# ANTI-DIARRHEAL DRUGS

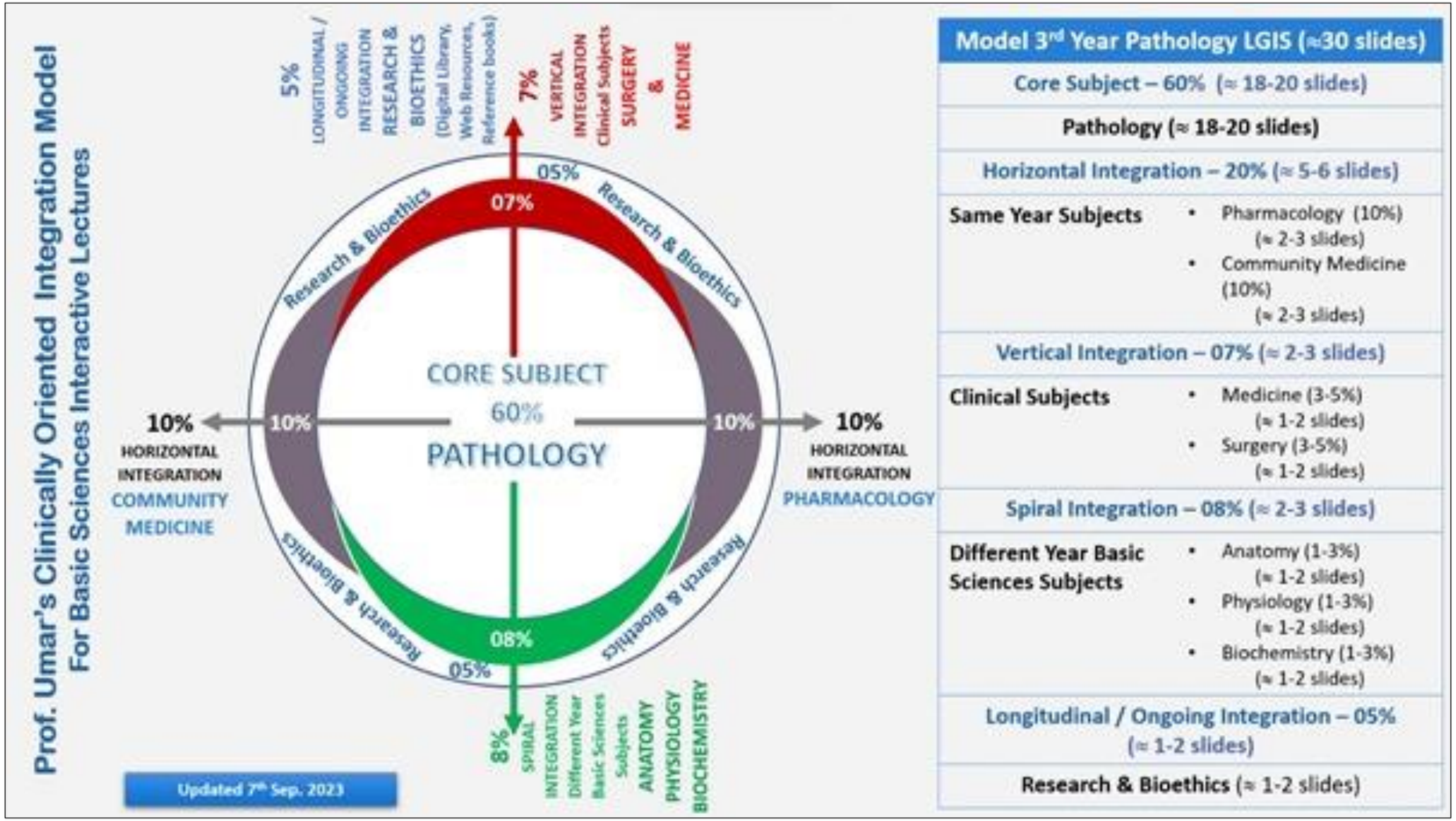
Dr. Zunera Hakim

- **Katzung's Basic & Clinical Pharmacology, 15th Edition**
- **Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition**

# MOTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

# UMAR'S MODEL OF INTEGRATION




| Model 3rd Year Pathology LGIS (≈30 slides) | |
|---|---|
| Core Subject – 60% (≈ 18-20 slides) | |
| Pathology (≈ 18-20 slides) | |
| Horizontal Integration – 20% (≈ 5-6 slides) | |
| Same Year Subjects | • Pharmacology (10%) (≈ 2-3 slides)<br>• Community Medicine (10%) (≈ 2-3 slides) |
| Vertical Integration – 07% (≈ 2-3 slides) | |
| Clinical Subjects | • Medicine (3-5%) (≈ 1-2 slides)<br>• Surgery (3-5%) (≈ 1-2 slides) |
| Spiral Integration – 08% (≈ 2-3 slides) | |
| Different Year Basic Sciences Subjects | • Anatomy (1-3%) (≈ 1-2 slides)<br>• Physiology (1-3%) (≈ 1-2 slides)<br>• Biochemistry (1-3%) (≈ 1-2 slides) |
| Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides) | |
| Research & Bioethics (≈ 1-2 slides) | |

# LEARNING OBJECTIVES

*At the end of the lecture, the students of 3rd year MBBS should be able to;*

- Define diarrhea
- Categorize diarrhea on basis of cause & onset of symptoms
- Classify anti-diarrheal drugs
- Describe the mechanism of various drug groups used for diarrhea
- Outline approaches to treat diarrhea
- Recognize the role &effectiveness of drugs in the treatment of various types of diarrhea

Diarrhea (Greek and Latin: dia, “through,” and rheein, “to flow or run”)

Passage of three or more loose or liquid stools per day (or more frequent liquid passage than is normal for the individual)

**WHO**

# TYPES OF DIARRHEA

Diarrhea may be acute or chronic:

