Drugs In Respiratory System

	Mechanism of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
β_2 Adrenoreceptor Agonists **(1st)** **Short acting:** *Salbutamol.* *Terbutaline.* **Long acting :** *Salmeterol* *Formoterol*	1. Smooth muscles relaxation. 2. Mast cells stabilization. 3. ↑ mucus clearance. 4. ↑ cAMP → bronchodilation	**Short acting:** ▪ Inhalation & (IV) attach during severe cases . ▪ Max effect =30 min. ▪ T 1/2= 4-6 h. **Long acting:** ↑ lipid solubility →inhalations. ▪ Slow onset ▪ Max effect= 30 min. ▪ T 1/2= 12 h. ▪ twice daily.	**Short acting:** The best choice for acute attack of asthma (*status asthmaticus*) **Long acting:** ▪ Adjacent therapy in patient inadequately controlled by glucocrticoides. ▪ Control nocturnal asthma	**3T's:** 1. Tremors. 2. Tolerance 3. Tachycardia **Advantages:** Minimal CVS side effects → Suitable for asthmatic patients with: ▪ Hypertension. ▪ Heart failure.
Muscarinic antagonists **(2nd)** *Ipratropium.* *Oxitropium.*	▪ Atropine derivatives ▪ Block all muscarinic receptors.	▪ inhalations . ▪ Not absorbed ▪ Slow onset ▪ = (30 min) ▪ $T_{1/2}$ =3-5 h .	▪ Adjuncts to β_2 agonists & steroids for acute asthma. ▪ COPD	▪ **Minimal central or systemic side effects:** - Dry mouth - Blurred vision

	Mechanism Of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Methylxanthines 1. ***Theophylline.*** 2. ***Aminophylline*** *(Theophylline + Ethylene diamine)*	▪ Phosphodiesterase inhibitors → ↑ cAMP → bronchodilation. ▪ Adenosine receptors antagonist **(A_1).** ▪ Anti inflammatory → mast cell stabilizer ▪ ↑ diaphragmatic contraction.	▪ Well absorbed orally → after meals. ▪ Metabolized by the liver P450 . ▪ **Low therapeutic index.** ▪ **<u>T ½ is *decreased* by:</u>** ☝Smoking & drinking ☝ Children. ☝Enzyme inducer ▪ **<u>T ½ *increased* by :</u>** ☝Liver dysfunction. ☝ (CHF , b-blockers). ☝Renal disease ☝Enzyme inhibitors	▪ Second line drug in asthma (orally), in addition to steroids in patient whose asthma does not respond well to B2-agonists ▪ For *status asthmaticus:* **slow IV loading** dose followed by **slow infusion** to prevent hypotension	**CNS:** insomnia, nervousness **GIT:** N,V & anorexia **CVS:** hypotension, arrhythmia and cardiac arrest. **Narrow safety margin.** ☝Monitoring of theophylline level is necessary (5-20 mg/L) .
Glucocorticoids	▪ –ve phospholipase A_2. ▪ ↓ T_{h2} cytokines ▪ Mast cell stabilizer. ▪ ↓ capillary permeability & mucosal edema. ▪ Up-regulate β_2 receptors. ▪	☝**1st : Inhalation** (*Fluticasone, Budesonide, Beclomethasone, Triamcinolone*). N.B. the best (*Fluticasone*) → less side effects ☝2nd :**PO** *(Prednisolone)* 3rd: **IV** only: *Hydrocortisone*	▪ As prophylactic agent **MAINLY.** ▪ 1st line in moderate to severe asthma→ **(inhalation)** ▪ *Status asthmaticus:* **IV** hydrocortisone. ▪ **<u>potentiated</u>** by B2 agonists . • ***Side effects :***	**Systematic** corticosteroids ☝Adrenal suppression. ☝Growth retardation. ☝Weight gain. ☝Bone loss. **Inhalation** has less AE 's : ☝candidacies (thrush). ☝Dysphonia

