Diuretics

Thiazide: Hydrochlorothiazide, Chlorothiazide, Chlorthalidone (Hygroton), Metolazone, and Indapamide. **Loop diuretics:** Furosemide (Lasix), Torsemide, Bumetanide (Bumex), and Ethacrynic acid. **Potassium-sparing diuretics:** Triamterene, Amiloride + H (Moduretic), Spironolactone (Aldactone) and Eplerenone (Eple-renone).

- Thiazide diuretics (They are sulfonamide derivatives) can be used as **initial drug therapy for hypertension unless** there are **compelling** reasons to choose another agent.
- Regardless of class, diuretics' initial mechanism of action is based upon **decreasing blood volume, which ultimately leads to decreased blood pressure.**
- **Low-dose** diuretic therapy **is safe**, **inexpensive**, and **effective** in preventing **stroke, myocardial infarction, and heart failure.**
- Routine serum electrolyte monitoring **should be done for all patients receiving diuretics.**
- **Dietary sodium restriction** has been known for many years to decrease blood pressure in hypertensive patients.
- **Effects of Diuretics**
- Diuretics lower blood pressure primarily by **depleting body sodium stores.**
- Initially, diuretics reduce blood pressure by **reducing blood volume and cardiac output; peripheral vascular resistance may increase.**
- **After 6–8 weeks, cardiac output returns to norma**l while **peripheral vascular resistance declines.**
- Sodium is believed to contribute to vascular resistance by **increasing vessel stiffness and neural reactivity**, possibly related to altered **sodium-calcium exchange with a resultant increase in intracellular calcium.** These effects are **reversed by diuretics or dietary sodium restriction.**
- Diuretics effectively lower blood pressure **by 10 - 15 mm Hg** in most patients, and diuretics alone often provide adequate treatment **for mild or moderate essential hypertension.**
- In more severe hypertension, diuretics are used in combination with **sympatholytic and vasodilator** drugs to control the tendency toward sodium retention caused by these agents.
- In severe hypertension, when multiple drugs are used, blood pressure may be well controlled when blood volume is 95% of normal but much too high when blood volume is 105% of normal.

Thiazide diuretics:

- **Thiazide diuretics**, such as **Hydrochlorothiazide, Chlorthalidone and Metolazone**, lower blood pressure initially by **increasing sodium and water excretion**. This causes a decrease in extracellular volume, decreasing cardiac output and renal blood flow.
- With long-term treatment, plasma volume approaches a normal value, but a **hypotensive effect** related to decreased peripheral resistance **persists**.
- Thiazides are useful in combination therapy with other antihypertensive agents, including **β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics.**
- Except for **Metolazone**, thiazide diuretics are ineffective in patients with **inadequate kidney function** (estimated glomerular filtration rate less than 30 mL/min/m^2). **Loop diuretics may be required in these patients.**
- **Thiazide** diuretics can induce **hypokalemia, hyperuricemia and, to a lesser extent, hyperglycemia in some patients.** New-onset diabetes has been reported more often with thiazides than with other antihypertensive agents. Patients with diabetes who are taking thiazides should monitor glucose to assess the need for an adjustment in diabetes therapy.
- **The efficacy of thiazides agents may be diminished with concomitant use of NSAIDs, such as indomethacin, which inhibit the production of renal prostaglandins, thereby reducing renal blood flow.**
- The thiazides can be useful in treating **idiopathic hypercalciuria**, because they inhibit urinary Ca^{2+} excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.

- Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can substitute for ADH in the treatment of nephrogenic **diabetes insipidus**. The urine volume of such individuals may drop from 11 L/d to about 3 L/d when treated with the drug.

Loop diuretics:

- The loop diuretics (**Furosemide, Torsemide, Bumetanide, and Ethacrynic Acid**) act promptly by **blocking sodium and chloride reabsorption** in the kidneys, **even** in patients with poor renal function or those who have **not responded to thiazide diuretics.**
- Loop diuretics cause decreased renal vascular resistance and increased renal blood flow. Like thiazides, they can cause **hypokalemia**. However, unlike thiazides, **loop diuretics increase the Ca^{2+} content of urine**, whereas thiazide diuretics **decrease it.**
- These agents are **rarely used alone** to treat hypertension, but they are **commonly used to manage symptoms of heart failure and oedema.**

Potassium-sparing diuretics:

- **Amiloride and Triamterene, directly acting** (acts by inhibiting Na^{+} reabsorption in the late distal tubules & collecting ducts). They have mild diuretic effects and cause Hyperkalemia.
- **Spironolactone and Eplerenone,** (**Aldosterone receptor antagonists**), reduce potassium loss in the urine. Aldosterone antagonists have the additional benefit of diminishing the cardiac remodelling that occurs in heart failure. **They have antiandrogen** activity and may cause male **sexual dysfunction** (Erectile dysfunction) & **Gynecomastia** (enlarged breast tissue in men)
- Used for: Hypertension, Heart failure, Severe acne, Hirsutism, Polycystic ovary, Hyperaldosteronism.
- In general, Potassium-sparing diuretics are sometimes combined with loop diuretics and thiazides to **reduce the potassium loss induced by these diuretics.**
- **Ototoxicity:** Reversible or permanent hearing loss may occur with loop diuretics, particularly when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics). Ethacrynic acid is the most likely to cause deafness.
- **Hyperuricemia:** Furosemide and ethacrynic acid compete with uric acid for the renal secretory systems, thus blocking its secretion and, in turn, causing or exacerbating gouty attacks.
- Acute hypovolemia: Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.
- **Hypomagnesemia:** Chronic use of loop diuretics combined with low dietary intake of Mg^{2+} can lead to hypomagnesemia, particularly in the elderly. This can be corrected by oral supplementation.

Use of Diuretics:

- **Thiazide diuretics** are appropriate for most patients with **mild or moderate** hypertension and **normal renal and cardiac function**.
- In comparison, all thiazides lower blood pressure, using **chlorthalidone** in preference to others. This is supported by evidence of improved 24-hour blood pressure control and reduced cardiovascular events in large clinical trials.
- **Chlorthalidone** is likely more effective than **hydrochlorothiazide** because it has a longer duration of action.
- More powerful diuretics (e.g., those acting on the loop of Henle) such as **furosemide** are necessary in **severe hypertension** when multiple drugs with **sodium-retaining properties** are used; **in renal insufficiency**, when glomerular filtration rate **is less than 30–40 mL/min**; and in **cardiac failure or hepatic cirrhosis,** in which sodium retention is marked.
- **Potassium-sparing diuretics** are useful **to avoid excessive potassium depletion** and **enhance other diuretics' natriuretic effects**.
- Although thiazide diuretics are more natriuretic at higher doses (up to 100–200 mg of hydrochlorothiazide) when used as a single agent, **lower doses (25–50 mg) exert as much antihypertensive effect as do higher**

doses. In contrast to thiazides, the **blood pressure response to loop diuretics continues to increase at doses many times greater than the usual therapeutic dose.**

- **Ascites:** Accumulation of fluid in the abdominal cavity (ascites)is a common complication of hepatic cirrhosis. **Spironolactone is effective in this condition.**
- **Polycystic ovary syndrome: Spironolactone is often used off-label** for the treatment of polycystic ovary syndrome. It blocks androgen receptors and inhibits steroid synthesis at high doses, thereby helping to offset increased androgen levels seen in this disorder.

