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MECHANISM OF ACTION OF MEDICATIONS USED IN DIARRHEA AND CONSTIPATION

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Abstract*: Gastrointestinal disorders such as diarrhea and constipation are common and clinically significant side effects of many pharmacological agents. This study aims to investigate potential associations between medication use and the prevalence of gastrointestinal symptoms in representative population groups worldwide.*

Keywords: *diarrhoea, constipation, loperamide, polypharmacy, gut motility.*

Аннотация: *Желудочно-кишечные расстройства, такие как диарея и запор, являются распространенными и клинически значимыми побочными эффектами многих фармакологических препаратов. Целью данного исследования является изучение потенциальных связей между применением лекарственных средств и распространенностью симптомов со стороны желудочно-кишечного тракта в репрезентативных группах населения по всему миру.*

Ключевые слова: *диарея, запор, лоперамид, полипрагмазия, моторика кишечника.*

Annotatsiya: *Diareya va qabziyat kabi oshqozon-ichak buzilishlari ko‘plab farmakologik dori vositalarining keng tarqalgan va klinik jihatdan muhim salbiy ta’sirlari hisoblanadi. Ushbu tadqiqotning maqsadi butun dunyo bo‘ylab aholining vakillik guruhlarida dori vositalarini qo‘llash va oshqozon-ichak tizimi simptomlarining tarqalishi o‘rtasidagi potentsial aloqadorliklarni o‘rganishdan iborat.*

Kalit so‘zlar**:** *ich ketishi, qotish, loperamid, polipragmaziya, ichak harakatchanligi.*

Purpose of the Study. *The primary aim of this study is to elucidate the mechanisms by which various pharmacological agents influence gastrointestinal motility and fluid balance, with a particular focus on their role in the development of diarrhoea and constipation. Given the growing prevalence of these gastrointestinal disorders as adverse drug reactions—especially in the context of polypharmacy—this investigation seeks to identify specific medications most commonly associated with these conditions and to analyze the underlying pathophysiological processes they modulate. By examining population-based data and reviewing pharmacodynamic profiles of commonly prescribed agents, the study endeavors to enhance clinical understanding of drug-induced gastrointestinal disturbances and support the development of evidence-based management strategies that minimize patient risk and optimize therapeutic outcomes.*

Introduction*. Gastrointestinal disturbances such as constipation and diarrhoea frequently emerge as commonly encountered symptoms and are regularly identified among adverse effects associated with pharmacological treatments. The objective of this study was to evaluate potential correlations between medication usage and the incidence of these gastrointestinal conditions within a representative population cohort.*

Approximately nine liters of fluid enter the lumen of the small intestine each day. Of this volume, only about two liters originate from ingested liquids, while the remaining seven liters are derived from endogenous secretions produced by various components of the gastrointestinal system. These include secretions from the salivary glands, gastric mucosa, hepatobiliary system (bile), pancreas, and intestinal mucosa. Together, these secretions create a dynamic biochemical

environment essential for facilitating both luminal (intracavitary) and brush-border (parietal) digestion, enabling the enzymatic breakdown and subsequent absorption of macronutrients [14].

Out of a total of 11,078 individuals invited to participate, 4,790 respondents fully completed the questionnaires. Among them, 692 participants (approximately 14.5%) met the criteria for constipation, while 438 individuals (around 9.1%) reported symptoms of diarrhoea. Initiation of pharmacotherapy was associated with a noticeable rise in the prevalence of both conditions, with constipation increasing by 3.1% and diarrhoea by 2.8%. Furthermore, polypharmacy emerged as a significant contributing factor, particularly elevating the risk of diarrhoea.

The use of medications such as furosemide, levothyroxine sodium, and ibuprofen demonstrated a statistically significant association with increased reports of constipation, whereas lithium and carbamazepine showed strong correlations with a heightened incidence of diarrhoea. The additional drug-related prevalence ranged from 6.2% in the case of ibuprofen-associated constipation to as high as 29.4% for lithium-associated diarrhea [9].