	Mechanism Of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Mast cell stabilizers *Sodium cromoglycate.* *Nedocromil.*	▪ Partially by mast cell stabilization ▪ Depress neuronal reflexes triggered by irritant receptors.	▪ Inhalation (aerosol, powder or nebulised solution). ▪ 10% is absorbed. ▪ T ½ is 19 minutes. ▪ Excreted unchanged in urine 50% and bile 50%.	▪ Prophylaxis of asthma especially in **children** ▪ Allergic rhinitis. ▪ Conjunctivitis.	▪ Minor URTI ▪ Hypersensitivity reaction ☝ **Contraindicated** in acute attack of asthma (reflex airway obstruction)☝.
5-lipoxygenase inhibitors *Zileuton*	▪ Block the production of Spasmogenic: ☝LTC_4 & LTD_4 ☝Chemotaxin (LTB_4).	▪ Given orally. ▪ Short duration of action. ▪ Short half life. ▪ Given 3-4 times daily.	▪ Mild to moderate asthma. ▪ Potentiate corticosteroid action.(low dose)→to↓adverse effects.	▪ Less effective than corticosteroids. ▪ Elevation of liver enzymes. ▪ Headache. ▪ Dyspepsia. ▪ Churg-strauss syndrome..
Leukotriene receptor antagonists *Zafirlukast.* *Pranlukast.* *Montelukast.* *Cinalukast*	▪ Potent competitive antagonist of LDT4 receptors.	▪ Taken orally	▪ Bronchodilators (1/3 of salbutamol). ▪ Mild asthma.. ▪ Aspirin induced asthma. ▪ Prevention of antigen and exercise induced bronchospasm	

Antipsychotic Agents

Mechanism of action of Antipsychotics	
Typical (traditional, old)	**Atypical (new)**
▪ D2 receptors blocking in the mesolimbic and mesofrontal system & other systems. ▪ Blocks $5HT_2$, H1 (histamine), α-adrenoreceptor and muscarinic receptors. So, ↑ side effects like increasing the body weight, incidence of DM and hyperlipidemia.	▪ Serotonergic (mainly)→$5HT_{2A}$ ▪ Dopaminergic blockers mainly in negative symptoms . ▪ It has low histamine, dopamine and autonomic effect. So, less adverse effects

Pharmacokinetics of Typical Antipsychotics			
Route of administration	**Absorption and distribution**	**Metabolism**	**Excretion**
▪ Orally (main). ▪ IV. ▪ Once/day at bed time → ↑ sedation. ▪ Fluphenazine & Haloperidol (IM) are long acting → every 4 weeks.	▪ Rapid but not complete ▪ Slow onset of action. ▪ Long T½= 10-24 hours. ▪ They are highly: 1. Lipid soluble →cross BBB & Placenta Plasma protein bind → drugs interactions.	▪ Completely in liver (1st pass) →↓ bioavailability. **Except** haloperidol & Thioridazine. ▪ Most of them produce not imp active metabolites, **Except** Mesoridazine which is more potent than the parent drug (Thioridazine).	▪ Kidney, as: 1. Metabolites (mostly) 2. Unchanged (less) ▪ Milk (contraindicated in lactation).

Typical Antipsychotics

Therapeutic Uses

Psychiatric illness:

1. Schizophrenia → **primary indication**.
2. Acute mania.
3. Manic depressive illness → during manic phase.
4. Schizoaffective disorders.
5. Non-manic excited state with BDZ.
6. Progressive senile dementia (Alzheimer type): atypical drugs used more.
7. Tourette's syndrome.

Non psychiatric :

1. Antiemetic .
2. Urticaria.
3. Anesthesia.
4. Sedation.

never in:

1. Pure anxiety .
2. OPIOID WITHDRAWAL

Adverse Effects

1) Behavior effects:
Pseudodepression &Toxic-confusional

2) Neurological effects:
Extrapyramidal & dyskinesia.

3) Seizures:
With chlorpromazine & clozapine

4) Eating disorders & wt gain:
with clozapine & olanzapine.

5) Antimuscarinic effects:
more with atypical.

6) CVS:
- Postural hypotension& tachycardia.
- ↑Q-T interval: mesoridazine.
- Torsade de pointes: ziprasidone.
- Fatal ventricular arrhythmia: Thioridazine overdose.

7) Metabolic & Endocrinal effects:
Weight gain. & Hyperprolactinemia in:
1. On ♀ : Galactorrhea , amenorrhea , ↑ libido, false-+ve pregnancy tests.
2. On ♂: Gynecomastia, impotence, ↓ libido.

8) Ocular adverse effects:
- Chlorpromazine & Quetiapine → deposits in cornea & lens.
- Thioridazine → **only** one causing (irreversible blindness, browning of vision, retinitis pigmentosa).

9) On H1 receptors: Sedation.

10) On blood:
- Agranulocytosis→ Clozapine
- Weekly blood count must be done .

11) Allergic reactions:
- Skin eruptions, dermatitis and obstructive jaundice.
- Skin pigmentations →Clozapine (purple color).

12) Neuroleptic Malignant Syn

13) Pregnancy teratogenic risk:
Relatively safe , but better to minimize or avoid uses.

