Antiemetic Drugs

Antiemetics is a group of drugs that suppress or prevent vomiting. The **chemoreceptor trigger zone (CTZ)**, the vestibular system, vagal and spinal afferents and other areas in the central nervous system relay to the **nucleus tractussolitarius (NTS, the vomiting center)**. As the CTZ (in area postrema) is unprotected by the blood brain barrier, it is exposed to drugs in the bloodstream, hormones, toxins and other substances that may stimulate emesis.

Classification of Antiemetics

Antiemetics are classified on the basis of their target receptors. The **CTZ** and **NTS** express many receptors including histamine (H1), serotonin (5-HT3), cholinergic (muscarinic), dopamine (D2), opioid and probably NK1.

S.NO	**Category**	**Drugs**
1	Serotonin (5-HT3) antagonists	**Ondansetron**, Granisetron, Dolasetron, Palonosetron, Tropisetron
2	Corticosteroids	**Dexamethasone**, Methylprednisolone
3	Neurokinin receptor antagonists	**Aprepitant**, Fosaprepitant
4	Phenothiazines and Butyrophenones	Prochlorperazine, **Promethazine**, Thiethylperazine, Droperidol, Doxylamine
5	Substituted Benzamides/Prokinetics	**Metoclopramide**, Trimethobenzamide Domperidone
6	H1 antihistamines	Diphenhydramine, Dimenhydrinate, Meclizine, **Hyoscine** (Scopolamine)
7	Benzodiazepines	Diazepam, **Lorazepam**

8	Cannabinoids	Dronabinol, Nabilone

- setrons are 5-HT3 antagonists
- azepams are Benzodiazepines

Individual drugs

Ondansetron: This **selective 5-HT3 antagonist** acts mainly by affecting the **peripheral 5-HT3 receptors** on the spinal and vagal afferents. Therefore, vomiting related to **vagal stimulation**(like **postoperative vomiting**) and chemotherapy-associated emesis are effectively controlled with this drug. **Motion sickness-related** vomiting is poorly controlled.

Ondansetron, Granisetron, and Dolasetron have a serum half-life of 4-9 hours. They are administered once daily orally or intravenously. They are usually administered 30 minutes prior to **chemotherapy.**

Granisetron is 10-15 times more potent than Ondansetron.

Palonosetron has a greater affinity to **5-HT3 receptors** and its serum half-life is 40 hours.

All of the above drugs undergo **hepatic metabolism** (dose reduction is not needed in renal disease).

These drugs are generally well-tolerated and safe. They can **prolong the QT interval** (most prolongation is accomplished with Dolasetron).

Dexamethasone: This corticosteroid **potentiates the effect of 5-HT3 antagonists**, especially in cases of chemotherapy. Side effects of steroids include **weight gain**, **osteoporosis**, increased hair growth, etc., and should be used only in highly **emetogenic chemotherapy**.

Aprepitant: This **Neurokinin receptor (NK1) antagonist** acts on the area postrema (central blockade). It is taken **orally** and has a half-life of 12 hours.

Fosaprepitant is administered **intravenously** and gets converted to Aprepitant within 30 minutes of infusion. Aprepitant undergoes hepatic metabolism (**CYP3A4**).

These drugs are used in combination with a **5-HT3 antagonist** and a corticosteroid to prevent delayed emesis in chemotherapy patients. Side effects include fatigue, **diarrhea,** and dizziness. Drugs that **inhibit CYP3A4** (eg., Ketoconazole, Ciprofloxacin, Clarithromycin) may lead to increased plasma levels of Aprepitant. It can also **decrease the INR** in individuals on Warfarin.

Promethazine and other phenothiazines have antiemetic and sedative actions in addition to being **antipsychotics**. Promethazine has a duration of action of 4-6 hours. Adverse effects include dryness of mouth and sedation. Intravenous administration can cause severe **tissue injury**, burning or **thrombophlebitis**, leading to even **gangrene** and the need for amputation. The preferred mode of administration is deep intramuscular. It is avoided in children less than 2 years old due to the risk of **respiratory depression**. It is metabolized in the liver (CYP2D6) and has a half-life of 10 hours (i.m.), 9-16 hours (i.v.), and 16-19 hours (oral).

