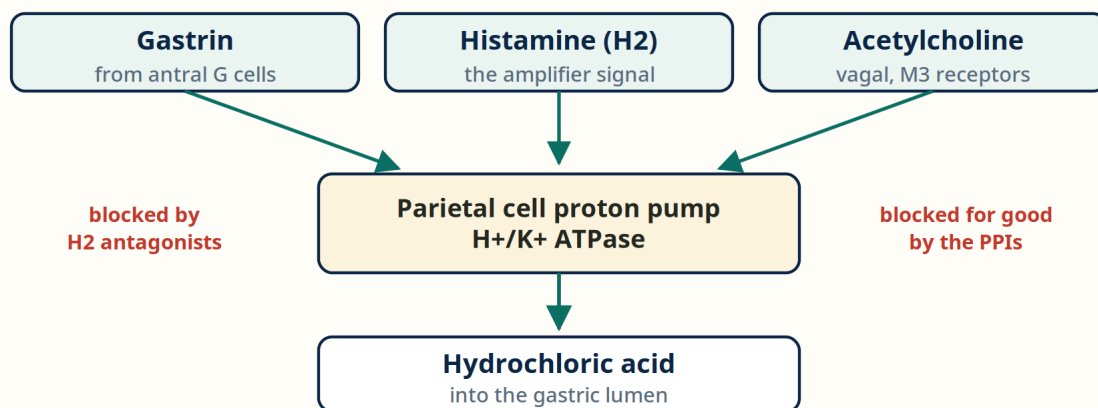


4.1 The parietal cell and the regulation of gastric acid

The gastric parietal cell secretes hydrochloric acid through one final machine, the **H⁺/K⁺ ATPase** proton pump in its canalicular membrane, driven by three stimulatory inputs that converge on it: **histamine** from enterochromaffin like cells acting at **H₂ receptors** (the amplifier, raised by gastrin), **gastrin** from antral G cells acting at CCK₂ receptors directly and through histamine release, and **acetylcholine** from vagal fibres at M₃ receptors. The brakes are prostaglandins E₂ and I₂ and somatostatin, which restrain histamine release and the parietal cell itself; this prostaglandin brake is why NSAIDs, which remove it, cause ulcers even without extra acid. Acid is both a digestive tool and a threat, held off the mucosa by the mucus bicarbonate barrier, mucosal blood flow and rapid epithelial repair: peptic ulcer disease and reflux are what happen when attack (acid, pepsin, *Helicobacter pylori*, NSAIDs) outlasts defence.

Regulation of Gastric Acid Secretion



Prostaglandins brake the system. NSAIDs remove the brake, which is why they cause ulcers.

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Figure: Regulation of gastric acid secretion. Three stimulants converge on the proton pump, which is why blocking the pump itself beats blocking any single input.

4.2 Antiulcer drugs and the eradication of *H. pylori*

Treatment either cuts acid or rebuilds defence. **Proton pump inhibitors** (omeprazole, pantoprazole, esomeprazole) are acid activated prodrugs that concentrate in the canaliculus and bind the proton pump covalently; because the bond is irreversible, acid secretion waits for new pumps, so one daily dose controls acid for a day and a half, and the dose is taken before the first meal, when pumps are inserted and active. They are the strongest and most durable acid suppressants and the backbone of ulcer healing, reflux disease and eradication regimens; long term use carries small but real costs (magnesium and B₁₂ malabsorption, fracture risk, gut infection risk). **H₂ receptor antagonists** (ranitidine's successors famotidine and others) block the histamine amplifier: effective, especially for night acid, but subject to tolerance and weaker than PPIs. **Antacids** (aluminium and magnesium hydroxides, calcium carbonate)

neutralise acid already secreted, fast and brief, useful for symptoms, with diarrhoea (magnesium), constipation (aluminium) and drug chelation as their footprints. **Mucosal protectives**: sucralfate polymerises in acid into a physical bandage over the ulcer base; misoprostol replaces the missing prostaglandin in NSAID users; colloidal bismuth coats and also kills *H. pylori*. **Helicobacter pylori**, the bacterium behind most peptic ulcers and gastric cancer risk, is eradicated, not merely suppressed: a PPI with two antibiotics (clarithromycin and amoxicillin, or metronidazole) for fourteen days, with bismuth quadruple therapy where clarithromycin resistance, now common, defeats the standard triple. Eradication, not lifelong acid suppression, is what changed ulcer disease from a surgical career into a two week prescription.

4.3 Prokinetic drugs

Prokinetics speed the gut by releasing its own excitatory transmitters or blocking its brakes.