Atypical Antipsychotics

	Mechanism of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Clozapine	- Binds more to D4 than D2 or D1 → less(EPS). - blocks 5HT2, α1 & H1 receptors. - Anticholinergic effects but it causes hypersalivation (instead of dry mouth).	- Bioavailability= 27-50 %. (1st pass metabolism) - T ½ = (12 hrs). - High protein bound. - Onset of action: several weeks. unlike typical drugs (rapid onset). - Cross BBB & distributed in breast milk. - Metabolize in the liver by CYP 1A2 & 3A4 to produce: 1. Active: Norclozapine 2. Inactive: Clozapine-N-oxide.	Used mainly to treat resistant cases, also when adverse effects such as EPS or TD are not indicated.	1. Agranulocytosis 2. toxicity in "2nd line) 3. Weight gain. 4. Postural hypotension. 5. Sialorrhea (↑ salivation). 6. Induce epileptic seizure 7. No drug - food interaction.(☺)
Risperidone	- Selective monoaminergic antagonist with ↑ affinity for both D2 (Typical) & 5HT2 receptors (Atypical).	- Orally (completely) absorbed. - In hepatic disease ↑ toxicity. - Both Risperidone & its metabolites increase PB. - Metabolized by liver CYP450 by (dealkylation). - Active metabolite (9 OH Risperidone) equal in efficacy to risperidone. - Excreted mainly in urine & in feces. - T ½ = 3 hr But metb= 42hr	1. in refractory cases of schizophrenia both +ve & -ve symptoms 2. in the treatment of dementia Only on Alzheimer, but not in Parkinson's disease.	- ↑ doses →Causes Extrapyramidal system dysfunction & ↓BP. - hyperprolactinemia. - Precipitate ventricular arrhythmia & ↑ Q-T interval. **(contraindicated in patients with long Q-T intervals)**.

Continue Atypical Antipsychotics

	Mechanism of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Olanzapine	**In vitro:** - Dopaminergic antagonist (D1 & 4). - Anticholinergic (M1 – M5) - Anti (5HT2 & H1). - α 1 – blockers . **In vivo:** - Potent antipsychotic. - Blocks both D2 & 5HT2 receptors, but mainly on 5-HT receptors → ↓ ↓ extra-pyramidal symptoms.	- Taken once daily & is well absorbed. - T ½= 21-54 hours (the longest). - The peak =6 hours. - 1st pass metabolism → p450 → inactive. - 93% is bound to α1-acid like protein.	1. Acute manic or mixed episodes associated with bipolar disorder. 2. IM →acute psychosis symptoms (psychotic agitation) associated with schizophrenia and bipolar mania	- Increase body weight - Dental pain and flu like syndrome. - Joint stiff & twitching. - Postural hypotension. - Sedation. - Flatulence, thirst & Sialorrhea. **Advantages** - ↓ incidence of EPS & hypotension. - Effective Vs both –ve & +ve symptoms.
Quetiapine	- Block both D2 & 5HT2 receptors but mainly on 5-HT.	- Has a short half-life. - Taken twice daily.	1. 1st line in Rx of schizophrenia. 2. refractory cases of schizophrenia **(DOC)** in old people with Alzheimer disease or with Parkinson's disease.	- Orthostatic hypotension. - Sedation & hyperglycemia - Leucopenia & neutropenia. But **NO Agranulocytosis**. - LEAST cause of weight gain. - enhance the effects of certain antihypertensive drugs.

