confusion & motor incoordination	
ADRs	**TCAs** block: 1-**M1** cholinergic receptors 2- **H1** histamines receptors 3- **α1** adrenergic receptors 4- **5-HT2** receptors -**Anticholinergic**: Dry mouth, blurred vision, constipation & urine retention, aggravation of glaucoma. -**Antihistaminic**: Sedation, confusion -**Anti-adrenergic**: Postural hypotension, arrhythmias, conduction defects -Weight gain, **Sexual dysfunction** & impotence -Lower seizure threshold -**TCAs have a large volume of distribution** therefore hemodialysis is **NOT** effective for treatment of TCAs toxicity	
Uses	• Endogenous (Major) **Depression** "moderate to severe". • **Imipramine** is used for treatment of ★**nocturnal enuresis** in children & geriatric patients as it constricts internal urethral sphincter(antimuscarinic effect). • Panic attack /acute episode of anxiety • Generalized Anxiety Disorder (GAD). • Obsessive Compulsive Disorder (OCD). • Attention Deficit Hyperkinetic Disorder (ADHD) • ★Chronic neuropathic pains or unexplained body pains.	C.I: -Glaucoma or enlarged prostate **-In manic-depressive illness** **-in Seizure disorders**
DDI	-Drugs that compete for their plasma protein binding site (Aspirin and Phenylbutazone) -TCAs are metabolized by liver microsomal enzymes therefore : 1.Reduced by inducers (Barbiturates) 2.Potentiated by inhibitors of liver enzymes (Oral contraceptives, Antipsychotics, and SSRIs). -TCAs+MAOIs= Serotonergic & hypertensive crisis -Additive to antipsychotics & anti-parkinsonisms → ↑anticholinergic effects	

MonoAmine Oxidase Inhibitors (MAOIs)

Drugs	**Non Selective (MAO-A & MOA-B):** 1-Phenelzine (Irreversible) long acting. 2-Tranylcypromine (Irreversible).	**Selective:** **1-Moclobemide(MAO-A) —>**Responsible for NE, 5-HT catabolism. It also metabolizes tyramine of ingested food 2-Selegiline(MAO-B)—> " dopamine metabolism"
Uses	Only used for refractory cases and in atypical depression where phobia and anxiety are prominent symptoms. Limited use because: 1- ADRs 2- Food and drug interactions 3- Low antidepressant efficacy = Low Benefit/ risk ratio.	
ADRs	- Antimuscarinic effects. -Postural hypotension. - Sedation,sleep disturbance. - Weight gain.	Specific ADRs for **Phenelzine** : -Hepatotoxicity. - Sexual dysfunction.
Cheese reaction	-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** :1-severe hypertension, 2-severe headache, 3- fatal intracranial haemorrhage. -No cheese reaction for ★ **Moclobemide**,	
DDI	Levodopa=mania+hypertensive crisis -Amphetamine & Ephedrine=hypertensive crisis -TCAs=hypertensive crisis -SSRIs=serotonin syndrome -Pethidine= severe hyperpyrexia, restlessness, coma, hypotension.	

L12&13 Antidepressants

New Group

Group	Drugs	M.O.A	Uses	ADRs	C.I
SSRIs "Selective Serotonin Reuptake Inhibitors"	Long acting (3-11 days): **Fluoxetine,** Moderate length (~24hr): Paroxetine, Sertraline, Citalopram **Escitalopram** **Fluvoxamine**	5-HT Reuptake inhibitors	• **Anxiety** disorders. • Eating disorders: -Bulimia nervosa (**Fluoxetine**), -Anorexia nervosa "restricting eating". • Post traumatic stress disorder (**PTSD**). • Attention Deficit Hyperkinetic Disorder (**ADHD**). • Treatment of **Premature Ejaculation** (via stimulation of **5HT2A**).	•5-HT3 stimulation: 1.GIT symptoms: ★**Nausea vomiting** & diarrhea. 2.Changes in appetite: •5-HT2A stimulation: **Sexual dysfunction**, **delayed ejaculation** •Sleep disturbances: Drowsiness with **Fluvoxamine**, • Anxiety & Tremors **Discontinuation syndrome**: • Symptoms are headache, malaise & flu-like symptoms, agitation , irritability & nervousness	-**inhibitors** of liver microsomal enzymes ; should not be used with **TCAs** -should not be used with **MAOIs** because of the risk of life threatening "**Serotonin syndrome**"
SARI Serotonin-2A Antagonist and Reuptake Inhibitors (SARI)	Trazodone Nefazodone	**Blocks 5-HT uptake selectively ;** powerful 5-HT2A antagonists	**-stimulates 5-HT1A** receptors, which may help reduce depression. -Block **5-HT2A** also reduces the risk of anxiety, sedation or **sexual** dysfunction	-	-
NaSSA Noradrenergic and specific serotonergic Antidepressants	★Mirtazapine	• **α2 receptors antagonist** • **Increases NE and 5-HT levels.** • **Blocks 5-HT2A, 5-HT3 reducing side effects of anxiety & Sexual dysfunction**	★★**Preferred in cancer patients because:** 1. Improves appetite. 2. ↓ **Nausea & vomiting** (Blocks 5-HT3). 3. ↑ Body weight. 4. Sedation (potent **Anti-histaminic).** 5. Less sexual dysfunction (5-HT2a blocking). 6. Has no antimuscarinic effects	Blocking 5-HT2C, and H1 receptors cause: - Sedation - Weight gain	-
SNRIs Serotonin and Noradrenaline Reuptake Inhibitors	Venlafaxine (Effexor)	**Selective 5-HT and NE uptake blockers**	• Depression • Generalized anxiety disorder • Social anxiety disorder in adults	-	-
NDRIs Norepinephrine & Dopamine Reuptake inhibitors	Bupropion	**NE (Norepinephrine) and DA (Dopamine) reuptake inhibitor, with no direct action on 5-HT.**	Treatment of major depression and bipolar depression. • Used for **smoking cessation** → As it reduces the severity of nicotine craving &withdrawal symptoms.	★**Seizures**; it ↓threshold of neuronal firing (increases the stimulating NT) → Similar to TCAs.	**Epilepsy**
NRIs Norepinephrine selective reuptake inhibitors	Reboxetine	**Blocks only NET** Norepinephrine transporter	**Safe to combine with SSRIs.**	Minimal side effects only related to activation of **ADR system** as : tremor, tachycardia, and urinary hesitancy.	-