In the management of diarrhoea, primary emphasis should be placed on addressing the underlying etiology responsible for its development. This principle underscores the need for individualized therapeutic strategies depending on the pathophysiological mechanism involved. For instance, the treatment of chronic watery diarrhoea associated with microscopic colitis—characterized by intraepithelial lymphocytic infiltration of the colonic mucosa while maintaining intact mucosal architecture—differs significantly from that of chronic exudative diarrhoea observed in cases of ulcerative colitis. In the latter, diarrhoea results from pronounced inflammatory damage to the mucosal lining of the large intestine, necessitating anti-inflammatory and immunosuppressive interventions. Thus, accurate diagnosis of the diarrhoeal subtype is essential for guiding targeted and effective treatment approaches [5].

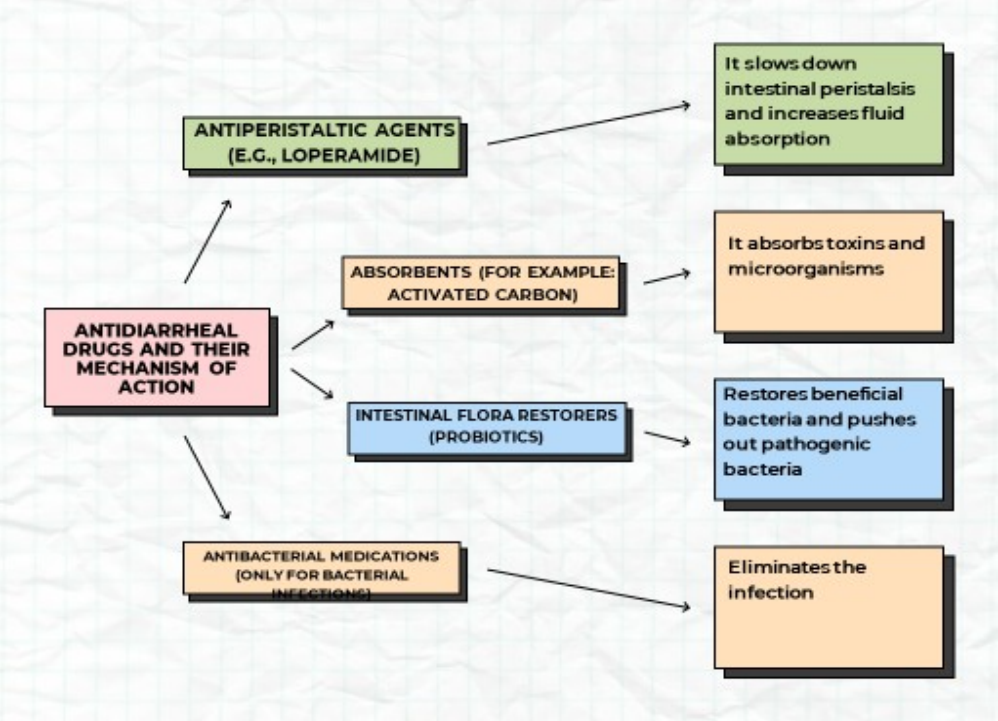

Figure 1. Mechanisms of action of antidiarrheal agents: a pharmacological overview

Simultaneously, a range of pharmacological agents are available that exert symptomatic control by targeting specific pathophysiological mechanisms involved in the development of chronic diarrhoea (see Table 1).