- **Acute**
- **Chronic/ Persistent**

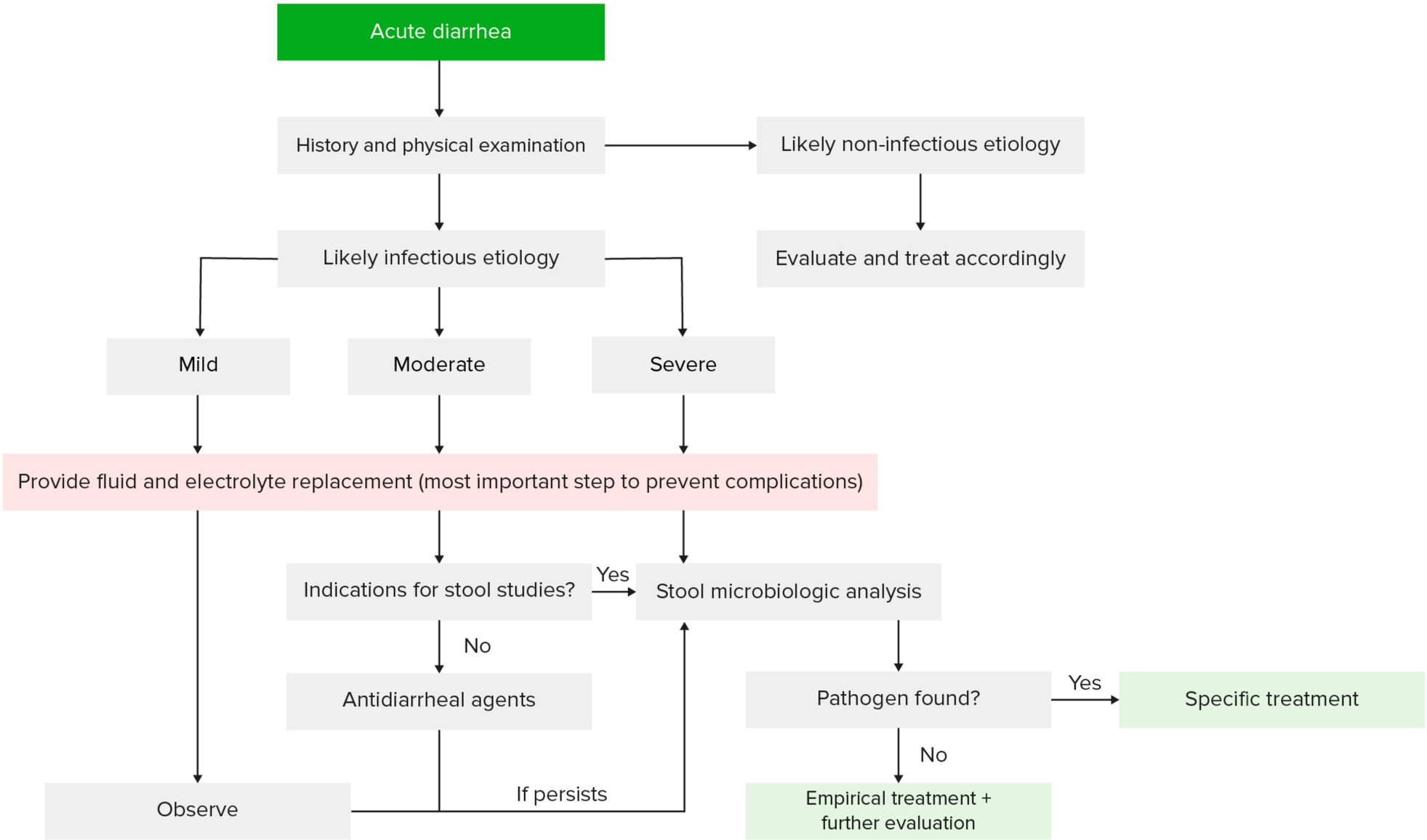
# CAUSES OF DIARRHEA

- Infective organisms (bacteria, viruses, parasites)
- Inflammatory intestinal diseases
- Malabsorption syndromes
- Tumors
- Drugs (antimicrobials)

# Approach to patients with diarrhea

- Maintenance of fluid and electrolyte balance
- Use of anti infective agents
- Use of anti diarrheal agents

# WORKUP OF DIARRHEA



# MAINTENANCE OF FLUID & ELECTROLYTE


Vertical integration –Community Medicine

# ANTIMICROBIAL THERAPY

- Fluoroquinolones
  ciprofloxacin
  norfloxacin
  ofloxacin
  levofloxacin
- Azithromycin
- Rifaximin
- TMP/SMZ

# 1. NON SPECIFIC ANTI-DIARRHEAL AGENTS:

**A. Anti Motility agents: (**Drugs that prolong Intestinal transit time by reducing motility)

- **Synthetic Opioid Compounds:**
  Diphenoxylate, Loperamide, Codeine, Paregoric (camphorated opium tincture), deodorized tincture of opium, eluxadoline
- **Anti-cholinergics:**
  Atropine, Propantheline, Dicylomine, Hyoscyamine, berberine

**B. Adsorbants: (bulk forming & hygroscopic agents)**

Kaolin
Pectin
Methyl cellulose
Ispaghula Husk
Chalk
Charcoal
Diosmectite

- **C. Agents that modify fluid & electrolyte transport**
  **Colloidal Bismuth compounds:** Bismuth subsalicylate
  Bile salt binding resins
  Octreotide
  Clonidine
  Opioid compound (Enkephalinase inhibitor)

