GI pharmacology
Lec 4 – Lec 6

Group/Disease	Drug	MOA	Adverse effects	Clinical uses	Notes
			LECTURE 4		
Antiemetic drugs	Serotonin 5-HT3-Receptor Antagonists: -Ondansetron -Granisetron. -Dolasetron. -Palonosetron -Hyoscine (scoplamine)		Safe drugs but can cause headache, dizziness, constipation and prolong QT interval (i.e. proarrhythmic).	-Used before chemotherapy, activity enhanced by dexamethasone and NK1 antagonist. - Can also be used in postoperative and post-radiation vomiting	-5-HT3 receptors are involved in three out of the five inputs involved with vomiting. -Activity restricted to vomiting due to vagal stimulation and chemotherapy. -Motion sickness is poorly controlled
	Neurokinin Receptor (NK1) Antagonists: -Apripetant	Central blockade in the area postrema	Can cause fatigue, dizziness and diarrhea		Used in combination with 5-HT3 antagonists
	Antipsychotic drugs: Prochlorperazine. - Promethazine - Droperidol	Inhibit dopamine and muscarinic receptors.	Can cause extrapyramidal effects, hypotension and prolong QT interval		
	Antihistamines and anticholinergic Drugs: -Diphenhydramine -Meclizine		Can cause dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention	Particularly useful in motion sickness	Hyoscine can be used as a transdermal patch
	Benzodiazepines: -Lorazepam -Diazepam	Reduce anticipatory vomiting caused by anxiety			Antianxiety-hypnotic drugs
	Cannabinoids: -Dronabinol -Nabilone		Can cause euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite (the munchies), hypotension, tachycardia, and conjunctival injection	useful for chemotherapy-induced vomiting	Delta-9- tetrahydrocannabinol from marijuana is useful for chemotherapy-induced vomiting
Emetic Agents	-Hypertonic saline -Apomorphine -Ipecac syrup				
			LECTURE 5		
Irritable Bowel Syndrome (IBS)	Antispasmodic / Anticholinergic Agents: -Dicyclomine -Hyoscyamine	They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle			-Spasm is not an important symptom of IBS. -At usual low doses, have minimal side effects
	Serotonin 5-HT 4-Receptor Agonists: Tegaserod	Reduces pain, bloating and hardness of stool		Approved for short-term treatment of women with IBS who predominantly have constipation	Expensive

Inflammatory Bowel Disease (Ulcerative Colitis & Crohn's disease)	Aminosalicylates	1. Azo Compounds: -Sulfasalazine - Balsalazide -Olsalazine	1. Modulate inflammatory mediators derived from both COX and lipoxygenase pathways. 2. Interfere with the production of inflammatory cytokines (Inhibit nuclear factor KB). 3. Inhibit cellular functions of natural killer cells, mucosal lymphocytes, and macrophages and may scavenge reactive oxygen metabolites.	Attributable to systemic absorption especially in slow acetylators Nausea, headache, arthralgia, myalgia, bone marrow suppression, and malaise, allergic reactions, oligospermia, and folate deficiency.	- First line drugs for the treatment of mild to moderate active ulcerative colitis. -Can induce and maintain remission in ulcerative colitis	-All contain 5-ASA bound by an azo bond (N=N) and in the intestine, bacteria cleave the bond to release the active 5-ASA
		2. Mesalamine Compounds: - Pentasa - Asacol - Rowasa - Canasa				- Pentasa: time release 5-ASA formulation. - Asacol: enteric coated in a pH sensitive resin. - Rowasa: enema. - Canasa: suppository
	<u>Glucocorticoids:</u> - Prednisolone and Prednisone (oral) - Hydrocortisone (Enemas, foam or suppositories) - Budesonide (Controlled release oral formulation)		Inhibit production of cytokines (TNF-a, IL-1) and chemokines (IL-8), inflammatory cell adhesion molecules, nitric oxide synthase, phospholipase A2, Cyclooxygenase-2 and NF-KB		- Moderate to severe active IBD. - Hydrocortisone, rectally, preferred for rectal and sigmoid involvement - Budesonide for ileal and proximal colon involvement	- Prednisolone orally or IV - Not useful for long term maintenance therapy
	<u>Antimetabolites:</u> - Azathioprim - 6-Mercaotopurine		Inhibit purine nucleotide metabolism and DNA synthesis and repair, resulting in inhibition of cell division and proliferation and may promote T-lymphocyte apoptosis	Nausea, vomiting, bone marrow suppression, hepatic toxicity, and allergic reactions (fever, rash, pancreatitis, diarrhea and hepatitis)	- Onset delayed for 17 weeks. - Used in induction and maintenance of remission. - Allow dose reduction or elimination of steroids	- Are purine analogs, which produce thioguanine nucleotides. -Immunosuppressive - Allopurinol increases levels of the drugs
	3. Methotrexate (orally, subcutaneously, and intramuscularly)		Works by inhibiting dihydrofolate reductase (DHFRase) enzyme which is important in the synthesis of thymidine and purines At high doses → it inhibits cellular proliferation. At low doses → used in IBD, it interferes with the inflammatory actions of interleukin- 1, stimulates adenosine release, apoptosis and death of activated T lymphocytes	At high doses, can cause bone marrow depression, megaloblastic anemia, alopecia and mucositis	- Used in cancer chemotherapy, rheumatoid arthritis and psoriasis. - Used for induction and maintenance of remissions of Crohn's disease	- Renal insufficiency may increase risk of hepatic accumulation and toxicity - Side effects counteracted by folate supplementation