Toxicity of Diuretics

- In the treatment of hypertension, the most common adverse effect of diuretics (except for potassium-sparing diuretics) is **potassium depletion**.
- Although **mild degrees of hypokalemia** are tolerated well by many patients, **hypokalemia may be hazardous in persons taking digitalis**, those who have **chronic arrhythmias**, or those with acute **myocardial infarction** or **left ventricular dysfunction**.
- **Potassium loss is coupled to sodium reabsorption**, and **restriction of dietary sodium intake minimizes potassium loss.**
- Diuretics may also cause **magnesium depletion**, **impair glucose tolerance**, and **increase serum lipid concentrations**.
- **Diuretics increase uric acid concentrations and may precipitate gout** (Diuretics can increase your risk of developing gout, a type of arthritis caused by the buildup of uric acid crystals in a joint. This may happen because diuretics increase urination, which reduces the amount of fluid in your body). The use of low doses minimizes these adverse metabolic effects without impairing the antihypertensive action.
- **Potassium-sparing diuretics** may produce **hyperkalemia**, particularly in patients with **renal insufficiency** and those taking **ACE inhibitors** or **angiotensin receptor blockers**; **spironolactone (a steroid) is associated with gynecomastia.**
- **Other possible side effects of diuretics include Frequent urination, Orthostatic hypotension, Dizziness, Headaches and Dehydration.**

Carbonic Anhydrase Inhibitor

- **Acetazolamide** and other carbonic anhydrase inhibitors are more often used for their other pharmacologic actions than for their diuretic effect because they **are much less efficacious than the thiazide or loop diuretics.**
- Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm).
- Acetazolamide **decreases the production of aqueous humor and reduces intraocular pressure** in patients with **chronic open-angle glaucoma**. Topical carbonic anhydrase inhibitors, such as **Dorzolamide and Brinzolamide**, have the advantage of **not causing systemic effects.**
- Acetazolamide can be used in the **prophylaxis** of **acute mountain sickness**. Acetazolamide prevents weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.
- Acetazolamide can be administered **orally or intravenously**. It is approximately 90% protein bound and eliminated renally by both active tubular secretion and passive reabsorption.
- **Adverse effects: Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur**. The drug should be avoided in patients with **hepatic cirrhosis because it could lead to a decreased excretion of Ammonium.**

Osmotic Diuretics

- A number of simple, hydrophilic chemical substances that are filtered through the glomerulus, such as **mannitol and urea**, result in some degree of **diuresis**. Filtered substances that undergo **little, or no reabsorption** will cause an increase in **urinary output**. The presence of these substances results in a higher osmolarity of the tubular fluid and **prevents further water reabsorption, resulting in osmotic diuresis**. Only

a small amount of additional salt may also be excreted. Because osmotic diuretics are used to **increase water excretion rather than Na^+ excretion, they are not useful for treating conditions in which Na^+ retention occurs.** They are used to maintain urine flow following **acute toxic ingestion of substances capable of producing acute renal failure.** Osmotic diuretics are a mainstay of treatment for patients with increased **intracranial pressure** or **acute renal failure** due to **shock, drug toxicities, and trauma**. Maintaining urine flow preserves long-term kidney function and may **save the patient from dialysis.**

- [Note: Mannitol is not absorbed when given orally and **should be given intravenously**.]
- Adverse effects include **extracellular water expansion and dehydration, as well as hypo- or hypernatremia.** The expansion of extracellular water results because the presence of mannitol in the extracellular fluid extracts water from the cells and causes hyponatremia until diuresis occurs.

Antihyperlipidemic Agents

- **HMG CoA Reductase Inhibitors (Statins):** Atorvastatin Lipitor, Fluvastatin Lescol, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin (Crestor), Simvastatin (Zocor).
- **Niacin:** Niacin.
- **Fibrates:** Gemfibrozil (Lopid) & Fenofibrate
- **Bile Acid Sequestrants:** Colesevelam (Cole-sevelam), Colestipol (Cole-stipol) & Cholestyramine.
- **Cholesterol Absorption Inhibitor:** Ezetimibe (Ezeti-mibe).
- **Omega-3 Fatty Acids:** Docosahexaenoic (docosa-hexa-enoic) acids and eicosapentaenoic (eicosa-penta-enoic) acids.
- **Various OTC preparations:** Icosapent ethyl (Icosa-pent-Ethyl).

HMG CoA reductase inhibitors

- A (HMG CoA) **reductase inhibitors** (commonly known as statins) lower elevated LDL, resulting in a substantial reduction in coronary events and death from CHD. They are considered **first-line treatment for patients with elevated risk of Atherosclerotic cardiovascular disease** (ASCVD). Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity.

- **Mechanism of action:**
- Lovastatin, simvastatin, pravastatin, atorvastatin, Fluvastatin, Pitavastatin, and rosuvastatin are **competitive inhibitors of HMG CoA reductase**, the rate-limiting step in cholesterol synthesis. Thus, plasma cholesterol is reduced, **by both decreased cholesterol synthesis and increased LDL catabolism.**
- **Pitavastatin, rosuvastatin, and atorvastatin are the most potent LDL cholesterol–lowering statins, followed by simvastatin, pravastatin, and then lovastatin and Fluvastatin.** The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL cholesterol levels in some patients.

- **Therapeutic uses:** These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias. However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.

- **Pharmacokinetics:**
- Absorption of the statins is variable (30% to 85%) following oral administration.
- All statins are metabolized in the liver, with some metabolites retaining activity.
- Excretion takes place principally through bile and feces, but some urinary elimination also occurs. Their half-lives are variable.
- Sometimes doctors may recommend taking it in the evening. This is because your body makes most cholesterol at night.

- **Adverse effects:**
- **Elevated liver enzymes** may occur with statin therapy. Therefore, liver function should be evaluated prior to starting therapy and if a patient has symptoms consistent with liver dysfunction. [Note: Hepatic insufficiency can cause drug accumulation.]
- **Myopathy and rhabdomyolysis** (disintegration of skeletal muscle; rare) have been reported. In most of these cases, patients usually had renal insufficiency or were taking drugs such as erythromycin, gemfibrozil, or niacin.
- Simvastatin is metabolized by cytochrome P450, and inhibitors of this enzyme may increase the risk of rhabdomyolysis.
- **Plasma creatine kinase** (PCK) levels should be determined in patients with muscle complaints.
- The HMG CoA reductase inhibitors may also **increase** the effect of **warfarin**. Thus, it is important to evaluate international normalized ratio (INR) frequently.
- These drugs are **contraindicated during pregnancy and lactation (Category X).**

Niacin (nicotinic acid)

- **Niacin** can reduce LDL by 10% to 20% and is the most effective agent for increasing HDL. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 grams/day.
- Niacin can be used in combination with statins, **and a fixed-dose combination of lovastatin and long-acting niacin is available.**

- **Mechanism of action:** At gram doses, niacin strongly **inhibits lipolysis** in adipose tissue, thereby reducing production of free fatty acids. The liver normally uses circulating free fatty acids as a major **precursor for triglyceride synthesis**. Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn **reduces LDL-C plasma concentrations**.

- **Therapeutic uses:** Since niacin lowers plasma levels of both cholesterol and triglycerides, it is useful in the treatment of **familial hyperlipidemias**. It is also used to treat other severe hypercholesterolemia, often in combination with other agents.

- **Pharmacokinetics:** Niacin is administered orally. Niacin, its nicotinamide derivative, and other metabolites are excreted in the urine.

- **Adverse effects:**
- The most common side effects of niacin are an intense cutaneous **flush** (accompanied by an uncomfortable feeling of warmth) and **pruritus.**
- Administration of **aspirin** prior to taking niacin decreases the flush, **which is prostaglandin mediated.**
- Some patients also experience nausea and abdominal pain. Slow titration of the dosage or usage of the sustained-release formulation of niacin reduces bothersome (annoying) initial adverse effects.
- Niacin inhibits tubular secretion of uric acid and, thus, predisposes to **hyperuricemia and gout.**
- Impaired glucose tolerance and hepatotoxicity have also been reported. The drug should be **avoided in hepatic disease.**

Fibrates

- **Fenofibrate** and **gemfibrozil** are derivatives of fibric acid that lower serum triglycerides and increase HDL levels.
- **Mechanism of action:**
- Lead to decreased triglyceride concentrations through increased expression of **lipoprotein lipase** and **decreasing apolipoprotein concentration.**
- **Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.**

- **Fibrates also increase the level of HDL cholesterol.**

- **Therapeutic uses:**
- The fibrates are used in the treatment **of hypertriglyceridemia.** They are particularly useful in treating type III hyperlipidemia.

- **Pharmacokinetics:**
- Gemfibrozil and fenofibrate are completely absorbed after oral administration and distribute widely, **bound to albumin.**
- **Fenofibrate is a prodrug**, which is converted to the active moiety **fenofibric acid.**
- Both drugs undergo extensive biotransformation and are excreted in the urine.

- **Adverse effects:**
- The most common adverse effects are mild gastrointestinal (GI) disturbances. These lessen as the therapy progresses.
- Because these drugs increase biliary cholesterol excretion, there is a predisposition to form **gallstones.**
- **Myositis** (inflammation of a voluntary muscle) can occur, and muscle weakness or tenderness should be evaluated.
- Patients with renal insufficiency **may be at risk.**
- Myopathy and rhabdomyolysis have been reported in patients taking **gemfibrozil and statins together.**
- The use of gemfibrozil is **contraindicated** with simvastatin.
- Both fibrates may **increase** the effects of warfarin. INR should, therefore, be monitored more frequently when a patient is taking both drugs.
- Fibrates **should not be used** in patients **with severe hepatic or renal dysfunction or in patients with preexisting gallbladder disease.**

- **Bile acid–binding resins:** Bile acid resins have significant LDL cholesterol–lowering effects, although the benefits are **less than those observed with statins.**

- **Mechanism of action:** Cholestyramine, Colestipol, and Colesevelam are anion-exchange resins that **bind negatively** charged bile acids and bile salts in the small intestine. The resin/bile acid complex **is excreted in the feces**, thus lowering the bile acid concentration.
- This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL.
- **Therapeutic uses:**
- The bile acid–binding resins are useful (often in combination with diet or niacin) for treating hyperlipidemias.
- Cholestyramine can also relieve **pruritus caused by accumulation of bile acids** in patients with biliary stasis.
- **Colesevelam is also indicated for type 2 diabetes due to its glucose-lowering effects.**

- **Pharmacokinetics:** Bile acid sequestrants are insoluble in water and have large molecular weights. After oral administration, they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in feces.