Table 1. Symptomatic antidiarrheal medications

Drug Categories
Oral rehydration products
Medications that reduce intestinal motility
Astringent and demulcent agents
Enterosorbents
Intestinal antiseptics and antibiotics
Anti-inflammatory medications
Prebiotics and probiotics
Enzyme preparations that improve intestinal digestion

Empirical symptomatic antidiarrheal therapy is typically indicated under three distinct clinical circumstances:

1. As an initial or provisional intervention aimed at alleviating symptoms before a comprehensive diagnostic evaluation is completed and the underlying etiology of diarrhoea is established;

2. Following diagnostic assessment when the underlying cause of diarrhoea remains unconfirmed or cannot be clearly identified despite thorough evaluation;

3. When a definitive diagnosis has been made, but targeted or disease-specific therapy is either inaccessible or proves ineffective in alleviating the diarrhoeal symptoms [12].

Oral rehydration therapy (ORT) with glucose-electrolyte solutions remains the most effective and physiologically appropriate approach for restoring fluid and electrolyte balance in patients with diarrhoea. In cases where clinical signs of dehydration are present, prompt administration of oral rehydration solutions (ORS) enriched with essential electrolytes and glucose is strongly recommended to prevent further fluid loss and maintain homeostasis [2].

Glucosolan (Glucosolanum) is a rehydration salt formulation designed for oral rehydration therapy. It is produced in the form of tablets and powders with two distinct compositions, packaged as sachets No. 1 and No. 2. Solani tablets and sachets No. 1 contain 3.5 g of sodium chloride, 1.5 g of potassium chloride, and 2.5 g of sodium bicarbonate. These are complemented by glucose-containing components—either 5 g glucose tablets or sachets No. 2 containing 20 g of glucose.

Glucosolan is administered orally, independent of food intake. For use, one Solani tablet and four glucose tablets—or the contents of both sachets No. 1 and No. 2—are dissolved in 100 ml of cooled, previously boiled water to prepare a rehydration solution suitable for correcting fluid and electrolyte deficiencies during diarrhoeal episodes [3].

Regidron (Rehydron) is a widely used oral rehydration solution available in 18.9 g sachets, each containing 2.9 g of sodium citrate, 2.5 g of potassium chloride, and 10 g of glucose. The contents of a single sachet are dissolved in 1 liter of water to prepare a rehydration fluid intended for oral administration.

Regidron may be used in conjunction with salt-free fluids such as tea, plain water, or unsweetened compote to support hydration. The solution has an osmolality of 260 mOsm/L and a pH of 8.2. Compared to standard WHO-recommended oral rehydration solutions, Regidron features a slightly reduced osmolality—an attribute supported by clinical evidence demonstrating enhanced rehydration efficacy. Additionally, it has a lower sodium concentration to reduce the risk of hypernatremia and a higher potassium content to facilitate more rapid correction of potassium depletion [6].

Additionally, patients may be advised to prepare a homemade oral rehydration solution using readily available ingredients. The recommended formulation includes 8 teaspoons of sugar,

1 teaspoon of table salt, freshly squeezed juice from 2 oranges or grapefruits, and sufficient water to bring the total volume to 1 liter. This solution should be consumed in small, regular amounts—approximately one glass per hour—to maintain adequate hydration and electrolyte balance during episodes of diarrhea [13].

Parenteral fluid therapy is required in only 5–15% of diarrhoeal cases, typically when oral rehydration is not feasible due to severe dehydration, persistent vomiting, or impaired consciousness. In such situations, intravenous administration of crystalloid solutions is preferred. Commonly used fluids include Trisol, Quartasol, Chlosol, Acesol, and isotonic saline (0.9% sodium chloride solution), which effectively restore circulating volume, correct electrolyte imbalances, and support hemodynamic stability [9].

Since the 1970s, synthetic agonists of intestinal opioid receptors—most notably loperamide—have been widely employed in the management of diarrhoea. Loperamide acts by reducing intestinal motility and enhancing water and electrolyte absorption in the gut, thereby decreasing stool frequency and improving consistency. Its peripheral mechanism of action, with minimal penetration across the blood-brain barrier, allows for effective symptomatic control of diarrhoea with a low risk of central opioid effects [10].