Drugs in Migraine

	Mechanism of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
NSAIDs	- Inhibit Prostaglandin synthesis centrally	- taken with antiemetic to increase absorption & oral bioavailability	**Do not** cause withdrawal symptoms as opioids or rebound headache as *Ergotamine*	- Gastric upset → gastric bleeding or ulceration. - can be used with mild VC as Isometheptene.
Ergot alkaloids *Ergotamine.* *Dihydroergotamine.*	- Agonist and antagonist effects on 5HT2 receptors - Partial agonist effect on α adrenoreceptor - **Cumulative drug** (long duration)	- given by *all* routes - Its effect is potentiated by concomitant administration of β blockers (severe VC)	- more effective during acute attack of migraine **CONTRAINDICATION :** 1. Pregnancy & HTN 2. with beta blockers , 3. use with sumatriptan 4. For prophylaxis of migraine	- GIT symptoms (N, V, D) - Numbness, paraesthesia - **rebound headache** (prolonged use) - CNS (hallucination) - Ergotim (fibrosis)
Antiemetics *Metoclopramide.* *Domperidone.* *Cyclizine.*	- dopamine receptor antagonist	- *Domperidone* does not cross BBB (given as suppository)	- given at the onset of the attack as **adjective therapy** to reduce gastric symptom	- Sedation, diarrhea and Extrapyramidal effect (due to dopamine antagonism)
Sumatriptan	- Selective agonist at HT1 receptors - Selective cerebral VC	- given orally , S.C. - but I.V. (cause IHD) - Metabolized in liver - T ½ 2 hours (short)	- Acute attack of migraine - Acute cluster headache **CONTRAINDICATIONS :** 1. with ergotamine or beta blockers 2. *not* given IV 3. HTN & IHD	- Mild pain & burning sensation at the injection site. - paraesthesia, tingling, warmth - Flushing, Dizziness, HTN - Cardiac side effects (anginal pain , MI)
Methysergide	- 5HT2 receptor antagonist	- Anti-inflammatory - Given orally	- only for prophylaxis - Not used for more than 6 months - Not used with ergotamine or beta blockers or valvular diseases	- retroperitoneal . pericardial, plural or valvular fibrosis. - GIT symptoms

Opioid Analgesics

	Mechanism of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Morphine ***Natural Opioid***	▪ Agonists at opioids receptors: μ, δ, κ and σ. ▪ -ve excitatory transmitters. ▪ Hyperpolarization of cell membrane.	- **Not** effective orally → 1st pass hepatic metabolism - **given** parentally, suppository or epidural. - **Metabolized** in **liver** → active metabolite. - T ½ = 4-6 h - **Crosses** BBB & placenta. - **Mainly** excreted by the **kidney.**	▪ As analgesic . ▪ Severe diarrhea. ▪ Dry cough (antitussive effect). ▪ Acute pulmonary edema. ▪ Preanesthetic medication .	▪ Respiratory Depression. ▪ N,V& C ▪ Urine Retention. ▪ Hypotension. ▪ Itching & Urticaria. ▪ Tolerance: **Except** For **Miosis & Constipation.** ▪ Addiction: rihnorrhea, lacrimation, salivation, goose felsh, tachycardia, hypertension, mydrasis, NV.
Pethidine ***Synthetic opioid***		▪ Effective ***orally*** **and parentally.** ▪ Metabolized → **l**iver → **active metabolite that has (CNS toxicity).** ▪ Excretion →kidney**.** ▪ **T ½ = 2-4 h** ▪ **(the shortest one)**	▪ **Analgesia in:** 1. Cancer patient. 2. Severe pain. 3. Severe visceral pain. 4. Obstructed analgesia (less fetal depressant). ▪ **Preanesthetic medication.**	▪ **CNS:** (due to the active metabolite): tremors, convulsion & hallucination. ▪ **CVS:** hypotension and tachycardia ▪ Tolerance ▪ Addiction ▪ Mydriasis. ▪ Hyperthermia ▪ Dry Mouth.

	Mechanism Of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Codeine ***semi synthetic***	▪ Same as morphine with less addiction	▪ Well absorbed orally ▪ Shorter duration than ▪ morphine	▪ Potent antitussive ▪ Given in combination with aspirin or acetaminophen.	▪ Less potent as analgesic than morphine ▪ Less euphoria→ (**advantage)**
Methadone ***Synthetic opioid***	▪ Acts on opioids & non opioids receptors.	▪ Given **orally**, IV, SC or rectally ↑ oral bioavailability than morphine). ▪ **Longer T ½** = 24 h. (morphine 4-6 h)	▪ Detoxification & maintenance of withdrawal syndrome of opioids addict **(main use)** ▪ Severe oral & facial pain. ▪ opioids abuse.	▪ Less euphoric than morphine. ▪ Produce mild withdrawal syndrome. ▪ Tolerance & physical dependence develop more slowly than morphine.
Tramadol ***Synthetic opioid***	▪ Synthetic opioid (M receptors mainly) ➲**N.B.** Its analgesic effect blocked by **ondansetron**(5-HT3 antagonist).	▪ Different routs (PO ,IV, IM, SC, Rectaly, epidural).	▪ Acute visceral pain ▪ Atypical pain (chronic neuropathic pain) like facial pain.	▪ Seizures, nausea, dry mouth, ▪ Less adverse effect on respiratory & CVS.**(☺)** **☒Contraindicated in epileptic patient.**