# 2. ANTIMICROBIAL AGENTS

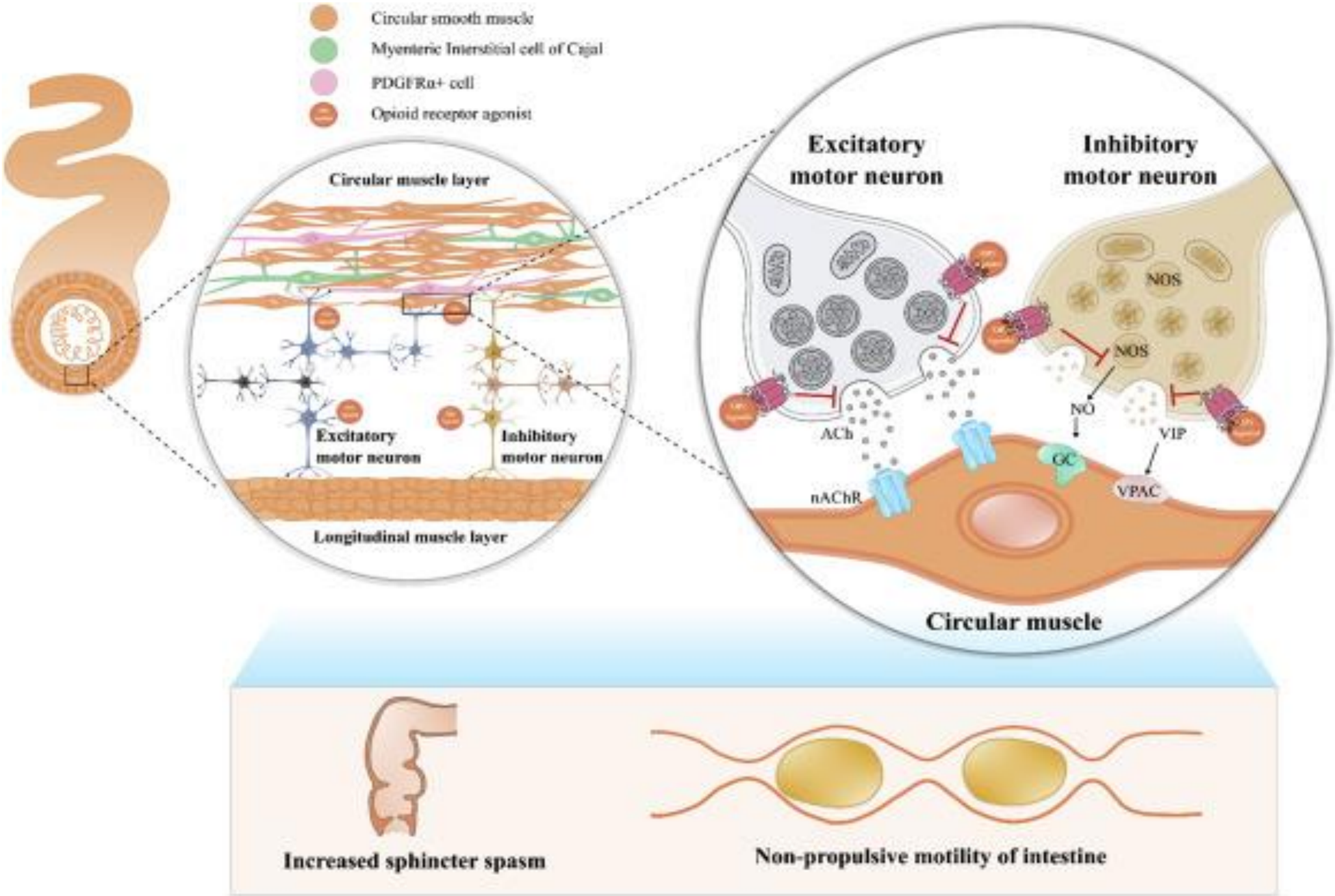
CLASSIFICATION

# ANTIMOTILITY DRUGS

# OPIOID COMPOUNDS

- Inhibit presynaptic cholinergic nerve in submucosal and myenteric plexus by binding to peripheral opioid receptors (MORs or DORs), that results in decreasing motility(MOR), leading to increased absorption of water(MOR & DOR)
- Increased tone of anal sphincter
- Decreased mass colonic movements and gastrocolic reflex

- Treatment of acute traveler’s diarrhea and chronic diarrhea


Circular smooth muscle
Myenteric Interstitial cell of Cajal
PDGFRα+ cell
Opioid receptor agonist
Circular muscle layer
Excitatory motor neuron
Inhibitory motor neuron
Longitudinal muscle layer
Excitatory motor neuron
Inhibitory motor neuron
NOS
NOS
NO
VIP
ACh
GC
nAChR
VPAC
Circular muscle
Increased sphincter spasm
Non-propulsive motility of intestine

## LOPERAMIDE

- Active as a parent drug at the opioid receptors
- 40-50 times more potent than morphine
- Penetrates CNS poorly (little abuse potential)
- 
- 
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- 25 µg of atropine sulfate per tablet with either 2.5 mg diphenoxylate hydrochloride **(LOMOTIL)** or 1 mg of difenoxin hydrochloride **(MOTEFEN)**
- In high doses, these drugs cause  as anticholinergic effects from the atropine (nausea, dry mouth, blurred vision, etc.)

## DIPHENOXYLATE

- Act through active metabolite (difenoxin) at the opioid receptors
- 8-10 times more potent than morphine
- Penetrates CNS (CNS ,respiratory depression and abuse potential)
- Maximum dose of 20mg/day (diphenoxylate),8mg/day (difenoxin), Overdosage can lead to constipation, CNS effects and toxic megacolon
- Coformulated with atropine to discourage habituation and overdosage

# CONTRAINDICATIONS

❖ **Inflammatory bowel disease**

- Increases chances of toxic mega colon leading to increased risk of perforation

❖ **Infective diarrhea**

- Bacillary dysentry
- Amoebic dysentery

- Anti-motility drugs decreases the motility, leading to increased chances of toxin absorption, producing systemic adverse effects