Metoclopramide blocks dopamine D2 receptors in the gut wall and chemoreceptor trigger zone and, at higher doses, adds 5-HT4 agonism (more acetylcholine release) and 5-HT3 antagonism: it empties the stomach in gastroparesis and doubles as an antiemetic, but crosses into the brain, so dystonias in the young, sedation and, with prolonged use, tardive dyskinesia and hyperprolactinaemia limit its course.

Domperidone is the same D2 logic kept outside the blood brain barrier: antiemetic and prokinetic with far fewer central effects, carrying instead a cardiac QT caution. **Mosapride and prucalopride** are selective 5-HT4 agonists producing motility without dopamine or cardiac baggage (prucalopride is used more for constipation, section 4.6). **Erythromycin** in low dose is a motilin receptor agonist, the fastest gastric emptier of the set, defeated by tachyphylaxis within weeks. Cisapride, the class's cautionary monument, was withdrawn for fatal QT arrhythmias, and every successor is examined against its ghost.

4.4 Antiemetic drugs

Vomiting is coordinated by a medullary centre fed by four inputs: the **chemoreceptor trigger zone** in the area postrema, outside the blood brain barrier, tasting blood for toxins through dopamine D2, serotonin 5-HT3, neurokinin NK1 and opioid receptors; the **vestibular apparatus**, signalling through histamine H1 and muscarine receptors (motion sickness); the **gut**, through vagal 5-HT3 receptors fired by mucosal serotonin release; and the **cortex**, anticipation and anxiety. Each drug family guards one gate:

Family	Gate guarded	Best uses
5-HT3 antagonists: ondansetron, granisetron, palonosetron	CTZ and gut vagal afferents	Chemotherapy, radiotherapy, postoperative vomiting; headache and constipation are their costs; QT care with dose
NK1 antagonists: aprepitant	CTZ, central	Delayed chemotherapy emesis, added to a setron and dexamethasone
D2 antagonists: metoclopramide, domperidone, prochlorperazine	CTZ	Migraine and gastroparesis emesis, general purpose cover, with the central costs of section 4.3
H1 antihistamines: promethazine, meclizine; anticholinergic hyoscine	Vestibular pathway	Motion sickness (hyoscine patch is the classic), vertigo
Corticosteroids: dexamethasone	Mechanism debated, central	Chemotherapy combinations
Cannabinoids: nabilone	Central	Refractory chemotherapy emesis, where legal

Highly emetogenic chemotherapy therefore gets a triple shield (NK1 antagonist plus setron plus dexamethasone), the same combination logic as chemotherapy itself.

4.5 Antidiarrhoeal drugs

Diarrhoea kills by water and salt loss, so the first drug is not a drug: **oral rehydration solution**, glucose driven sodium and water absorption, which has saved more lives than every antimotility agent combined. Drugs then work on secretion and motility. **Opioid antimotility agents** (loperamide, and codeine or diphenoxylate behind it) act at gut mu receptors to slow transit and increase absorption; loperamide is engineered to stay out of the brain, and all are dangerous in invasive bacterial dysentery and ulcerative colitis, where stopping the gut traps the pathogen and can dilate the colon to perforation. **Racecadotril** inhibits intestinal enkephalinase, protecting the gut's own antisecretory enkephalins: less secretion with no motility arrest, safe in children. **Adsorbents and bismuth** (kaolin, bismuth subsalicylate) are modest symptom helpers. **Antibiotics** are for specific causes (cholera, shigella, traveller's diarrhoea, Clostridioides difficile, which answers to oral vancomycin or fidaxomicin), not for diarrhoea in general, and antimotility drugs never substitute for finding the cause in a sick patient.

4.6 Drugs for constipation

Constipation is treated by adding water, bulk or propulsion, in that order of gentleness. **Bulk forming agents** (ispaghula, methylcellulose) are indigestible fibre that holds water and stretches the bowel into action, the physiological option, useless without fluid intake. **Osmotic laxatives** hold water by solute force: lactulose (also trapping ammonia in hepatic encephalopathy), macrogols (polyethylene glycol), and the saline agents magnesium hydroxide and sodium phosphate, the last two risky in renal failure. **Stimulant laxatives** (senna, bisacodyl) irritate the enteric nerves into propulsive contraction: effective, fast, unfairly feared, since dependence and bowel damage at normal doses are largely myth, though cramping is real. **Stool softeners** (docusate) are weak detergents of marginal effect. The modern targeted agents work on secretion and receptors: **lubiprostone** opens chloride channels, **linaclotide** activates guanylate cyclase C (both pouring fluid into the lumen), and **prucalopride** (section 4.3) drives motility through 5-HT₄, all reserved for chronic constipation that simpler measures fail. Opioid induced constipation answers to the same ladder plus, in palliative care, peripherally acting mu antagonists such as methylnaltrexone.