	4. <u>Anti-Tumor Necrosis Factor:</u> - Infliximab "Remicade" - Adalimumab - Certolizumab	- Binds to cell surface as well as to membrane-bound TNF-alpha receptors, preventing the cytokine from binding to its receptors - The Fc portion of human IgG1 region promotes complement activation and antibody-mediated apoptosis and cellular cytotoxicity of activated lymphocytes and macrophages	- Infection due to immunosuppression, occur in 6% of patients on infliximab, e.g. reactivation of TB or dissemination, pneumonia, sepsis, pneumocystis, listeriosis, and reactivation of hepatitis B - Antibody formation against the murine epitope of infliximab develops in 1/3rd of patients leading to loss of response or infusion reactions - Acute Infusion Reactions: fever, headache, dizziness, urticaria, chest pain, and dyspnea, hypotension, shortness of breath, muscle spasm and chest discomfort - Delayed Reactions or Serum Sickness-like Reactions: occur after retreatment with infliximab include myalgia, arthralgia, jaw tightness, fever, rash, urticaria, and edema - Positive antinuclear antibodies, anti-double stranded DNA, Lupus-like syndrome, severe hepatic reactions, lymphoma, multiple sclerosis and congestive heart failure		- Infliximab → Is a chimeric mouse-human monoclonal antibody to human TNF-alpha, Given IV. - Adalimumab → Fully humanized IgG antibody, given SC - Certolizumab →Polyethylene glycol Fab fragment of humanized anti- TNF-alpha, also given SC - Half-life 8-10 days with persistence of antibodies in plasma for 8-12 weeks - Used in acute and chronic treatment of patients with moderate to severe IBD - ±Given in repeated doses at 0, 2, and 6 weeks for induction - If response is adequate, infusions are repeated every 8 weeks - Response might be lost due to development of antibodies to infliximab
LECTURE 6					
	Pancrelipase		- Diarrhea, constipation, headache, abdominal pain/cramps/bloating, gas, dizziness, cough, nausea, or vomiting. - It may cause mucositis if not swallowed quickly	Used in conditions where the pancreas cannot make or does not release enough digestive enzymes into the small intestines to digest the food (e.g., chronic pancreatitis, cystic fibrosis, cancer of the pancreas, post-pancreatectomy, post-gastrointestinal bypass surgery).	- Available in sizes with different amounts of lipase, amylase and protease. - Dose should be adjusted according to age, weight, degree of pancreatic insufficiency, and the amount of dietary fat intake -Taken with plenty of fluids. - Used regularly to get the most benefit from it. - Taken with every meal or snack
Bile Acid therapy for Gallstones	Ursodiol	-Absorbed in the g.i.t. and conjugated in the liver with glycine or taurine and excreted in the bile. - Blocks hepatic cholesterol synthesis and thereby decreases secretion of cholesterol by the liver and the amount of cholesterol in bile		- To dissolve small cholesterol gallstones in patients who refuse cholecystectomy or who are poor surgical candidtes. - Prevention of gallstones in obese patients. - Early stage biliary cirrhosis. - Free of side effects	