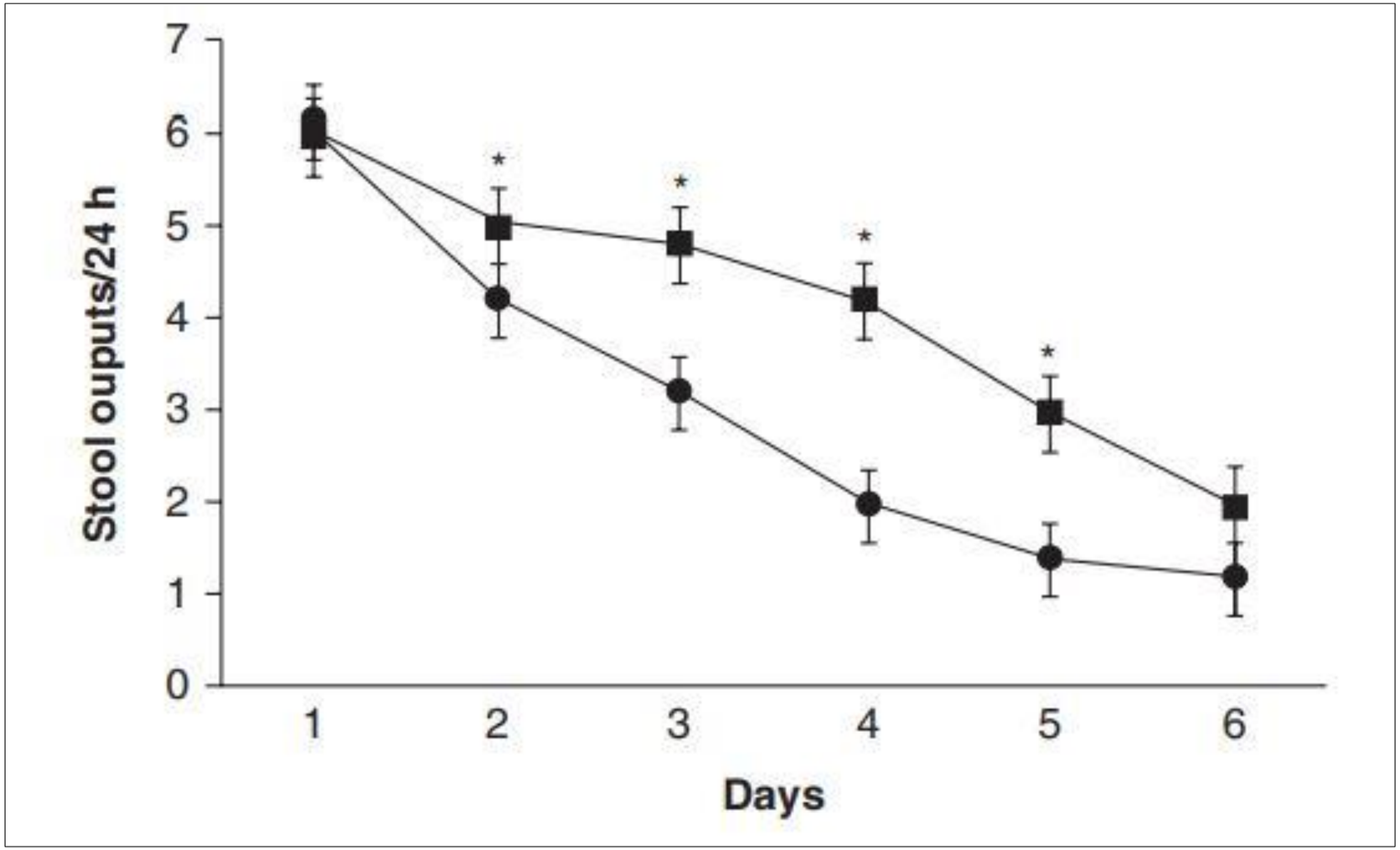
- Should not be used in children and infants

# ADSORBANTS

# Kaolin and Pectin

- Kaolin is naturally occurring hydrated aluminum disilicate prepared as finely divided powder
- Pectin indigestible carbohydrate derived from apple
- Both act as absorbents of bacterial toxins and fluids and decrease stool fluidity and frequency
- **Stool consistency is more affected than stool frequency**
- **Side Effects**
    - Well tolerated
    - May cause constipation
    - Used cautiously when other drugs are used because they will hamper their absorption

# Effects of Diosmectite on Frequency of Stools




Frequency of stools receiving oral rehydration solution (ORS:□) or ORS and dioctahedral smectite (DS:•). Administration of DS was associated with significant reduction of the number of stools (*p < 0.05)

# ANTISECRETORY DRUGS

- Bind bile acids in the intestinal lumen & prevent excess fecal loss of bile acids

- Useful in bile-salt induced diarrhea as in resection of the distal ileum or after cholecystectomy (excessive concentrations of bile salts reach the colon and stimulate water and electrolyte secretion)

- **Adverse effects**
  - Bloating flatulence, constipation and fecal impaction.
  - Fat malabsorption in patient with decrease bile acid pools.
  - Malabsorption of vitamin K, folic acid
  - Increase formation of gall stones.