Loperamide demonstrates a high affinity for μ-opioid receptors located in the intestinal wall, where it selectively accumulates in the smooth muscle layers and enteric nerve plexuses. Unlike morphine, loperamide does not produce systemic opioid effects despite being absorbed in the gastrointestinal tract. This is attributed to its rapid transport via the portal venous system to the liver, where it undergoes extensive first-pass metabolism, including conjugation. Consequently, only a minimal fraction of the administered dose—less than 0.3%—enters systemic circulation. Due to its limited bioavailability and inability to cross the blood-brain barrier, loperamide lacks central nervous system activity and does not induce typical opioid-related central side effects. The drug is primarily excreted as hepatic conjugates via bile and feces, with a smaller portion eliminated in the urine. Its therapeutic effect begins quickly after administration and typically lasts between 4 to 6 hours, making it a safe and effective agent for the symptomatic treatment of diarrhea [1].

The primary mechanism of action of loperamide (as summarized in Table 2) involves the suppression of intestinal motility. This is achieved through the inhibition of presynaptic acetylcholine release in the enteric nervous system and the suppression of phase II of the migrating motor complex (MMC). These effects lead to a significant prolongation of intestinal transit time, which in turn facilitates increased absorption of water and electrolytes across the intestinal mucosa, thereby contributing to the reduction of stool frequency and liquidity in patients with diarrhea [4].

In addition to its effects on intestinal motility, loperamide increases the tone of the anal sphincter, contributing to improved continence in patients with diarrhoea. It also reduces the secretion of mucus in the colon and further enhances the absorption of water and electrolytes throughout the intestinal tract. Moreover, loperamide exerts an antisecretory effect by inhibiting calmodulin activity and blocking calcium channels, thereby reducing intracellular calcium-mediated secretion. It also antagonizes the action of various intestinal peptides and neurotransmitters that elevate epithelial membrane permeability, thus stabilizing the intestinal barrier and minimizing fluid loss [7].

Table 2. The main mechanisms of the antidiarrheal action of loperamide

Slowing of intestinal transit	Secretion inhibition	Other mechanisms
- *Inhibition of propulsive*	- *Calcium channel*	- *Increased tone of the anal*

peristalsis	*blockade*	*sphincter*
- Suppression of phase II MMC	*- Suppression of the secretory effects of neuroendocrine peptides*	
	- Decreased secretion of mucus	

Loperamide is marketed under various trade names in the Russian Federation. Commonly available formulations include: Diarol, Diasorb, Imodium, Lopedium, Loperacap, Loperamide hydrochloride, Loperamid-Akri, Neoenteroseptol, Superilo, and Enterobene. These preparations may differ slightly in excipients, release forms (capsules, tablets, orodispersible forms), and manufacturers, but all contain loperamide as the active antidiarrheal agent.

In the management of chronic diarrhoea, loperamide is initially administered at a dose of 4 mg (equivalent to 2 capsules), followed by 2 mg after each subsequent episode of defecation. The maximum allowable daily dose is 16 mg when used under medical supervision, while for unsupervised or over-the-counter use, the limit is 8 mg per day. If the use of maximum therapeutic doses over a period of at least 10 consecutive days fails to result in a significant reduction or cessation of diarrhoeal symptoms, treatment should be discontinued and further diagnostic evaluation should be considered [12].

During treatment with octreotide, patients require regular monitoring to ensure safety and therapeutic efficacy. Stool analysis for fat content should be conducted every 3 days to detect possible steatorrhea, indicating impaired fat absorption. Blood glucose levels must be measured at the initiation of therapy and upon any change in dosage, due to the risk of glucose metabolism disturbances. For patients undergoing long-term treatment, serum thyroxine (T4) levels should be assessed periodically to monitor potential thyroid function alterations. Additionally, to evaluate treatment response, it is recommended to measure biomarkers such as 5-hydroxyindoleacetic acid (5-HIAA) and vasoactive intestinal peptide (VIP) during the treatment course. Prolonged use of octreotide is also associated with an increased risk of cholelithiasis, necessitating vigilance for gallstone formation [11].