- **Adverse effects:** The most common side effects are **GI disturbances, such as constipation, nausea, and flatulence.** Colesevelam **has fewer GI side effects** than other bile acid sequestrants. These agents may impair the absorption of the fat-soluble vitamins (A, D, E, and K), and they **interfere with the absorption of many drugs (for example, digoxin, warfarin, and thyroid hormone).** Therefore, other drugs should be taken **at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid–binding resins. These agents may raise**

triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥400 mg/dL).

Cholesterol absorption inhibitor

- **Ezetimibe** selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a **reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.** Ezetimibe lowers LDL cholesterol by approximately 17%. Due its modest LDL-lowering effects, **ezetimibe is often used as an adjunct to statin therapy or in statin-intolerant patients.** Ezetimibe is primarily metabolized in the small intestine and liver. Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe. **Adverse effects are uncommon with use of ezetimibe.**

Omega-3 fatty acids Omega-3

- **(Poly Unsaturated Fatty Acids) (PUFAs)** are essential fatty acids that are predominately used **for triglyceride lowering.** Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 PUFAs **eicosa**penta**enoic** acid (EPA) and **docosa**hexa**enoic** acid (DHA) are found in marine sources such as **tuna, halibut, and salmon**. Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, **with small increases in LDL-C and HDL-C.** Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone.

- **Icosapent ethyl** is a prescription product that contains only EPA and, unlike other fish oil supplements, **does not significantly raise LDL.** Omega-3 PUFAs can be **considered as an adjunct to** other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL). Although effective for triglyceride lowering, omega-3 PUFA supplementation **has not been shown to reduce cardiovascular morbidity and mortality.** The most common side effects of omega-3 PUFAs include **GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelets.**

Combination drug therapy: It is often necessary to use two antihyperlipidemic drugs to achieve treatment goals in plasma lipid levels.

- **The combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has been shown to be very useful in lowering LDL levels.**
- **Simvastatin and ezetimibe, as well as simvastatin and niacin, are currently available combined in one pill to treat elevated LDL cholesterol.**
- Many experts recommend maximizing statin dosages and adding niacin or fibrates only in those with **persistently elevated triglycerides** (greater than 500 mg/dL) or those with **low HDL cholesterol levels (less than 40 mg/dL).** Combination drug therapy **is not without risks.** Liver and muscle toxicity occurs more frequently with **lipid-lowering drug combinations.**

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓

Figure 23.12

Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

Characteristic	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Serum LDL cholesterol reduction produced (%)	55	24	34	43	34	60	41
Serum triglyceride reduction produced (%)	29	10	16	18	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	8	12	8	12
Plasma half-life (h)	14	1–2	2	12	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	15	20	10	13

Figure 23.6

Summary of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. LDL = low-density lipoprotein; HDL = high-density lipoprotein.

TIKRIT UNIVERSITY

Pharmacy College

Pharmacology

PCTU (2023-2024)

Drugs Used in the Respiratory System

Year 4

Dr. SINAN MOHAMMED

Respiratory System

1.Drugs Used in **Treatment of Cough**
2.Cough is a protective reflex intended **to remove irritants and accumulated secretions** from the respiratory passages.

Drugs used in the symptomatic treatment of cough are:

1. **Antitussives (cough centre suppressants):** Codeine, dextromethorphan, antihistamines.
2. **Pharyngeal demulcents** Lozenges, liquorice.
3. **Expectorants:** Potassium iodide, guaiphenesin, ammonium chloride.
4. **Mucolytics** Bromhexine, acetylcysteine.

Cough may be:

1. Productive cough: Helps to clear the airway. Suppression of productive cough is harmful as it may lead to infections. Treatment includes antibiotics for infection, expectorants and mucolytics for cough.
2. Nonproductive cough: It is useless and should be suppressed.

Antitussives

They inhibit the cough reflex by suppressing the cough centre in the medulla. They are used for the **symptomatic treatment** of **dry, unproductive cough**. Antitussives should be avoided in children below the age of 1 year.

1.Codeine:

1. Has **cough centre suppressant** effect.
2. It causes mild CNS depression; hence, drowsiness can occur.
3. Causes constipation by decreasing intestinal movements.

2.Dextromethorphan: It is a **centrally acting** antitussive agent. It **has no** analgesic properties and does not cause constipation and addiction.

3.Antihistamines: Diphenhydramine, chlorpheniramine, promethazine, etc., help cough due to their sedative, antiallergic, and anticholinergic actions. They produce symptomatic relief in colds and coughs associated with allergic conditions of the respiratory tract.

Pharyngeal Demulcents

Syrups, lozenges or liquorice may be used when a cough arises due to irritation above the larynx. They increase salivation and produce a protective, soothing effect on the inflamed mucosa.

Expectorants (Mucokinetics)

They increase the volume of bronchial secretion and reduce the viscosity of the sputum; hence, the cough becomes less tiring and productive. They include iodides, chlorides, bicarbonates, acetates, volatile oils, etc. These drugs are useful in the **treatment of chronic cough.**

Mucolytics

These agents break the thick, tenacious sputum and lower the viscosity of sputum, so that the sputum comes out easily with less effort. E.g.
Bromhexine: The side effects are rhinorrhea and lacrimation.
Acetylcysteine and carbocisteine: The side effects are nausea, vomiting and bronchospasm.

Drugs Used In the Treatment of Bronchial Asthma

- In bronchial asthma, there is impairment of airflow due to **contraction of bronchial smooth muscle (bronchospasm), swelling of bronchial mucosa (mucosal oedema) and increased bronchial mucus secretion.**

- Several factors may precipitate attacks of asthma in susceptible individuals: **They include allergy, infection and psychological factors.**
- Airway obstruction in asthma is mainly due **to the release of mediators from sensitized mast cells in the lungs.** They are **histamine, serotonin (5-HT), PGs, leukotrienes, etc.**

Bronchial asthma may be either episodic or chronic.

- **Acute asthma:** It is characterized by episode of **dyspnoea associated with expiratory wheezing.**

- **Chronic asthma:** Continuous wheezing and breathlessness on exertion; cough and mucoid sputum with recurrent respiratory infection are common.
- **Status asthmaticus (acute severe asthma):**
- When an attack of asthma is prolonged with severe **intractable wheezing, it is known as acute severe asthma.**

Classification of anti-asthmatic drugs

1. **Bronchodilators**

a. Sympathomimetics

I. Selective β_2-adrenergic agonists: Salbutamol and Terbutaline short-acting.

II. Nonselective: Adrenaline.

b. *Methylxanthines:* Theophylline, aminophylline.

c. *Anticholinergics:* Ipratropium bromide.

2. Leukotriene receptor antagonists: Montelukast.

3. Mast cell stabilizers: Sodium cromoglycate, ketotifen.

4. Glucocorticoids

a. ***Inhaled glucocorticoids:*** Beclomethasone, fluticasone.

b. ***Systemic glucocorticoids:*** Hydrocortisone, prednisolone, methylprednisolone.

Adrenaline (non-selective sympathomimetic)
Bronchodilatation is useful in an **acute attack of asthma**. Its use has declined because of its **dangerous cardiac side effects.**

Selective β_2-adrenergic agonists
Salbutamol and Terbutaline short-acting **are the first-line bronchial asthma drugs**. They are well tolerated when inhaled. At high doses, they may cause **tremors, tachycardia, palpitation, hypokalemia and rarely cardiac arrhythmia**.