# BILE ACID SEQUESTRANTS

Cholestyramine, colestipol, and colesevelam

# OCTREOTIDE

- Octapeptide analogue of somatostatin
- Longer t1/2 of 1-2 hours
- S/C , I/M or I/V

## MECHANISM OF ACTION

- It inhibits the secretion of numerous hormones and transmitters, including gastrin, cholecystokinin, glucagon, growth hormone, insulin, secretin, pancreatic polypeptide, vasoactive intestinal peptide, and 5-HT.
- It reduces intestinal fluid secretion and pancreatic secretion.
- It slows gastrointestinal motility and inhibits gallbladder contraction.
- It reduces portal and splanchnic blood flow.
- It inhibits secretion of some anterior pituitary hormones.

# CLONIDINE

## alpha 2-adrenergic agonist

- Clonidine can interact with specific receptors on enteric neurons and enterocytes, thereby stimulating absorption and inhibiting secretion of fluid and electrolytes and increasing intestinal transit time.
- Useful in diabetics with chronic diarrhea & diarrhea of opioid withdrawal (oral or topical)
- Side effects such as hypotension, depression, and perceived fatigue may be dose limiting in susceptible patients

# RACECADOTRIL

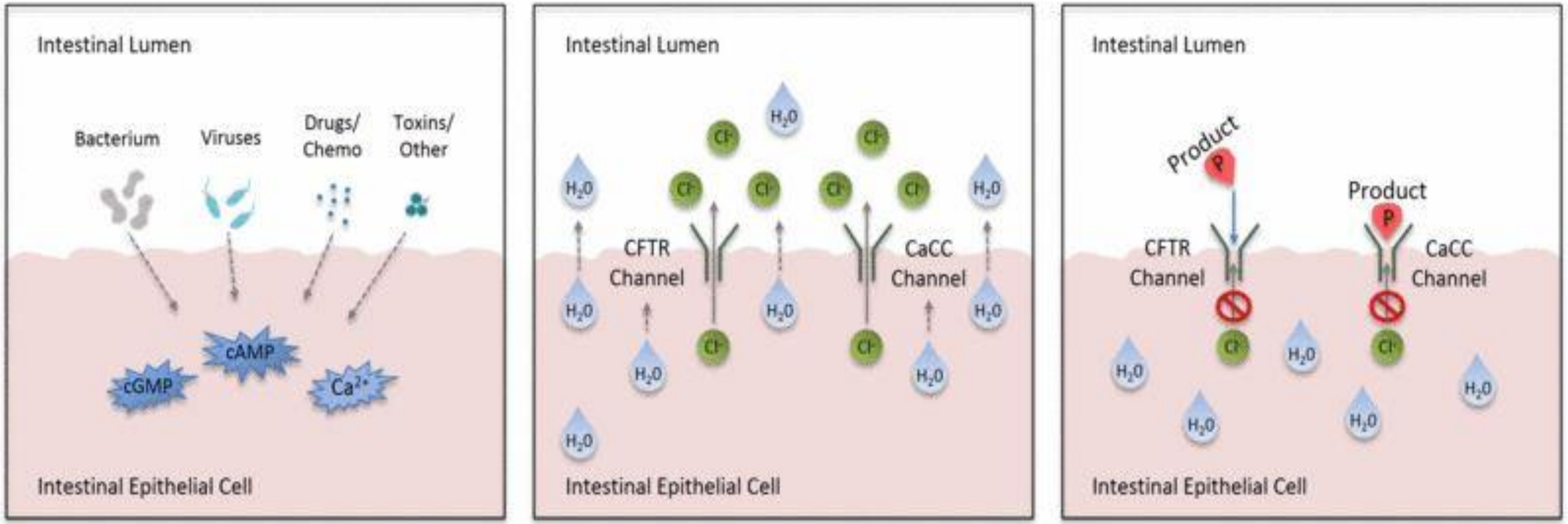
## OPIOID COMPOUND

- A  prodrug, which is rapidly converted in the body to thiorphan, a dipeptide inhibitor of enkephalinase
- By inhibiting peripheral enkephalin degradation, thiorphan potentiates the effects of endogenous enkephalins on the MOR in the GI tract to produce an antidiarrheal effect predominantly as an antisecretory agent
- Inhibition of enkephalinase activity could elevate the levels of other messengers (neuropeptide Y, atrial and brain natriuretic peptides, substance P, and neurotensins)
- Used for acute diarrhea in adults and children
- Less constipation than loperamide and other minimal side effects *(headache and itching)*