L14: Headache & Migraine

Prophylaxis & Rescue

	Prophylaxis			Rescue	
	Antiepileptics	**Antidepressant**	**Antihypertensives**	**Analgesic**	**Antiemetic**
Drugs	**E.g. Topiramate, Valproic acid**	**TCAs; Amitriptyline & Nortriptyline**	**β-blockers; Propranolol**	**Acetaminophen**	**Dopamine Antagonists:** - **Domperidone** → Gastric-Prokinetic: ↑ Absorption & bioavailability of abortive therapy. - **Phenothiazines** (**Promethazine**): Has a sedative effect.
				NSAIDs: **-Aspirin** (weaker than Acetaminophen) **-Ibuprofen, Naproxen** → for mild to moderate attack with **no** nausea & vomiting.	**5-HT$_3$ Antagonists:** For severe nausea & vomiting. Eg: **Ondansetron, Granisetron.**
				Opioids: **Weak μ agonist → Tramadol** also inhibits 5HT reuptake.	**H$_1$ Antagonist:** Has Antihistamine, Sedative & Anticholinergic effects Eg: **Meclizine, diphenhydramine**
MOA	Block Na channel & augment GABA at GABAa receptors	5-TH & NA reuptake inhibitors	Beta blocker	-	-

Abortive

	Triptans			Ergots	
Drugs	Suma**triptan**	Zolmi**triptan**	Nara**triptan**	**Ergotamine Tartrate** Restricted: rare clinical use due to severe adverse effects	**DiHydroErgotamine** (DHE) Preferred in clinical setting
P.k	Present as: oral, nasal spray, & injectable forms Bioavailability: - Oral → low - **Subcutaneous** → 97% - Peaks after 2 min & t1/2 ~ 2h. (fast action with SC, good for patient with vomiting)	Present as: nasal spray Bioavailability: - Oral → 40%, - Peaks after 2h	Present as: injection, nasal spray and oral preparations Bioavailability: - Oral - 70% - Peaks after 2 h & t1/2 ~ 6h (slower onset; less side effects)	- Given: orally, sublingual, rectal suppository, inhaler. - Oral absorption is incomplete (erratic) & slow → low bioavailability. - Can be taken orally (Cafergot is a formula which contains caffeine & ergotamine). - Despite t1/2 nearly 2 h, ergotamine produces vasoconstriction → 24 h or longer due to high & long tissue binding ability. - Has significant side effects, and may worsen the nausea & vomiting associated with migraine.	- Given: parenterally, nasal spray, inhaler and injectable forms (**good to use if patient is vomiting).** - Eliminated more rapidly than ergotamin presumably due to its rapid hepatic clearance & has less adverse effects.
MOA	- **Selective agonism at 5-HT1 (5-HT1D/1B)** receptors. - Similar to ergotamine except that triptans are **more selective** as serotonergic agonist. - **No α1, α2, β-adrenergic, dopamine or muscarinic receptors.** - Inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem. - Inhibit transmission in the trigeminal nucleus caudalis.			1) **Non-selective partial agonism at 5-HT1 receptors:** (5-HT1D/1B found in cerebral & meningeal vessels) - ↓ Release of vasodilating peptides. - ↓ Excessive firing of nerve endings → reducing pain sensation. - At blood vessels → ↓ vasodilation & stretching of the pain endings. 2) **Partial agonist effect on α-adrenoceptors** → vasoconstriction .	
Uses	- To abort attacks in patients with: A) **frequent, moderate or B) infrequent but severe** attacks. -In cluster headache.			- Only used to **abort** the attacks (except DHE can be given for severe, recurrent attacks **not responding** to other drugs). - Their use is **restricted** to patients with **frequent, moderate** attack or **infrequent but severe** attacks.	
ADRs ★	- Most of ADRS are the same as with ergot **but triptans are better tolerated.** - Mild pain & burning sensation at the site of injection. - Vasospasm, **ischemic heart, angina & arrhythmias.** **- Zolmitriptan**: chest & neck tightness, **coronary vasospasm** & somnolence)			- GIT upset. **- Feeling of cold & numbness of limbs, tingling.** - Anginal pain due to coronary spasm, and disturbed cardiac rhythm (tachycardia or bradycardia). - **Prolong use** → **★ rebound headache** due to vasodilation followed by vasoconstriction. - **Prolong use & high dose** → paraesthesia (tingling or burning sensation).	
CI ★	- Peripheral vasospastic diseases. - Uncontrolled hypertension. - History of ischemia (may cause coronary spasm). - Cerebrovascular disorders - Renal or hepatic impairment. * **In concurrent use with MAOIs, lithium, SSRIs** → 5-HT increased to toxic level. * **In concurrent use with ergots** or others inducing vasospasm.			- Pregnancy; fetal distress & miscarriage (**ergot is uterine stimulant & vasoconstrictor).** - Peripheral & coronary vascular diseases. - Hypertension. - Liver & kidney diseases . - Prophylaxis of migraine. - In **concurrent use with triptans** (given at least 6 h from last dose of triptans or 24 h from stopping ergotamine & B-blockers).	