When used as an antidiarrheal agent in patients with gastrointestinal tract tumors, octreotide is administered subcutaneously. The initial dose is typically 50 micrograms (0.05 mg) once or twice daily, with gradual titration based on individual tolerance and clinical response. The total daily dose may be increased to 100–600 micrograms (0.1–0.6 mg), divided into 2 to 4 administrations per day [9].

Preferred injection sites include the thigh or abdominal area, with rotation of injection sites recommended to minimize local irritation or induration. To optimize absorption and reduce gastrointestinal side effects, injections should be given between meals and before bedtime.

Among the various classes of antidiarrheal agents, special attention is given to alosetron, a selective 5-HT_3 (serotonin) receptor antagonist. Its primary indication is the treatment of severe, refractory diarrhoea-predominant irritable bowel syndrome (IBS-D) in female patients who have not responded adequately to conventional therapies. Due to the risk of serious adverse effects, including ischemic colitis and severe constipation, alosetron is prescribed only under strict medical supervision and in accordance with specific regulatory guidelines (see Table 3).

Table 3. Antidiarrheal Drugs

Names of medications	Mechanisms of action	Specific instructions
5-HT_3 receptor antagonist *- Alosetron,*	*Alosetron exerts its therapeutic effect by blocking serotonin (5-HT_3) receptors on the enteric nerve endings within the*	*Indications: IBS with diarrhea* *Side effects:*

- Silansetron, *- Ondansetron,* *Granisetron*	*gastrointestinal tract. This action leads to the suppression of water and electrolyte secretion in the intestines, inhibition of colonic motility, and a reduction in visceral hypersensitivity—factors that collectively contribute to the alleviation of diarrhoeal symptoms and abdominal discomfort in patients with irritable bowel syndrome.*	*increased risk of ischemic colitis*
Enkephalin-like peptide *- Nifalatide*	*Enkephalins, which are endogenous opioid peptides, exert their physiological effects by activating δ-opioid receptors located in the gastrointestinal tract. This activation leads to enhanced absorption and reduced secretion of electrolytes—particularly sodium and chloride ions—in the small intestine. As a result, enkephalins contribute to the regulation of intestinal fluid balance and exhibit a natural antidiarrheal effect.*	*In clinical practice, is not yet being applied*
Enkephalinase inhibitor *- Racecadotril (acetorphan).*	*It exhibits only an antisecretory effect and does not affect intestinal motility. It reduces water and electrolyte hypersecretion in the small intestine caused by cholera toxin or inflammation, but does not affect the basal secretory activity.*	*Used as an adjunctive therapy in the management of acute diarrhoea in infants and children over 3 months of age, particularly in cases where oral rehydration alone is insufficient to adequately control the clinical symptoms and restore fluidelectrolyte balance.*

CONCLUSION

Gastrointestinal disturbances such as diarrhea and constipation are frequently encountered adverse effects associated with various pharmacological therapies. This study underscores the critical role that specific medications—including furosemide, levothyroxine, ibuprofen, lithium, and carbamazepine—play in modulating gut motility and fluid balance, thereby contributing to the development of these conditions. Notably, polypharmacy significantly increases the risk of diarrhea, emphasizing the importance of cautious drug prescribing practices. Symptomatic management strategies for diarrhea require a tailored approach based on the underlying pathophysiology. The use of oral rehydration therapy remains foundational for fluid and electrolyte restoration, while pharmacological interventions—such as loperamide, octreotide, and serotonin receptor antagonists—offer effective symptomatic control by targeting motility,

secretion, and absorption mechanisms. In particular, loperamide demonstrates efficacy through its selective action on intestinal μ-opioid receptors, slowing transit time and enhancing reabsorption.

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