Methylxanthines

The use of methylxanthines in asthma has markedly diminished because of their **narrow margin of safety**. They can cause **tachycardia, palpitation, hypotension (due to vasodilatation) and sometimes sudden death due to cardiac arrhythmias.**

SRS-A: The slow-reacting substance of anaphylaxis

Mechanism of action

- Theophylline
- Aminophylline

→ Inhibit phosphodiesterase (PDE) → ⇧cAMP →

- Bronchodilatation
- Inhibit the release of histamine and SRS-A from mast cells
- Improve mucociliary clearance in respiratory passages

Anticholinergics

- **Ipratropium bromide and tiotropium bromide** are **atropine** substitutes. They selectively block the effects of acetylcholine in the bronchial smooth muscles and **cause bronchodilatation.**
- They have a **slow onset of action** and are less effective than sympathomimetic drugs in bronchial asthma.
- These anticholinergics are the **preferred bronchodilators in COPD and can also be used in bronchial asthma.**
- They are administered by inhalational route.
- Combined use of ipratropium with $\boldsymbol{\beta 2}$ adrenergic agonists produces more significant or more prolonged bronchodilation; hence, they are used in acute and severe asthma.

Leukotriene Antagonists

- These drugs competitively block the effects of leukotrienes on **bronchial smooth muscle**.
- Thus, they produce **bronchodilatation**, suppress **bronchial inflammation** and decrease **hyperreactivity**.
- They are well absorbed after oral administration, highly bound to plasma proteins and metabolized extensively in the liver.
- They are effective for the **prophylactic treatment of mild asthma.**
- They are well tolerated and produce fewer adverse effects, such as **headaches and skin rashes.**

Mast Cell Stabilizers

- **Sodium cromoglycate** and **ketotifen** are mast cell stabilizers. **They are not bronchodilators.**
- They inhibit the release of various mediators, histamine, LTs, PGs, etc., by stabilizing the mast cell membrane.
- They also **reduce bronchial hyperreactivity to some extent, but antigen–antibody reaction** (AG–AB reaction) **is not affected.**

Sodium cromoglycate is not effective orally as it is **poorly absorbed** from the gut. **In bronchial asthma, sodium cromoglycate is given by inhalation.**

Uses

1.Allergic asthma: Sodium cromoglycate is used as **a prophylactic agent** to prevent **bronchospasm induced by allergens and irritants**.

2.It can also be used in **allergic conjunctivitis, rhinitis, and dermatitis.**

Ketotifen: The mechanism of action is like sodium cromoglycate, which has an additional **H_1-blocking effect**. It is orally effective but has a slow onset of action.

Glucocorticoids

1. **Systemic:** Hydrocortisone, prednisolone, methylprednisolone and others.
2. **Inhalational:** Beclomethasone, fluticasone, etc.

Glucocorticoids have **antiallergic, anti-inflammatory and immunosuppressant effects.**

They:

1. Suppress inflammatory response to AG–AB reaction.
2. Decrease mucosal oedema.
3. Reduce bronchial hyperactivity.

Glucocorticoids do not have a direct **bronchodilating effect but potentiate the effects of *β*-adrenergic agonists.**

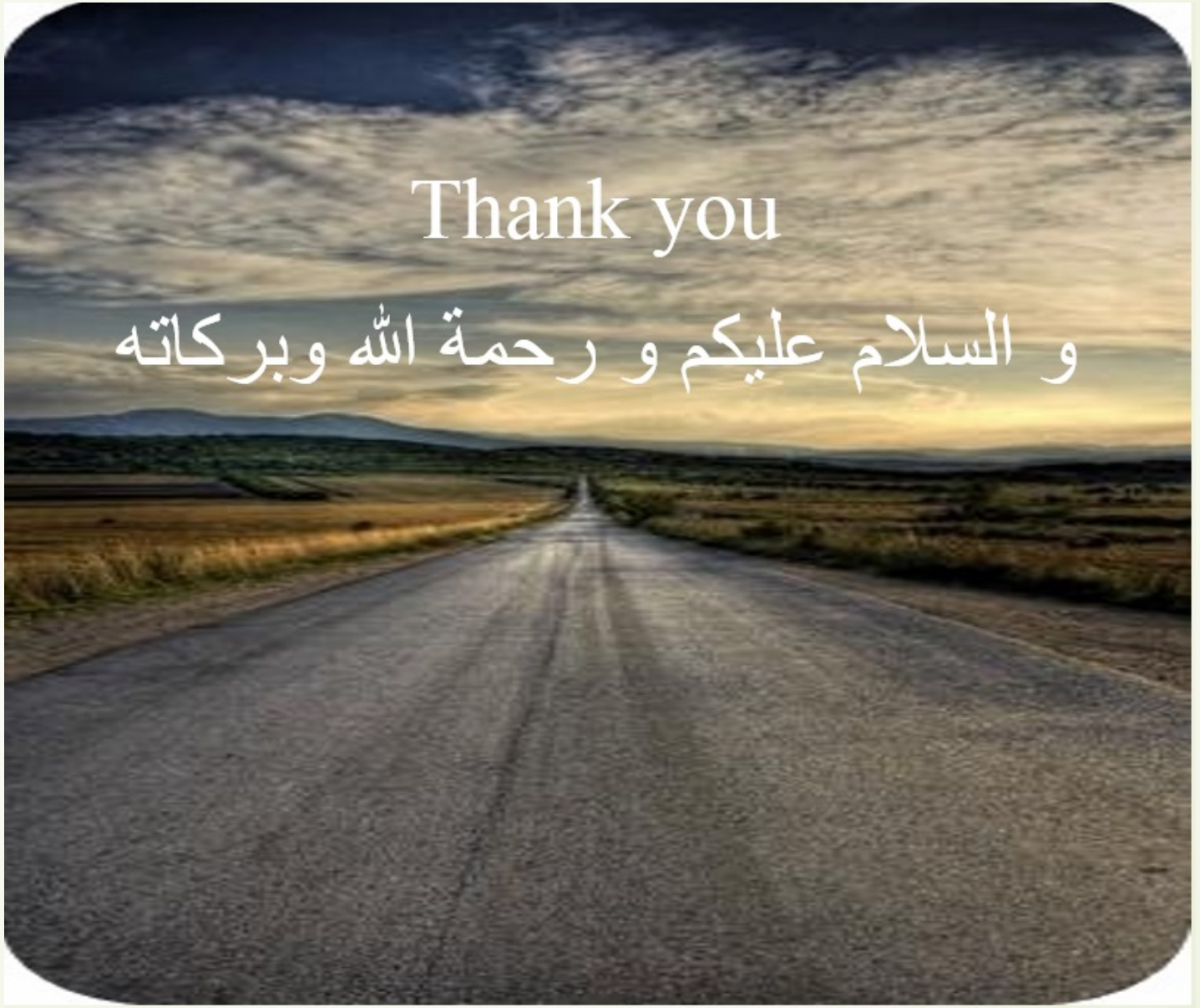
Inhaled glucocorticoids such as beclomethasone, budesonide and fluticasone are **prophylactic agents in bronchial asthma.**

Glucocorticoids

- The common side effects **are hoarseness of voice, dysphonia and oropharyngeal candidiasis**.
- These can be reduced by using a spacer rinsing the mouth after each dose and can be treated effectively **by topical antifungal agent nystatin.**
- A combination of a long-acting ***β***-agonist with a steroid is available, e.g., fluticasone + salmeterol; budesonide + formoterol. They have synergistic action; used in bronchial asthma and COPD.
- Systemic glucocorticoids are used in acute severe asthma and chronic severe asthma.
- **Long-term use of systemic steroids produce severe side effects such as gastric irritation, Na^+ and water retention, hypertension, muscle weakness, osteoporosis, hypothalamo–pituitary–adrenal axis (HPA axis) suppression, etc.**

Treatment of Acute Severe Asthma (Status Asthmaticus)

1.Oxygen inhalation.
2.Nebulized **β2 -adrenergic agonist** (salbutamol /terbutaline) + **anticholinergic agent** (ipratropium bromide).
3.Systemic **glucocorticoids**: Intravenous hydrocortisone or oral prednisolone, depending on the patient's condition.
4.Intravenous fluids to correct dehydration.
5.Potassium supplements: To correct **hypokalaemia** produced by repeated doses of salbutamol/ terbutaline.
6.Sodium bicarbonate to treat acidosis.
7.Antibiotics to treat infection.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TIKRIT UNIVERSITY

Pharmacy College

Pharmacology

PCTU (2023-2024)

Drugs Used in the Treatment of Gastrointestinal Diseases

Year 4

Dr. SINAN MOHAMMED

Drugs used in the treatment of Gastrointestinal diseases

1. Drugs used in acid-peptic diseases
2. Mucosal protective agents
3. Drugs that act on gastric motility (Nausea and vomiting)
4. Drugs used in Constipation (Laxatives)
5. Drugs used in non-specific diarrhoea (Antidiarrheal agents)
6. Drugs used to treat inflammatory bowel disease (IBD)
7. Bile acid agents
8. Irritable bowel syndrome (IBS)
9. Pancreatic enzyme supplements

Drugs Used in Acid-peptic Diseases

Antacids and antacid/alginate preparations

- Antacids are weak alkalis (bases), so they **partly neutralize** free acid in the stomach.
- They may also stimulate **mucosal repair** mechanisms around ulcers, possibly through local prostaglandin release.