4.7 Drugs for irritable bowel syndrome

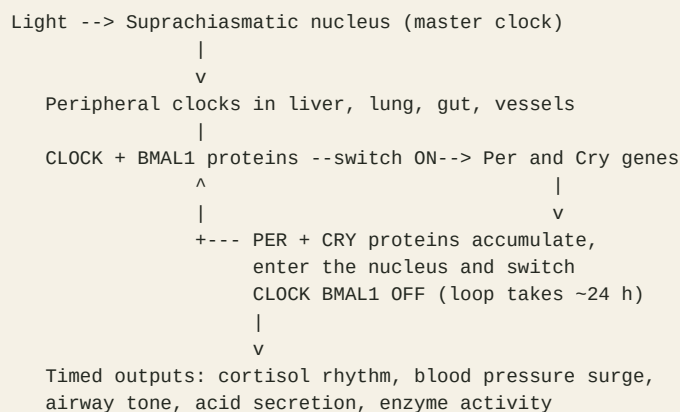
Irritable bowel syndrome is a disorder of gut brain interaction: pain, bloating and disordered bowel habit without structural disease, so therapy is symptom aimed. **Antispasmodics** (mebeverine, dicyclomine, peppermint oil) relax gut smooth muscle against pain and spasm. For constipation predominant IBS, the secretagogues of section 4.6 (linaclotide, lubiprostone) and simple osmotic laxatives serve; for diarrhoea predominant IBS, loperamide, the bile acid binder colesevelam in bile acid diarrhoea, **rifaximin** (a non absorbed antibiotic for bloating and diarrhoea), and alosetron, a 5-HT₃ antagonist restricted for its ischaemic colitis risk. Low dose **tricyclic antidepressants** (amitriptyline) quiet visceral hypersensitivity, an analgesic use unrelated to mood, while SSRIs help the pain and the anxiety that travels with the syndrome. Dietary work (a supervised low FODMAP approach) is a genuine co therapy, and the honest pharmacological summary is that IBS drugs manage, they do not cure.

4.8 Chronopharmacology: biological and circadian rhythms

The body is not the same patient at different hours. A master clock in the hypothalamic **suprachiasmatic nucleus**, set daily by light, drives roughly 24 hour (**circadian**) rhythms of cortisol (peak at waking), temperature, blood pressure (the early morning surge), airway calibre (narrowest near 4 am), gastric acid (highest at night), and drug handling itself, through clock genes (CLOCK, BMAL1, PER, CRY) running feedback loops in almost every cell. Two pharmacological consequences follow. **Chronokinetics**: absorption, distribution, metabolism and excretion vary with the hour, so the same dose gives different levels at different times. **Chronodynamics**: the target's sensitivity varies too: the HMG CoA reductase of cholesterol synthesis works hardest at night, asthmatic airways tighten at night, rheumatoid inflammation

flares in the early morning on an interleukin 6 rhythm.

THE MOLECULAR CLOCK, SIMPLIFIED



4.9 Chronotherapy in practice: timing the dose to the disease

Chronotherapy schedules the dose so peak drug meets peak disease. In **cardiovascular disease**, events cluster in the morning surge of pressure, platelet activity and sympathetic tone; trials of bedtime dosing of antihypertensives reported large benefits and remain debated, but the principle that timing matters is established, and short acting statins such as simvastatin are dosed in the evening to meet the night peak of cholesterol synthesis (the long acting atorvastatin and rosuvastatin are indifferent to the clock). In **asthma**, symptoms and airway narrowing peak in the early morning hours, so once daily inhaled steroid and long acting bronchodilator cover is arranged to be strongest overnight, and a single afternoon dose of systemic steroid in exacerbations protects the night. In **peptic ulcer**, acid secretion peaks at night and the ulcer heals in a quiet stomach, so H2 blockers were classically given as a single bedtime dose and PPIs are timed before the meal that wakes the pumps. In **diabetes**, insulin regimens mimic the rhythm they replace: long acting basal insulin in the evening or morning matched to the dawn rise in glucose (the dawn phenomenon of early morning growth hormone and cortisol), rapid acting doses with meals. Rheumatoid arthritis answers to modified release prednisone taken at night and releasing near 2 am, ahead of the morning inflammatory peak. The examination point is symmetrical to the rest of pharmacology: dose, route and duration are joined by a fourth variable, time.

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