L15/ Drugs Used in Meningitis

1.B-Lactams Inhibitors of cell wall synthesis

M.O.A: Inhibit bacterial cell wall synthesis by inhibiting the peptidoglycan layer of bacterial cell wall (bactericidal).

Group	Penicillins		Cephalosporins (3rd G)	Carbapenems
Drugs	Penicillin G (benzyl penicillin) I.V	Aminopenicillins: Amoxicillin, Ampicillin I.V-I.M-pO	Ceftriaxone, Ceftazidime, Cefotaxime I.V	Imipenem I.V
Spectrum	-Narrow	-Broad/ gram + & -ve -Not active against pseudomonas aeruginosa	-Broad/ gram + & -ve -Highly effective against Gm –ve bacilli -Ceftazidime—> against P. Aeruginosa -Use: bacterial meningitis caused by pneumococci, meningococci, H. Influenzae	• Has a wide spectrum of activity (aerobic & anaerobic Gm -ve & Gm +ve bacteria, including pseudomonads)
P.K	-B-lactamase sensitive (penicillinase sensitive) -given IV -poor oral absorption Destroyed by gastric acidity -Short acting (4-6 hrs) -Half-life 30-60 min.	- B-lactamase sensitive: Given with B- lactamase inhibitors: 1-Amoxicillin + clavulanic acid (orally) 2-Ampicillin + sulbactam (I.V) **Combo intended to: prevent hydrolysis by the enzyme and extend spectrum* • are acid stable (effective orally) •Amoxicillin is better absorbed from the gut & not affected by food. •Can also be given I.V or I.M	- B-lactamase resistant	• Not absorbed orally, taken by **I.V** & Half- life about 1 hr. • **Inactivated by dehydropeptidase** in renal tubules to a less active & **nephrotoxic metabolite**, so it is co-formulated with the **dehydropeptidase inhibitor** for clinical use (**Cilastatin**) "↓toxicity" • Cilastatin has no antibacterial action, like b-lactamase inhibitors it only prolongs the action of the antibiotic • Penetrates body tissues and fluids including CSF. • Excreted primarily by the kidney, doses must be reduced in renal failure.
ADRs	-Hypersensitivity (Anaphylactic reactions). -Antibiotic associated diarrhea. Super-infections or secondary infections (candidiasis, oral thrush). -Nephritis -High dose in renal failure (seizure		• Allergy • GIT upset and diarrhea • Super-infection • Thrombophlebitis at site of injection "irritation" • Renal toxicity	• Skin rash & reaction at the site of infusion • Nausea, vomiting, diarrhea "GI upset" • Patients allergic to penicillins may be allergic to carbapenems • High doses may cause **seizure** in patients with renal failure

Group	2.Other inhibitor of cell wall synthesis	3.Inhibitors of protein synthesis (30S subunit)
Drug	Vancomycin (Mainly I.V)	Aminoglycosides: Gentamicin (I.V)
Activity	-Narrow(+ve bacteria) -Uses: 1.Meningitis ,combined with: -3rd gen cephalosporins for meningitis caused by penicillin resistant pneumococci -ampicillin/ceftazidime as an initial therapy of meningitis in infant, elderly and immunocompromised patient. *2. Uses other than meningitis* - against (MRSA) - orally to treat GIT infections caused by clostridium difficile (pseudomembranous colitis)	-Bactericidal -Not absorbed orally
ADRs	-Ototoxicity -Nephrotoxicity	
	-Phlebitis at site of injections -Histamine release(due to nonspecific mast cell degranulation) leading to: 1-Red man or red neck syndrome 2-Hypotension	Neuromuscular blockade (very high dose).

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