	Mechanism Of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Fentanyl ***Synthetic opioid***	▪ Same as morphine	▪ IV ,IM Or transdermal Rapid onset & short duration of action	▪ Neuroleptanalgesia with droperidol ▪ Used as IV anesthesia ▪ transdermal patch →cancer patient	▪ Same to morphine
Pentazocine ***Mixed agonist/antagonist***	☝Agonist at κ & antagonist μ receptor	▪ high oral bioavailability. ▪ Short duration of action . ▪ Less potent than morphine.		▪ **CNS** : psychotic and hallucination ▪ **CVS**: HTN& tachycardia ▪ Convulsions **CONTRAINDICATIONS:** **1.** morphine. **2.** Cardiac or hypertension. **3.** Epilepsy (psychotic patient).
Buprenorphine ***Partial agonist/antagonist***	▪ Partial μ receptor agonist & κ antagonist.	▪ Poor oral bioavailability. ▪ Used parentally, sublingually or as a spray. ▪ Long duration of action.	▪ Is effective as methadone in the **detoxification & maintenance of heroin addiction.**	▪ It causes respiratory depression that is difficult to be reversed by naloxone (opioid antagonist).

Opioid Antagonists

	Mechanism Of Action	Pharmacokinetics	Clinical Uses	Adverse Effects
Naloxone	▪ Pure antagonist of μ (mu) receptor.	▪ **IV only.** ▪ Has rapid onset of action (second) ▪ short duration of action (30-60 min)	▪ For treatment of opioid overdose (acute toxicity)	**All opioid antagonists :** ▪ When given in absence of agonist → no effect ▪ In dependent subject (Addict) precipitate an abstinene syndrome ▪ No tolerance to their antagonist action ▪ No abstrenence syndrome with withdrawal after chronic use
Nalmefene	▪ Derivative of Naltrexone (same action)	▪ Given only by **IV** route ▪ Long T½ (8-10 h).	▪ Used to treat opioid overdosage.	
Naltrexone	▪ Same action	▪ Effective **orally** ▪ Long duration of action (10 h)	▪ Treatment of chronic alcoholism. ▪ maintenance for opioid addiction.	▪ **Hepatotoxic.**

Local Anesthesia

- *Activity of Local anesthetics increase with rise pH.*
- ***Esters** are hydrolyzed in blood by pseudocholinesterase. However, they can't be metabolized by acetylcholinesteras.e*
- ***Amides** are hydrolyzed by liver microsomal cytochrome P450.*
- *Amides act for longer duration of action than esters.*
- *Increased lipid solubility increases the potency*
- *Increased plasma protein binding increases the duration of action.*
- *Decreased pKa leads to rapid onset of action.*
- ***Cocaine** cause **vasoconstriction** where as other local anesthetic cause vasodilatation.*
- *All local anesthetics are arteriodilators which leads to hypotension except cocaine which produce vasoconstriction & hypertension.*
- ***bupivacaine** is more **cardiotoxic***
- ***Methemoglobinemia** usually with **prilocaine.***

Cocaine	Procaine (Novocaine)
- **Natural** alkaloid (ester). - CNS stimulant. - Small doses produce slowing of heart rate. - Moderate doses produce increase in the heart rate. - Produces **vasoconstriction.** - Anti-fatigue action on skeletal muscles. - Surface anesthetic (toxic). - Lead to addiction.	- Local anesthetic action effective only by injection. - Systemic analgesic action as given intravenously. - Antagonized the action of sulfonamides. - **Not** effective in Surface anesthesia.
Lignocaine (Lidocaine, Xylocaine)	**Tetracaine (Amethocaine)**
- Rapid, shorter than procaine - More potent and more effective - **Effective** in Surface anesthesia	- 2 times more powerfully than procaine but more toxic.
Nupercaine (Dibucaine, Cinchocaine)	**Carbocaine (Mepivacaine)**
- Very active local anesthetic, & very toxic. - Rapid and prolonged effect.	- Quicker onset of action and a longer duration than lignocaine.
Prilocaine (Citanest)	**Benzocaine (Ethyl 4-aminobenzoate)**
- Slower onset and longer duration of action than lignocaine.	- Water insoluble anesthetic - Slowly absorbed