# CROFELMER

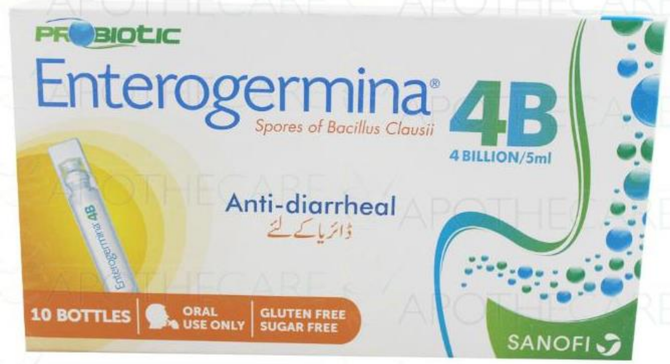
- Purified oligomeric proanthocyanidin from “dragon’s blood
- Works by inhibiting the cyclic amp–stimulated CFTR Cl− channel and Ca2+-activated chloride ion channels on the luminal aspect of the enterocyte, thereby reducing the water loss associated with chloride secretion into the lumen.
- Diarrhea with anti-retroviral therapy in HIV/AIDS
- **A/E:** upper respiratory tract infections, cough, flatulence, nausea, joint and back pain, and some other GI conditions

# CROFELMER


Intestinal Lumen
Bacterium
Viruses
Drugs/ Chemo
Toxins/ Other
cGMP
cAMP
Ca2+
Intestinal Epithelial Cell
Intestinal Lumen
H2O
Cl-
CFTR Channel
CaCC Channel
Intestinal Epithelial Cell
Intestinal Lumen
Product
P
CFTR Channel
CaCC Channel
Intestinal Epithelial Cell

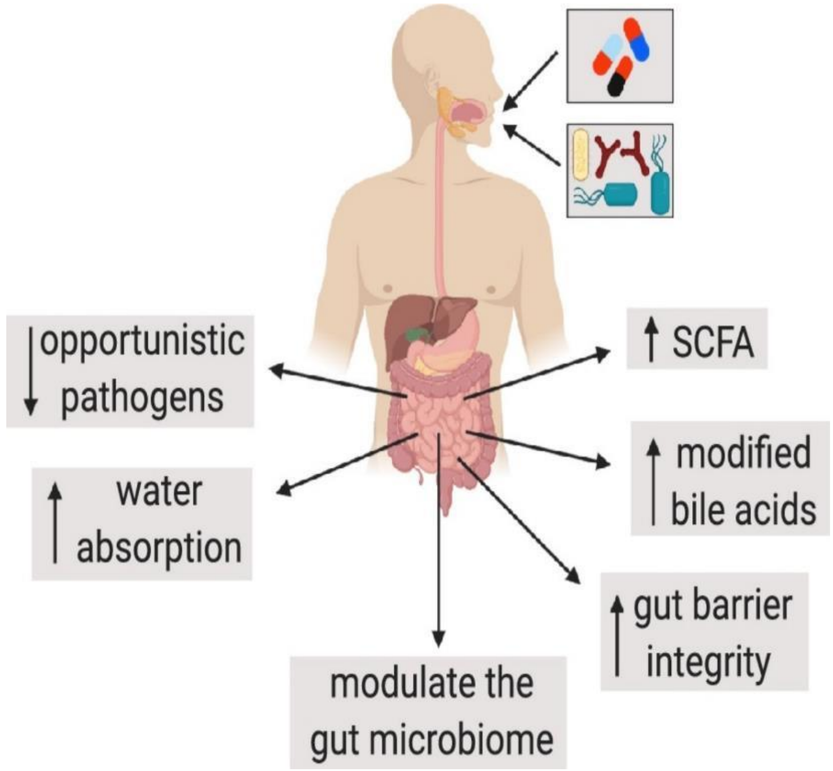
# PROBIOTICS

- Probiotics comprise a large group of microorganisms, which have different properties and thus confer different benefits.
- Probiotic preparations include several different genera and species of bacteria and yeast. Commonly used bacteria are species of Lactobacillus (rhamnosus) and salivarius), while the yeast Saccharomyces boulardii is also often chosen
- The beneficial effect has been linked to modulation of gut microbiota and restoration of GI homoestasis
- They are effective in treatment of acute diarrheal conditions and antibiotic associated diarrhea in children and adult

# RESEARCH

Mekonnen SA, Merenstein D, Fraser CM, Marco ML. Molecular mechanisms of probiotic prevention of antibiotic-associated diarrhea. Current opinion in biotechnology. 2020 Feb 1;61:226-34.