Antiprotozoal Agents	Metronidazole (Flagyl)	Penetrate protozoal and bacterial cells but not mammalian cells. Work as an electron sink, so, reduced at 5-nitro group by the enzyme Nitroreductase, which is only found in anaerobic organisms. The reduced molecule disrupts replication and transcription and inhibits DNA repair	Nausea, headache, dry mouth and metallic taste. Urine discoloration. Vertigo, unsteadiness, ataxia, paresthesia, neuropathy, encephalopathy. Neutropenia. Disulfiram-like reactio	- E. histolytica - G. lamblia - T. vaginalis - Blastocystis hominis - B. coli - Dracunculus medinensis - Anaerobic G+ve and Gve bacteria - All forms of amebiasis, except for the cyst passers (Diloxanide Furoate, Paromomycin or diiodohydroxyquin). - Giardiasis. - Trichomoniasis. - Anaerobic bacterial infection(in dentistry). - D. medinensis (guinea worm)	Resistance is rare Kinetics:→ Good absorption and distribution, t½ 8h. Metabolized by oxidation and glucuronide formation
	Tinidazole				Tinidazole is better tolerated.
	Diloxanide Furoate	Mechanism unknown	Flatulence, nausea, cramps, rashes	Effective luminal amebicide Drug of choice for asymptomatic cyst passers	
Antibiotics	Erythromycin Tetracycline	Alter bacterial flora and prevent secondary infection			
	Paromomycin	Direct action on ameba in the lumen		Anthelminthic and for visceral leishmaniasis	Aminoglycoside
Anthelmintic Drugs	Albendazole	Broad spectrum, which inhibits microtubule synthesis		- Hydatid disease. - Cysticercosis: usually given with corticosteroids to decrease inflammation caused by dying organisms. - Pinworm. - Hookworm. - Ascariasis. - Trichuriasis. - Strongyloidiasis.	
	Bithionol			- Drug of choice for Fascioliasis - Alternative drug for pulmonary paragonimiasis	
	Ivermectin	- Strongyloidosis: Paralyzes nematodes and arthropods by intensifying GABA-mediated transmission of signals in peripheral nerves. - Onchocerciasis:	- Mazotti Reaction: Occurs in 5-30% of patients, usually mild - Fever, headache, dizziness, somnolence, weakness, rash, pruritus, diarrhea, joint and muscle pains, hypotension, tachycardia	- Strongyloidosis - Onchocerciasis: - Controlling scabies, lice, and cutaneous larva migrans	

		Blocks the release of microfilaria for some months after therapy			
	Mebendazole	Inhibits microtubule synthesis		- Ascariasis. - Trichuriasis. - Hookworm. - Pinworm	- Wide spectrum - Tablets chewed before swallowing. - Safe drug.
	Niclosamide	- Kills adult worms, but not the ova. - Works by inhibition of oxidative phosphrylation		Second-line drug for most tapeworm infections	- 2 gm single dose on an empty stomach, chewed and swallowed. - Purgative needed
	Piperazine	Causes paralysis by blocking acetylcholine, worms expelled by normal peristalsis		Ascariasis	70 mg/day for 2-8 days Or repeat after 2 weeks
	Praziquantel	Increases permeability of the worm to calcium, resulting in paralysis, dislodgment and death	Mild and transient adverse effects, except for neurocysticercosis.	- Schistosomes, all species, drug of choice. - Trematodes: Clonorchiasis, Opisthorchiasis and Paragonimiasis - Cestodes including cysticercosis	
	Pyrantel Pamoate	Works as a neuromuscular blocker.		- Broad spectrum - Pinworm. - Ascaris. - Trichostrongylus orientalis. - Hookworms.	- Effective within the intestinal tract, not in the tissues or against the ova - 11 mg/kg, single dose

NOTE: This summary doesn't include laxative agents in lecture 4

Done by:

Shahed Atiyat