Drugs for Peptic Ulcer

	Mechanism of action	Clinical Uses	Adverse effects	Comments
Antacids *NaHCO3, CaCO3* *Al (OH)3, Mg (OH)2*	Antagonize acid. And may indirectly decrease pepsin activity	-Treatment of H,pylori infection and prevention of further ulcer recurring. -Treatment of hypersecretory states (Zollinger–Ellison syndrome). -Prophylaxis from drug-induced peptic ulcer (NSAIDs). -Treatment of gastroesophageal reflux disease (GERD).	Diarrhea with (Mg) Constipation with (Al) Milk alkali syndrome with (Ca)	Sodium bicarbonate ($NaHCO_3$) → Cannot be given in heart failure**.**
Anti-secretory drugs *Cimetidine.* *Ranitidine.* *Famotidine.*	They competitively and reversibly bind to h2 receptors on the parietal cells		cimitidine is an enzyme inhibitor so it has alot of interactions & some anti-androgenic actions (Gynacomatsia)	- Rantidine are more potent than cimitidine.
Proton Pump inhibitors *Omeprazole* *Lansoprazole* *Pantoprazole*	**Irreversibly** binds to partial cell proton pump.		-Headache, nausea and diarrhea. -Decrease gastric acid secretion → hypergastremia & mucosal hyperplasia. -Gastric carcinoid	- shouldn't be used together with H2-antagonists or antacids→ they require gastric acidity.
Agents which protect mucosa *Sucralfate* *Bismuth subsalicylate* *Prostaglandins (misoprostol).*	**Sucralfate:** release of prostaglandins.		**Sucralfate** → Constipation **Bismuth subsalicylate** → -black stool -teeth discoloration -encephalopathy **Prostaglandins** → Diarrhea	Prostaglandins (misoprostol) are contraindicated in pregnancy (Abortion).

Drugs in Irritable Bowel Syndrome

	Mechanism of action	Clinical uses	Side effects
5-HT$_3$ receptor antagonists *Alosetron* *cilanestron*		Used for diarrhea associated IBS	1. Constipation 2. ischemic colitis
5-HT$_4$ partial agonist *Tegaserod*	-Stimulation of 5-HT4 receptor to enhance the release of ACH which increases peristalsis.	Used for constipation-predominant IBS in women.	1. Diarrhea 2. headache

DRUGS USED FOR GALLSTONES

- We can use the hydrophilic dehydroxylated bile acid ***ursodeoxycholic acid*** (Ursodiol)
- **Mechanism of action:** Gallstone dissolution by decreasing the ratio of cholesterol to bile acid.

Drugs used for Diarrhea

ADSORBANTS	**Kaopectin^R** (Kaolin + Pectin) works by adsorption of bacterial toxin **Bismuth subsalicylate** (Pepto-Bismol).	
ANTI-MOTILITY DRUGS	***Opioids like***	**Codeine sulphate:** Not preferred because it is a drug of abuse and it causes respiratory depression
		Diphenoxylate: Atropine is added to discourage abuse, because of thier anticholinergic effects.
		Loperamide (lmodium®).
	Anticholinergics (Antispasmodic Agents)	Propantheline, dicyclomine and mebeverine (smooth muscle relaxant).

Drugs for Nausea And Vomiting

H1 receptor antagonist	*Muscarinic receptor antagonists*	*D2 receptor antagonist*	*5-HT3 receptor antagonist*	*Cannabinoids*
Cyclizine: motion sickness. **Cinnarizine:** motion sickness, vestibular disorders (e.g. Meniere's disease). **Promethazine:** severe morning sickness of pregnancy (but only if absolutely essential).	**Hyoscine:** motion sickness (drug of choice). **Anti-**histamine and anticholinergics are both used as a prophylaxis in motion sickness but once it happens we give dopamine antagonists. -Hyosine and anti-histamines are not used for radiotherapy, cancer and post op nausea and vomiting. In these cases we use antiserotinergics and antidopaminergics	**1.Phenothiazines** (thiethylperazine): In vomiting caused by uremia, radiation, viral gastroenteritis (drugs of choice), severe morning sickness of pregnancy (but only if absolutely essential). Its uses have been significantly reduced because of extrapyramidal side effects. **2.Metoclopramide (Plasil):** vomiting caused by uremia, radiation, gastrointestinal disorders and the use of cytotoxic drugs. It is a 5HT3 blocker and dopamine blocker so, it also produces extrapyramidal side effects but less than phenothiazine. **3.Domperidone (Motilium^{R})**: It works on dopamine receptors **<u>peripherally</u>**. It has no 5HT3 blocking action. It has no extrapyramidal side effects.	e.g. Granisetron and Tropisetron. They are the drugs of choice for nausea and vomiting caused by cytotoxic anticancer drugs. Also used postoperative vomiting and radiation-induced vomiting. -Cause constipation. -They can be combined with dexamethasone (corticosteroid).	Used for vomiting caused by cytotoxic anticancer drugs.