Physiology of Acid Secretion

- The parietal cell contains **Gastrin**, **Histamine** (H_2), and **Acetylcholine** receptors**.**
- When acetylcholine and gastrin bind to the parietal cell receptors, they cause an **increase in cytosolic calcium**, which stimulates **protein kinases** that **stimulate acid secretion** from a H^+/K^+-ATPase (the proton pump).

1. Sodium bicarbonate reacts rapidly with hydrochloric acid (HCl) to produce **carbon dioxide**[1] and **sodium chloride**[2].

- Formation of carbon dioxide results in **gastric distention and belching (burp).**
- Unreacted alkali is readily absorbed, potentially causing **metabolic alkalosis when given in high doses or to patients with renal insufficiency.**
- **Sodium chloride** absorption may **exacerbate fluid retention** in patients with heart failure, hypertension, and renal insufficiency.

2. Calcium carbonate is less soluble and reacts more slowly than sodium bicarbonate with HCl to form **carbon dioxide** and calcium chloride.

- Like sodium bicarbonate, calcium carbonate may cause **belching or metabolic alkalosis**.
- Excessive doses of either sodium bicarbonate or calcium carbonate with calcium-containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (**milk-alkali syndrome**).

3. Formulations containing magnesium hydroxide or aluminium hydroxide react slowly with HCl to form **magnesium chloride**[1] or **aluminium chloride**[2] and water.

- Because no gas is generated, belching does not occur. Metabolic alkalosis is also uncommon because of the efficiency of the neutralization reaction.
- **Because unabsorbed magnesium salts may cause osmotic diarrhoea and aluminium salts may cause constipation, these agents are commonly administered together.**
- Both magnesium and aluminium are absorbed and excreted by the kidneys. Hence, patients with renal insufficiency **should not** take these agents long-term.
- All antacids may **affect the absorption of other medications** by binding the drug (reducing its absorption) or by increasing intra-gastric pH so that the drug's dissolution or solubility (especially weakly basic or acidic drugs) is altered. Therefore, **antacids should not be given within 2 hours** of doses of **tetracyclines, fluoroquinolones, itraconazole, and iron.**

H_2 - Receptor Antagonists

- Four H_2 antagonists are in clinical use: Cimetidine, Ranitidine, Famotidine, and Nizatidine.
- All four agents are rapidly absorbed from the intestine.
- Cimetidine, ranitidine, and famotidine **undergo first-pass hepatic metabolism,** resulting in a bioavailability of **approximately 50%.**
- Nizatidine has **little** first-pass metabolism.
- The serum **half-lives** of the four agents range from **1.1 to 4 hours**; however, the duration of action depends **on the dose given**.
- A combination clears H_2 antagonists of hepatic metabolism, glomerular filtration, and renal tubular secretion.
- Dose reduction is required in patients with moderate to severe renal (and possibly severe hepatic) insufficiency.
- In the elderly, there is a decline of up to 50% in drug clearance , as well as a significant reduction in volume of distribution.

- H_2-receptor antagonists are **competitive antagonists** for histamine at the H_2-receptor found on parietal cells, resulting in **reduced acid secretion** by the parietal cells.
- They are highly selective and do not affect H_1 or H_3 receptors.
- They are **less effective** in reducing **food-stimulated acid secretion.**
- The volume of gastric secretion and the concentration of pepsin are also reduced.
- H_2 antagonists are especially **effective** at **inhibiting nocturnal acid secretion (which depends largely on histamine), but they have a modest impact on meal-stimulated acid secretion (which is stimulated by gastrin and acetylcholine as well as histamine).**
- Recommended prescription doses maintain greater than 50% acid inhibition for 10 hours; hence, these drugs are commonly **given twice daily.** At doses available in over-the-counter formulations, the duration of acid **inhibition is 6–10 hours**.

Clinical Uses

H_2-receptor antagonists continue to be prescribed, but PPIs are more commonly prescribed than H_2 antagonists for most clinical indications.

1. **Gastroesophageal reflux disease (GERD).**
2. **Peptic ulcer disease**.
3. **Non-ulcer dyspepsia:** H_2 antagonists are commonly used as over-the-counter and prescription agents for treating intermittent dyspepsia not caused by peptic ulcer.
4. **Preventing bleeding from stress-related gastritis: Clinically important bleeding from upper gastrointestinal erosions or ulcers occurs in 1–5% of critically ill patients due to** impaired mucosal defence mechanisms caused by poor perfusion.

Adverse Effects

- H_2 antagonists are extremely safe drugs. Adverse effects occur in less than 3% of patients, including **diarrhoea, headache, fatigue, myalgias, and constipation.**
- Some studies suggest that intravenous H_2 antagonists (or PPIs) may increase the risk of **nosocomial pneumonia** in critically ill patients.
- Mental status changes (**confusion, hallucinations, agitation**) may occur with the administration of intravenous H_2 antagonists, especially in patients in the intensive care unit who are elderly or who have renal or hepatic dysfunction. These events may be more common with **cimetidine.**
- **Cimetidine** inhibits the binding of **dihydrotestosterone** to androgen receptors, **inhibits estradiol metabolism**, and **increases serum prolactin levels**. When used **long-term** or in **high doses**, it may cause **gynecomastia or impotence** in men and **galactorrhoea** in women. These effects are specific to **cimetidine** and do not occur with the other H_2 antagonists.

- Although no known harmful effects exist on the fetus, H_2 antagonists cross the placenta. Therefore, they should not be administered to pregnant women **unless** necessary.
- The H_2 antagonists are **secreted into breast milk** and may affect nursing infants.
- Rapid intravenous infusion may cause **bradycardia and hypotension** through the blockade of cardiac H_2 receptors; therefore, intravenous infusions **should be given over 30 minutes**.
- **NOTE:** In the heart, two types of histamine receptors are present: H_1- and H_2-receptors. H_2-receptors cause an increase in heart rate, contractility, and coronary vasodilatation, whereas H_1-receptors mediate **chronotropic** effects and coronary vasoconstriction.

Drug Interactions

- Cimetidine interferes with several important hepatic cytochrome P450 drug metabolism pathways. Hence, the **half-lives** of drugs metabolized by these pathways may be **prolonged**. (Enzyme inhibitor)
- Ranitidine binds 4–10 times less than cimetidine to cytochrome P450.
- Negligible CYP (Cytochrome P450 Family) interaction occurs with nizatidine and famotidine.
- H_2 antagonists **compete** with creatinine and certain drugs (eg, procainamide) for renal tubular secretion.
- All these drugs, except **Famotidine**, inhibit gastric **first-pass metabolism** of **Ethanol**, especially in women, and could increase blood ethanol levels.

NOTE: Alcoholic liver disease develops **more readily in women than in men**. Women also have higher blood ethanol concentrations than men after an equivalent oral dose. This difference has been attributed to a **smaller volume of distribution of ethanol because of a lower water content in the body in women than in men.** However, blood ethanol concentrations in women and men are similar after intravenous administration. An alternative explanation for the sex-related differences in blood concentrations of ethanol after its ingestion could be differences in **the stomach's capacity to oxidize ethanol.**

Proton pump inhibitors (PPIs)

Six PPIs are available for clinical use: **Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole And Esomeprazole.**

Pharmacodynamics

- In contrast to H_2 antagonists, PPIs inhibit **fasting and meal-stimulated secretion** because they block the **final common pathway** of acid secretion, the proton pump.
- The proton pump is an enzyme (H^+/K^+-ATPase) that actively secretes **hydrogen ions** into the gastric lumen. It is the final common pathway in the process of **acid secretion**. Blocking this enzyme **suppresses gastric acid secretion** to any stimulus, including food.
- PPIs inhibit 90–98% of 24-hour acid secretion in standard doses. When administered at equivalent doses, the different agents show little difference in clinical efficacy.

- PPIs are administered as **inactive prodrugs.**
- Oral products are formulated for **delayed release** as acid-resistant, **enteric-coated capsules or tablets to protect the acid-labile (unstable) prodrug from rapid destruction within the gastric lumen.**
- Capsule formulations (but not tablets) may be **opened for children or patients with dysphagia** or enteral feeding tubes, and the **micro granules** mixed with apple or orange juice or soft foods.
- Esomeprazole, omeprazole, and pantoprazole are also available as **oral suspensions.**
- **Lansoprazole** is available as a **tablet formulation** that disintegrates in the mouth, and **rabeprazole** is available in a formulation that may be **sprinkled on food.**
- Omeprazole is also available as a **powder formulation** (capsule or packet) that contains sodium bicarbonate to protect the naked (non-enteric-coated) drug from acid degradation. When administered on an empty stomach by mouth or enteral tube, this “immediate-release” suspension results in rapid omeprazole absorption and the onset of acid inhibition.