# ARTIFICIAL INTELLIGENCE

Ogwel B, Mzazi V, Nyawanda BO, Otieno G, Omore R. Predictive modeling for infectious diarrheal disease in pediatric populations: A systematic review. Learning Health Systems. 2024 Jan;8(1):e10382.

Lee KS, Kim ES. Explainable artificial intelligence in the early diagnosis of gastrointestinal disease. Diagnostics. 2022 Nov 9;12(11):2740.

# BIOETHICS

RISING TOXICITY OF THE ANTIDIARRHEAL DRUG: LOPERAMIDE IN PAKISTAN

Ann Med Surg (Lond). 2023 Mar; 85(3): 569–570. doi: 10.1097/MS9.0000000000000170

- Clinicians must always be on the lookout for loperamide misuse in the appropriate setting, and they must diligently report any new instances of loperamide’s usage as a cardiac toxin.

- To prevent the catastrophic effects of loperamide misuse, it is imperative to raise public awareness of the toxicity of loperamide and to recognize loperamide abuse as a significant cause of cardiac dysrhythmias and syncope.

# END OF LECTURE ASSESSMENT

- A 50-year-old male with a history of irritable bowel syndrome (IBS) is prescribed diphenoxylate-atropine for the management of his frequent episodes of diarrhea. During a follow-up visit, he asks why atropine is included in the medication. The patient is concerned about the potential side effects of atropine and wants to understand its role in the treatment. What is the primary purpose of adding atropine to diphenoxylate in this medication?

A. To enhance the anti-diarrheal effect by reducing intestinal motility

**B. To prevent the abuse of diphenoxylate by causing unpleasant side effects at high doses**

C. To provide an anti-inflammatory effect to the gastrointestinal tract

D. To counteract any potential sedative effects of diphenoxylate

E. To act as an excipient in the formulation

- A 67-year-old male with a history of chronic heart failure, currently on digoxin and furosemide, presents with diarrhea for the past 3 days and feels weak and dizzy. Considering his medical history and current medications, which of the following treatments should be approached with caution due to potential drug interactions?

A. Bismuth subsalicylate
**B. Loperamide**
C. Oral Rehydration Solution (ORS)
D. Diphenoxylate-atropine
E. Ocreotide

# END OF LECTURE ASSESSMENT

- A 29-year-old male with a known history of Irritable Bowel Syndrome (IBS) complains of intermittent diarrhea accompanied by cramping, but no blood in the stool. He notes that his symptoms worsen with stress. For management of his IBS-related diarrhea, which of the following medications could be considered?

A. Lactulose
**B. Alosetron**
C. Metronidazole
D. Ciprofloxacin
E. Diphenoxylate

- A 32-year-old woman presents with acute onset of diarrhea characterized by frequent, watery stools. She is experiencing moderate abdominal cramps but no fever, vomiting, or signs of dehydration. She mentions she has not traveled recently and has no history of chronic gastrointestinal conditions. She asks about different treatment options to manage her symptoms effectively. For which of the following conditions is racecadotril specifically indicated as an appropriate treatment?

A. Chronic diarrhea associated with irritable bowel syndrome (IBS)
B. Diarrhea caused by bacterial infections
**C. Acute diarrhea in adults and children as an adjunct to rehydration therapy**
D. Diarrhea due to inflammatory bowel disease (IBD)
E. Traveler's diarrhea

# END OF LECTURE ASSESSMENT

- A 45-year-old woman presented to her physician because of a 2-week history of painless diarrhea that was urgent and usually occurred during meals. After physical examination, lab tests, and colonoscopy, a diagnosis of irritable bowel syndrome was made, and the woman was prescribed an appropriate therapy that included loperamide. Direct activation of which of the following receptors most likely mediated the therapeutic effect of the drug in this patient?

A. Beta-2 adrenergic
B. 5-HT3 serotonergic
C. Alpha-2 adrenergic
**D. Mu opioid**
E. M3 cholinergic


Jazakallah khayr.
THANK YOU