LAXATIVES

Bulk forming laxatives

Drug	*Mechanism of action*	*Clinical uses*	*Adverse effects*
Hydrophilic *Psyllium* *Sterculia* *Methylcellulose &* *wheat bran*	Act by increasing the fecal mass → stimulation of peristalsis	- Hemorrhoids - Anal fissure - Pregnancy - Colostomy & ileostomy - IBS & UC - Chronic diarrhea as with diverticular disease.	-Decrease Ca and iron absorption. -Flatulence and abdominal distension. -Intestinal obstruction if not taken with enough water
Osmotic *inorganic (Mg sulphate)* *organic (Lactulose)*	retaining fluid in the bowel by osmosis → ↓pH and ↑ colonic peristalsis.	Liver cirrhosis in high doses	Flatulence

Stimulant laxatives

Natural	***Castor Oil*****(زيت الخروع)**:Broken down by lipase to ricinoleic acid (active form). Used for urgent laxation and contraindicated in pregnancy
	Senna and Cascara glycosides: hydrolyzed by bacterial flora to Senossides A & B (Active forms)
Synthetic	Diphenylmethane derivatives: Bisacodyl and Sodium Picosulfate. Phenolphthalein.
Glycerol *suppository in pediatrics*	***Advantages:*** Very effective and available as suppositories which may decrease the need for enema. ***Disadvantages:*** Abdominal cramp, prolonged use may lead to atonic nonfunctioning colon (Very Serious).

Stool Softeners

Lubricant Laxatives	Mineral oil and liquid paraffin. **Side effects:** Decrease absorption of fat soluble vitamins
Docusate sodium	Act by decreasing the surface tension

Drugs used in inflammatory Bowel Disease

Drug's name			Mechanism of action	Pharmacokinetics	Uses	Side effects
ANTI-INFLAMMATORY DRUGS	5-AMINOSALICYCLIC ACID	***Sulpha-containing***	Act by inhibiting prostaglandin and leukotriens synthesis, decrease neutrophil chemotaxis.	Sulfasalazine is prodrug composed of Sulfapyridine and 5- ASA which are linked together by Azo group. Sulfasalazine is a minimally (20-30 %) absorbed by intestine, secreted in the bile and hydrolysed by bacteria in the ileum and colon.	It is used in maintenance therapy less effective in acute attack. Use for ulcerative colitis and Crohn's colitis but not Crohn's of small intestine.	Nausea, vomiting and diarrhea Muscular pain (29%). Hypersensitivity reactions as: skin rash, fever and aplastic anemia because it contains sulpha group. Inhibits absorption of folic acid → megaloplastic anemia. Infertility in man (decrease sperm counts). However, it is safe in pregnancy. interstitial nephritis occurs with 5-aminosalicylic acid.
		Non-sulpha containing		**Mesalazine:** oral control release form of 5-ASA, has less side effects but expensive. **Olsalazine:** two molecules (dimer) of 5-ASA linked together by diazo bond.		**Mesalamine:** sulfa-free but irritant for upper GIT thus given rectally.
	Corticosteroids		Used for treatment of moderate and severe ulcerative colitis but less effective prophylactically. Used also for extracolonic manifestations such as ocular lesion, skin disease and peripheral arthritis. Used intravenously for the treatment of acute attacks.			

Continue **DRUGS IN IBD**			
	Mechanism of action	***Uses***	***Side effects***
Immuno-suppressive agents	*Azathioprine, Mercaptopurine, Cyclosporine & Methotrexate.* They act by suppressing the body's immune system.	Used for treatment of severe conditions and steroids dependent or resistant.	
Biological Therapy *Infliximab*	- TNF-a is an inflammatory cytokine which has a contributory role in producing chronic inflammation. - Infliximab (Remicade®) neutralizes TNF effects by blocking soluble TNF and transmembrane TNF. Thus may promote apoptosis of the mononuclear inflammatory cells through complement. - Is a monoclonal IgG antibodies (tumor necrosis factor, anti TNF-monoclonal antibody).	▪ **Induction** therapy with infliximab is indicated for treatment of refractory Crohn's disease and for reduction in the number of draining fistulas in fistulizing Crohn's disease. ▪ Indications for **maintenance** therapy with infliximab include maintenance of remission in active Crohn's disease patient who responded to initial induction therapy with infliximab and maintenance of fistula improvement who responded to initial therapy with infliximab. ▪ Used for induction and maintenance of rheumatoid arthritis . ▪ Used for induction and maintenance of remission in crohn's disease and rheumatoid arthritis.	1. Infusion-related like **hypersensitivity reaction** which is temporary and responds to a decrease in the infusion rate. 2. One report of a case of infliximab-associated **optic neuritis** with favorable outcome after systemic steroid treatment. 3. An **increase of infections** (some of them severe) has occurred, especially **tuberculosis.** 4. Other side effects that can be considered infrequent include demyelinization, heart failure, blood dyscrasias and lymphomas, which means that a thorough knowledge of these drugs is necessary for their use. 5. Immunogenicity and induction of DNA antibodies.