- Food decreases all agents' bioavailability by approximately 50%; hence, the drugs should be administered on **an empty stomach**.
- PPIs should be administered approximately **1 hour before** a meal (usually breakfast) so that the peak serum concentration coincides (be concurrent) with the maximal activity of proton-pump secretion.
- The drugs have a short serum half-life of about 1.5 hours, but acid inhibition lasts **up to 24 hours.**
- Because not all proton pumps are inactivated with the first dose of medication, up to **3–4 days** of daily medication are **required** before the full acid-inhibiting potential is reached. **Similarly, after stopping the drug, it takes 3–4 days for full acid secretion to return.**

- PPIs undergo rapid first-pass and systemic hepatic metabolism and have negligible renal clearance.
- Dose reduction is **not needed** for patients with **renal insufficiency** or mild to moderate liver disease **but should be considered** in patients with **severe liver impairment**.
- The intravenous formulations of esomeprazole and pantoprazole have characteristics **like those of oral drugs**.
- Because the half-life of a single injection of the intravenous formulation is short, thus, to provide maximal inhibition during the first 24–48 hours of treatment, the intravenous formulations must be **given as a continuous infusion** or as repeated **bolus injections**.
- **From a pharmacokinetic perspective, PPIs are ideal drugs: they have a short serum half-life, they are concentrated and activated near their site of action, and they have a long duration of action.**

Clinical Uses

1. **Gastroesophageal reflux disease**
2. **Peptic ulcer disease**
3. **H pylori-associated ulcers**
4. **NSAID-associated ulcers:** For patients with ulcers caused by aspirin or other NSAIDs, either H_2 antagonists or PPIs provide rapid ulcer healing so long as the NSAID is discontinued; however, continued use of the NSAID impairs ulcer healing. In patients with NSAID-induced ulcers who require continued NSAID therapy, treatment with a PPI more reliably (surely) promotes ulcer healing.
5. **Prevention of rebleeding from peptic ulcers**
6. **Non-ulcer dyspepsia**
7. **Prevention of stress-related mucosal disease (SRMD) bleeding.**
8. **Gastrinoma and other hypersecretory conditions:** With PPIs, excellent acid suppression can be achieved in all patients.

Adverse effects

- **General:** Diarrhoea, headache, and abdominal pain are reported in 1–5% of patients.
- **Nutrition:** Acid is important in releasing vitamin B_{12} from food. A minor reduction in oral cyanocobalamin absorption occurs during proton-pump inhibition, potentially leading to **subnormal B_{12}** levels with **prolonged therapy.**
- PPIs may reduce **calcium absorption** or inhibit osteoclast function. All PPIs carry an FDA-mandated warning of a possible increased risk of hip, spine, and wrist **fractures**.
- **Respiratory and enteric infections:** Gastric acid is an important barrier to colonization and infection of the stomach and intestine from ingested bacteria. Increases in gastric bacterial concentrations are detected in patients taking PPIs.
- **Other potential problems due to decreased gastric acidity:** Among patients infected with H pylori, long-term acid suppression leads to increased chronic inflammation in the gastric body and decreased inflammation in the antrum. Concerns have been raised that increased gastric inflammation may accelerate gastric gland atrophy (atrophic gastritis) and intestinal metaplasia (known risk factors for **gastric adenocarcinoma**).

Drug Interactions

- Decreased gastric acidity may alter the absorption of drugs for which intragastric acidity affects drug bioavailability, e.g., ketoconazole, itraconazole, digoxin, and atazanavir.
- Hepatic P450 cytochromes metabolize all PPIs. Because of the short half-lives of PPIs, clinically significant drug interactions are rare.
- Omeprazole may **inhibit** the metabolism of clopidogrel, warfarin, diazepam, and phenytoin.
- Esomeprazole may also **decrease** the metabolism of diazepam.
- Lansoprazole may **enhance** the clearance of theophylline.
- Rabeprazole and pantoprazole **have no significant** drug interactions.
- The FDA has issued a warning about a potentially crucial adverse interaction between **clopidogrel and PPIs**. Clopidogrel is a prodrug that requires activation by the hepatic P450, which also is involved to varying degrees in the metabolism of PPIs (especially omeprazole, esomeprazole, lansoprazole, and dexlansoprazole). **Thus, PPIs could reduce clopidogrel activation (and its antiplatelet action) in some patients.**

Mucosal protective agents

Sucralfate **(sucrose aluminium octasulphate)**

Chemistry & Pharmacokinetics

- Sucralfate is a salt of sucrose complexed to sulfated aluminium hydroxide. In water or acidic solutions, it forms a **viscous, tenacious (sticky) paste** that binds selectively to ulcers or erosions for up to 6 hours.
- Sucralfate has limited solubility, breaking down into sucrose sulfate and aluminium salt. Less than 3% of intact drug and aluminium **is absorbed** from the intestinal tract; the remainder is **excreted in the faeces**.

Pharmacodynamics

- Various beneficial effects have been attributed to sucralfate, but the precise mechanism of action is unclear. The **negatively charged** sucrose sulfate is believed to bind to **positively charged proteins in the base of ulcers or erosion**, forming a **physical barrier that restricts further caustic damage** and stimulates mucosal prostaglandin and bicarbonate secretion.

Clinical Uses

- Sucralfate is administered 1 g **four times** daily on an **empty stomach** (at least 1 hour before meals).
- At present, its clinical uses are limited. Sucralfate reduces the incidence of clinically significant upper gastrointestinal bleeding in critically ill patients hospitalized in the intensive care unit, although it is slightly less effective than intravenous H_2 antagonists.
- Many clinicians still use sucralfate for **the prevention of stress-related bleeding because of concerns that acid-inhibitory** therapies (antacids, H_2 antagonists, and PPIs) may **increase the risk of nosocomial pneumonia**.

Adverse Effects

- Because it is not absorbed, sucralfate is virtually devoid (without) of systemic adverse effects.
- **Constipation** occurs in 2% of patients due to **the aluminium salt**.
- Because a small amount of aluminium is absorbed, it **should not be used** for prolonged periods in patients with renal insufficiency.

Drug Interactions: Sucralfate may bind to other medications, **impairing their absorption.**

Prostaglandin E Analogue (Misoprostol)

Pharmacological Action

Prostaglandin E analogue acts as an endogenous prostaglandin in the GI tract to decrease acid secretion, increase the secretion of **bicarbonate and protective mucus**, and **promote vasodilation to maintain sub-mucosal blood flow**. These actions all serve to **prevent gastric ulcers.**

Therapeutic Uses: Prostaglandin E analogue is used in patients taking **long-term NSAIDs to prevent gastric ulcers.** Prostaglandin E analogue is used in patients who are pregnant to induce labour **by causing cervical ripening (mature).**

Adverse effects: Diarrhea and abdominal pain, nausea, vomiting.

Pregnancy Risk Category X

Bismuth Compounds

Chemistry & Pharmacokinetics

- Two bismuth compounds are available: bismuth subsalicylate, a nonprescription formulation containing **bismuth and salicylate**, and **bismuth subcitrate potassium.**
- Bismuth subsalicylate undergoes rapid dissociation within the stomach, allowing absorption of salicylate. Over 99% of the bismuth appears in the stool. Although minimal (<1%), bismuth is absorbed; it is stored in many tissues and has slow renal excretion. Salicylate (like aspirin) is readily absorbed and excreted in the urine.

Pharmacodynamics

- The precise mechanisms of action of bismuth are unknown. **Bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin.**
- It may also **stimulate prostaglandin**, mucus, and bicarbonate secretion.
- Bismuth subsalicylate **reduces stool frequency** and liquidity in acute infectious diarrhoea due to salicylate inhibition of intestinal prostaglandin and chloride secretion.
- Bismuth has **direct antimicrobial effects** and binds enterotoxins, accounting for its benefit in preventing and **treating traveller's diarrhoea**.
- Bismuth compounds have direct antimicrobial activity against H pylori.