Antidepressants				
Drug name	**M.o.A**	**Pharmacokinetics**	**Clinical uses**	**Adverse effects**
Tricyclic Antidepressants (TCA) *Imipramine.* *Amitriptyline.*	inhibit the reuptake of norepinephrine & serotonin. Imipramine its active form Desipramine. Amitriptyline its active form Nortripyline	- Undergoes first pass metabolism. - Highly bound to plasma proteins. - Long plasma T ½. - Overdose is NOT treated by hemodialysis & peritoneal dialysis so we treat toxicity.	**1.** Depression **2.** Panic disorder **3.** Nocturnal enuresis **4.** anorexia nervosa **5.** Hyperactive children **6.** Attention deficit disorder **7.** Generalized anxiety disorder	1. Antimuscarinic effects: (dry mouth, ….) 2. Postural hypotension, arrhythmia and heart block. 3. Sexual dysfunction & impotence 4. Sedation & lower seizure threshold. 5. Weight gain and galactorrhea
Heterocyclics	LIKE (TCA) **2nd generation :** *Amoxapine* *Maprotiline* *Trazodone &* *Bupropion* **3rd generation:** *Nefazodone* *Venlafaxine &* *Mirtazapine*	LIKE (TCA) • ***Maprotiline*** has fewer sedation & antimuscarinic effects • ***Trazodone*** is a potent hypnotic. • ***Venlafaxine:*** 1. potent inhibitor of serotonin & NE re-uptake . 2. Less antimuscarinic effects → preferred in prostate hypertrophy 3. Decrease appetite & weight	• ***Amoxapine*** (dopamine receptor antagonist): **1.** depression in psychotic patient **2.** parkinsonism, amenorrhea-galactorrhea syndrome • ***Mirtazapine*** **1.** A potent antihistaminic **&** sedating effect **2.** Inhibit 5HT2 → decrease sexual function **3.** Inhibit 5HT3 → ↓N & V **4.** suitable drug in cancer patient → improve appetite → increase weight.	LIKE (TCA)

	Mechanism of action	Pharmacokinetics	Clinical uses	Side Effects
MAO Inhibitors **Hydrazides** *Phenelzine* **Non-hydrazides:** *Tranylcypromine* *Moclobemide*	inhibit the metabolism (breakdown) of neurotransmitters by MAO. ***Tranylcypromine:*** non selective (works on MAOa & MAOb) ***Moclobemide:*** selective (works on MAOa)	Readily absorbed. Persist for 7 days (tranylcypromine) or 2-3 weeks with (Phenelzine) after discontinuation of the drug. It is better to use one drug (monotherapy).	1. MAO b (dopamine) in parkinsonism disease 2. MAO a (serotonin & norepinephrine) in antidepressive drugs or use non selective group to treat ☒ **Contraindication:** 1. MAOI + SSRIs, 2. Pethidine + SSRIs (fetal syndrome), 3. Old cheese or TCA, 4. MAOI + sympathomimetic (hypertensive crisis).	1. Antimuscarinic effects. 2. Postural hypotension. 3. Sexual dysfunction (more with phenelzine). 4. Sedation in general & sleep disturbance with tranylcypromine. 5. Weight gain. 6. Sudden withdrawal leads to withdrawal symptoms
SSRIs *Fluoxetine, Fluvoxamine, Paroxetine & Citalopram*	inhibit the reuptake of serotonin	- Fluoxetine has a long plasma t1/2 (2 days), its active metabolite (norfuxetine)→ t½ = 7-9 days - Fluoxetine, fluvoxamine and citalopram are potent enzyme inhibitors	1. Depression 2. Obsessive-Compulsive Disorder (OCD) 3. Bulimia 4. Premature ejaculation 5. Social phobia.	1. Nervousness, agitation (mainly with fluoxetine) and sedation (mainly with paroxetine). 2. Sexual dysfunction e.g delayed ejection and decrease libido. 3. Weight loss, Nausea and diarrhea. 4. Mild antimuscarinic effects. They are preferred with prostatic hypertrophy. 5. Mild CVS effects.