Clinical Uses

- Patients widely use bismuth compounds for the nonspecific treatment of dyspepsia and acute diarrhoea.
- Bismuth subsalicylate is also used to prevent traveller's diarrhoea.
- **Bismuth compounds are used in four-drug regimens to eradicate H pylori infection.**

Adverse Effects

- All bismuth formulations have **excellent safety profiles.**
- Bismuth causes the harmless **blackening of the stool**, which may be confused with gastrointestinal bleeding.
- Liquid formulations may cause harmless darkening of the tongue.
- Bismuth agents should be used for short periods only and avoided in patients **with renal insufficiency**.
- Prolonged usage of some bismuth compounds may rarely lead to bismuth toxicity, resulting in **encephalopathy** (**ataxia, headaches, confusion, seizures**). However, such toxicity is not reported with bismuth subsalicylate or bismuth citrate. High dosages of bismuth subsalicylate may lead to salicylate toxicity.

Drug combinations to eradicate *H. pylori*

- Where NSAIDs are not a factor, most patients with DU, and many with GU, are chronically infected with *H. pylori.*
- Successful **eradication** is usually associated with a permanent cure of ulcer recurrence. Reinfection after eradication appears to be rare in developed countries.
- Eradication of *H. pylori* requires both acid **suppression and antibiotic treatment.**
- The most widely used regimen combines **PPI[1]** with **clarithromycin[2] and amoxicillin[3]** for **one week.**
- **Metronidazole** can replace **amoxicillin** in patients who have a penicillin allergy.
- Eradication **does not** need to be confirmed unless symptoms persist.
- Currently, there are many regimens to eradicate H. Pylori, including:

Levofloxacin, Bismuth, Tetracycline, Rifabutin, Tinidazole and Probiotics.

Drugs that act on gastric motility (Nausea and vomiting)

- Drugs that selectively stimulate gut motor function (**prokinetic** agents) have significant potential clinical usefulness.
- Agents that increase lower oesophagal sphincter pressures may be helpful for **GERD**.
- Drugs that improve gastric emptying may benefit **gastroparesis and delay postsurgical gastric emptying**.
- Agents stimulating the small intestine may benefit **postoperative ileus or chronic intestinal pseudo-obstruction**.
- Agents that enhance colonic transit may be helpful in the **treatment of constipation.**

Nausea and vomiting Relevant pathophysiology

- Vomiting is mediated by **TWO** separate brainstem centers: the **chemoreceptor trigger zone (CTZ)** and the **vomiting centre.** The trigger zone may be activated endogenously or exogenously by toxins or drugs such as opiates. It is rich in **dopaminergic receptors.** Activation of the trigger zone **stimulates** the vomiting centre. **Muscarinic and histamine H_1-receptors** are highly concentrated around the area of the **vomiting centre.**

Drugs used in the treatment of vomiting

Anticholinergic drugs: Hyoscine

- Anticholinergic drugs compete with acetylcholine at muscarinic receptors in the **Gut** and **CNS** and have anti-spasmodic action in the gut wall.
- They **may be successful in motion sickness** because of their **central action.**

Adverse effects

Adverse effects include **drowsiness** and **typical anticholinergic effects** of **dry mouth, blurred vision and difficulty in micturition.**

Clinical use

A 0.3–0.6 mg hyoscine dose is usually adequate **prophylaxis** for **motion sickness.**

Antihistamines: promethazine Mechanism

Antihistamines are competitive histamine antagonists at H1-receptors, acting mainly on the vomiting centre rather than the chemoreceptor trigger zone. They have **weak** anticholinergic effects. **Adverse effects** include drowsiness, insomnia and euphoria. Central effects are accentuated by alcohol.

Clinical use: Antihistamines are used in **motion sickness or vestibular disorders.** They are widely used to treat allergic rhinitis and other allergic reactions.

Dopamine antagonists: phenothiazines, chlorpromazine, prochlorperazine

Mechanism: They act mainly on the **chemoreceptor trigger zone** with **dopamine receptor antagonist** properties as well as **anticholinergic**.

Adverse effects: Prolonged use may produce **Parkinsonian-type tremor or other dyskinesia.**

Clinical use and dose: **Phenothiazines** are effective in a variety of situations, including the **vomiting of chronic renal failure** and **neoplastic disease** and d**rug-induced vomiting**.

Dopamine antagonist: Metoclopramide

Metoclopramide is a **central dopamine receptor antagonist** that blocks stimuli to the chemoreceptor trigger zone.

Adverse effects: Metoclopramide may cause acute extrapyramidal reactions, such as spasms of the muscles, oculogyric (ocu-lo-gyric) crisis or other dystonias. These are particularly a hazard when **metoclopramide is used in the treatment of children and young adults.** They can be treated with an intravenous **anticholinergic agent, such as benztropine. Metoclopramide raises serum prolactin** levels and may cause **gynaecomastia** by its **antidopaminergic effects.**

Drug interactions: Metoclopramide potentiates the **extrapyramidal side effects** of phenothiazines.

Clinical use and dose: Metoclopramide is effective in most causes of **vomiting, apart from motion sickness.**

Dopamine antagonist: domperidone

Domperidone is a **dopamine antagonist**, effective at the **chemoreceptor trigger zone.**

Adverse effects: Domperidone is **less likely** to cause extrapyramidal reactions than metoclopramide. It raises **prolactin levels and may produce cardiac dysrhythmias following rapid intravenous injection.**

Clinical use: Domperidone is effective in most situations, especially nausea and vomiting related to **cytotoxic drug therapy.**

Cannabinoids: Nabilone: Tetrahydrocannabinol is one of the active constituents of marijuana. Nabilone is a synthetic cannabinoid used in the treatment of **nausea and vomiting during cytotoxic therapy**. Its mode of action is unclear.

Adverse effects: Nabilone causes **drowsiness, dizziness and dryness** of the mouth. **Euphoria and hallucinations are rare.**

Serotonin antagonists: Ondansetron

Ondansetron is a **selective antagonist of serotonin at 5-HT_3 (hydroxytryptamine) receptors**. The mode of action in controlling nausea and vomiting is unclear, but it **has both CNS and peripheral actions.**

Adverse effects: Ondansetron causes **constipation and headache; flushing may occur.**

Clinical use and dose: Ondansetron is indicated for treating **nausea and vomiting associated with cytotoxic therapy or radiotherapy**. The dose and rate of administration depend on the severity of the problem and the chemotherapy used.

Note about Macrolide

- Macrolide antibiotics such as **Erythromycin** directly stimulate motilin (amino acid peptide) receptors on gastrointestinal smooth muscle and promote the onset of a migrating motor complex.
- Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops.
- It may be used in patients with acute upper gastrointestinal haemorrhage to promote gastric emptying of blood before endoscopy.

Drugs used in non-specific diarrhoea

Codeine phosphate

- This is useful for symptomatic control of diarrhoea.
- **It raises intracolonic pressure and sphincter tone**.
- It should **not** be given to patients with colonic diverticular disease. It should be used cautiously in patients with inflammatory bowel disease and only under the careful supervision of a gastroenterologist.

Diphenoxylate: This is an opiate derivative. **It is combined with atropine in the preparation of Lomotil. Why?**

Loperamide is a synthetic opiate **with some anticholinergic activity.** It may cause dizziness or dryness of the mouth.

Laxatives

Drugs that increase faecal bulk

- These consist of non-absorbable polysaccharides, as in **bran ispaghula.**
- They are generally effective in **simple constipation.**
- They are the agents of choice where treatment is likely to be prolonged.
- **They increase faecal mass and stimulate peristalsis but require adequate fluid intake.**

Stimulant laxatives

- These agents **stimulate intestinal motility**, e.g., **senna and bisacodyl**.
- Avoid if intestinal obstruction is suspected. Prolonged use may lead to hypotonicity of the bowel and thereby exacerbate chronic constipation.

Stool softeners

- Stool softeners **increase the water content of stool** to make it easier to pass, e.g., **docusate sodium** in either a liquid or capsule form.
- **Glycerin suppositories are** useful to combat impacted stool and promote bowel movement.

Osmotic laxatives

- These agents retain and/or draw water into the bowel.
- **They increase faecal bulk and moisten faeces**, e.g., non-absorbable disaccharide **lactulose and magnesium salts**.

5-HT_4 agents

- Serotonin receptors (5-HT_4) have a significant role in gastrointestinal motility, and plasma levels of serotonin are low in some people with chronic constipation.
- The only currently licensed selective serotonin receptor agonist in the UK is **prucalopride (pruca-lopride)** (Resotran^R) for **use in women** with chronic constipation, where maximum doses of other laxatives have failed to provide symptomatic relief.

Drugs used in the treatment of inflammatory bowel disease

Ulcerative colitis and **Crohn's disease**

Corticosteroids

- **Steroids** are of proven value in the treatment of acute relapses of **ulcerative colitis** and **Crohn's disease.**
- **They may be given rectally, orally or intravenously, depending on the extent and severity of the condition.**
- The most used are **prednisolone** (orally or per rectum) and **hydrocortisone** (intravenously).
- **Budesonide (Bu-deso-nide)** is a synthetic corticosteroid with potentially **less systemic side effects as it undergoes extensive first-pass metabolism in the liver.**
- An oral controlled-release formulation of **budesonide** is used to treat **terminal Crohn's disease and for microscopic colitis.**

Aminosalicylates (**5-aminosalicylic acid 5ASA)**

- Several preparations are designed to deliver active drugs to the colon (orally in a tablet or granule formation) or topically via the rectum (liquid, foam enema or suppository).
- **Mesalazine** and **sulphasalazine** are split from their carrier molecules in the colon **by bacterial azo-reductases**.
- The more commonly used **Mesalazine** is available in various delivery systems via pH-dependent or time-controlled release mechanisms or a multi-matrix delivery system.

Mechanism: It is thought that 5-ASA exerts a **local anti-inflammatory effect.**
Adverse effects: Blood dyscrasia, renal damage and (with olsalazine) watery diarrhoea (if not taken with food).

Clinical use

- These drugs can be used alone to induce remission of mild moderate ulcerative colitis **and together** with corticosteroids in more severe disease.
- **There is also accumulating evidence that they have a chemoprotective effect, reducing the risk of future bowel cancer in patients with ulcerative colitis by up to 75%.**

Thiopurines (azathioprine, 6-mercaptopurine)

These immunosuppressants may be useful in patients with **severe inflammatory bowel disease.**

Side effects

- They may cause **bone marrow suppression.** They also may **reduce the immune response,** particularly to viral infections. Due to the increased susceptibility to non-melanoma skin cancer, patients should be counselled strongly to avoid heavy sun exposure/sun beds and to use high-strength sunblock.

Other immunosuppressants

- **Ciclosporin** is used in patients with severe ulcerative colitis that has not responded to corticosteroids.

- **Methotrexate** may induce and maintain remission (reduction) in patients with Crohn's disease who are not able to tolerate or who are unresponsive to thiopurines.

Drugs adversely affecting gastrointestinal function

Antibiotic-related diarrhoea is usually attributed to an **alteration** in the intracolonic bacterial **flora**, but antibiotic-associated colitis or **pseudomembranous colitis can occur**. This results from the proliferation of ***Clostridium difficile*** in the bowel and the secretion of an endotoxin.

Prevention is achieved by the **limited, wise use of antibiotics and good hygiene** in clinical areas. Treatment depends on the prescription of an antibiotic, which is poorly absorbed when given orally. Two suitable agents are **vancomycin and metronidazole.**

Cholesterol Gallstones treatment

Bile Acid Agents: **Ursodiol** (ursodeoxycholic acid) is a naturally occurring bile acid that makes up less than 5% of the circulating bile salt pool in humans and a much higher percentage in bears.

Clinical Use: Ursodiol is used for the dissolution of small cholesterol gallstones in patients with symptomatic gallbladder disease who refuse cholecystectomy or who are poor surgical candidates.

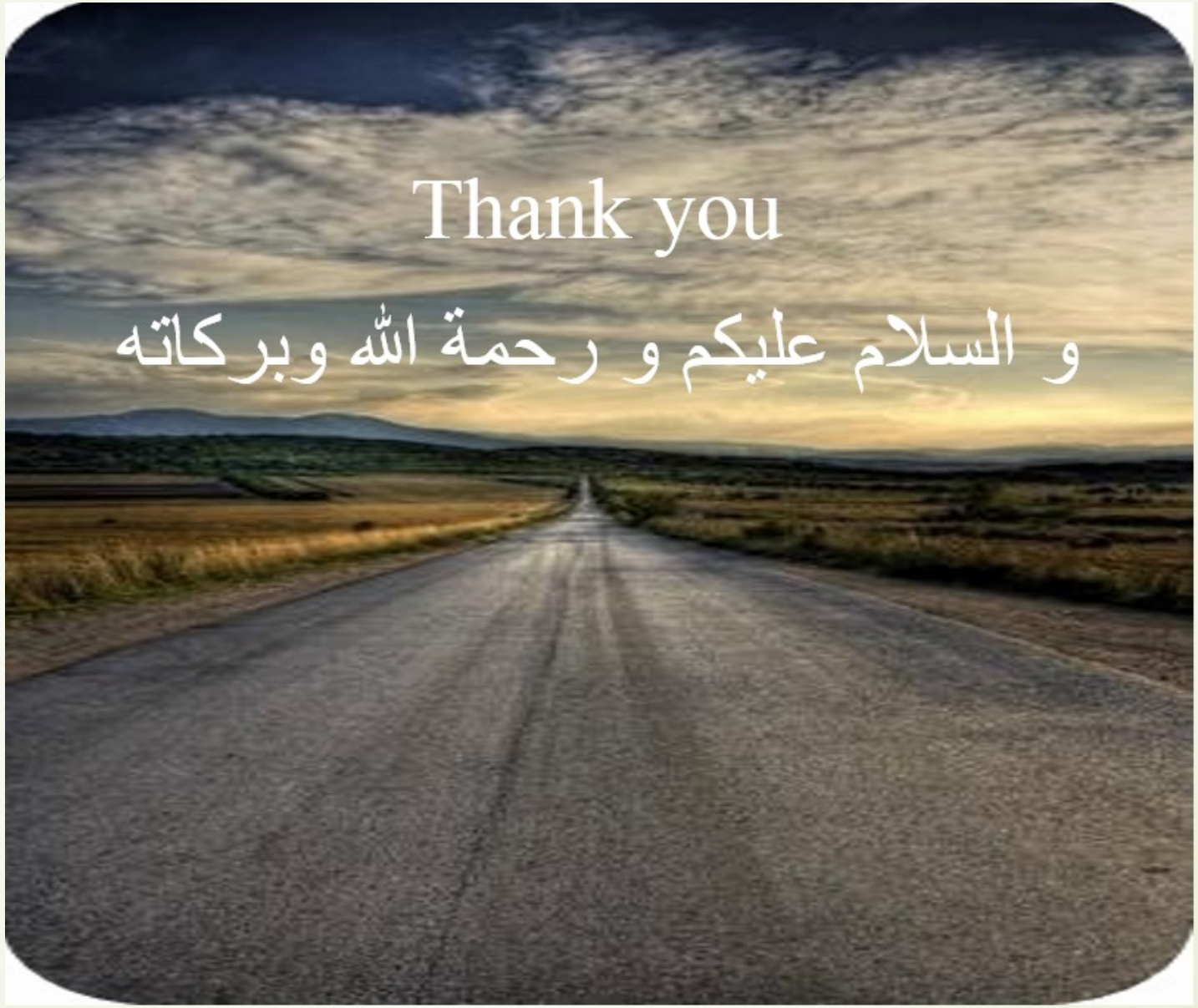
Adverse Effects: Ursodiol is practically free of serious adverse effects. Bile salt-induced diarrhoea is uncommon.

Irritable bowel syndrome

- This common condition is the most frequent cause of chronic, recurrent abdominal pain. It may also cause bloating and upset of bowel habits (with diarrhoea, constipation or both). **There is a relationship between psychological stress and symptoms in some patients.** Management consists of non-pharmacological treatment (lifestyle advice) with combinations of antispasmodics and titrated doses of antimotility drugs or laxatives with tricyclics/SSRIs employed as a second line to provide visceral analgesia.
- **Mebeverine** is an antispasmodic agent without significant anticholinergic effects. It is useful in relieving symptoms in some patients.
- Enteric-coated capsules of **peppermint oil** are useful in relieving gut spasms in some patients.
- If laxatives are required, **soluble fibres such as ispaghula husk** should be used, **avoiding non-soluble fibres and lactulose as these exacerbate bloating.**
- **Tricyclic antidepressant** drugs can be an effective therapeutic strategy if second-line therapy is required.
- There is also some evidence to support the use of the selective **serotonin reuptake inhibitor (SSRI) drug citalopram for this indication.**

Pancreatic insufficiency management

- Exogenous pancreatic enzymes containing **trypsin, lipase and amylase** are taken with meals by patients with **chronic pancreatic exocrine insufficiency**, such as in **chronic pancreatitis or cystic fibrosis.** These are prescribed as **Pancreatic Enzyme Replacement Therapy.**
- **H_2-receptor antagonists or PPIs may also be given.** These prevent **denaturation** of the pancreatic enzymes by gastric acid and **reduce the demand** for pancreatic bicarbonate secretion, which may **reduce pain.**


Thank you
و السلام عليكم و رحمة الله وبركاته