Droperidol, an antipsychotic butyrophenone, exhibits antiemetic properties secondary to central dopaminergic blockade. The onset of action is within 3-10 minutes of intake. Usually, its action lasts for 2-4 hours, though sometimes it reaches up to 12 hours. Side effects include extrapyramidal symptoms and hypotension. It may cause QT prolongation leading to **torsades de pointes**.

Doxylamine is an H1 antihistaminic that has a pronounced anticholinergic activity. It is specifically promoted in India in combination with Pyridoxine for **pregnancy-related emesis**. However, it is not recommended for this use in the USA or the UK.

Metoclopramide is thought to prevent emesis by **dopamine receptor blockade**. It enhances **gastric peristalsis** and causes relaxation of the pylorus and the proximal duodenum. Consequently, gastric emptying is sped up. Moreover, it increases the lower esophageal sphincter tone, preventing **gastroesophageal reflux**. Its antiemetic action is brought about by **antidopaminergic (D2**) action on the CTZ. Adverse effects include sedation, dizziness, **galactorrhea, gynecomastia** and **extrapyramidal features** like dystonia, **parkinsonism,** and restlessness. It can block the therapeutic action of levodopa due to DA receptor blockade in the basal ganglia.

Domperidone is a **D2 antagonist**, related chemically to Haloperidol, but related pharmacologically to Metoclopramide. However, it has a lower antiemetic and **prokinetic effect**when compared to Metoclopramide. Domperidone crosses the blood-brain barrier poorly

and hence, extrapyramidal side effects are rare, but **hyperprolactinaemia** may occur. It acts on the CTZ which is not protected by the blood-brain barrier. It has been administered with Levodopa and Bromocriptine as it counteracts their dose-limiting emetic action in parkinsonism, while the therapeutic effect remains unchanged. Domperidone is absorbed orally, but due to considerable first-pass metabolism, bioavailability is only 15%. The metabolites are released via urine. Its plasma half-life is around 7.5 hours. Side effects are less compared to Metoclopramide. However, **cardiac arrhythmias** have been reported with rapid intravenous administration.

Diphenhydramine is a first-generation H1 antihistaminic agent which has a good sedative effect. It is indicated for **motion sickness**. Its onset of action is within 15-30 minutes, and its duration reaches up to 10-12 hours. It undergoes first-pass metabolism in the liver, and the metabolites are excreted mainly via urine. Side effects include **anticholinergic effects** like dry mouth, cycloplegia, urinary retention, and confusion.

Meclizine is also an H1 antihistaminic, which has a lot less anticholinergic effects. Other than its use for motion sickness, it may also be used for the treatment of **vertigo** due to **labyrinthitis**. Its onset of action is within 30-60 minutes and lasts for 12-24 hours. It is metabolized in the liver **(CYP2D6).**

Hyoscine (Scopolamine) is a muscarinic receptor antagonist which is one of the **most preferred agents for motion sickness**. As the anticholinergic manifestations are high when administered orally or parenterally, it is usually used as a **transdermal patch**. The transdermal patch contains 1.5 mg of Hyoscine which can be placed behind the pinna and delivers the drug over a span of three days. This patch should be applied four hours before the planned travel. Hyoscine is metabolized by the liver and excreted in the urine. It has a half-life of 9.5 hours.

Lorazepam and Diazepam are used prior to chemotherapy to decrease anticipatory or anxiety-related vomiting. They increase the **frequency of opening** of $GABA_A$: BZD receptor-Cl^- Channels. Its onset of action is within 1-3 minutes and lasts for up to 8 hours. It undergoes **glucuronic acid conjugation** in the liver, and the inactive metabolites are excreted via urine.

Dronabinol is, in fact, **Δ^9-tetrahydrocannabinol (THC),** the main psychoactive constituent in marijuana. It undergoes significant first-pass metabolism in the liver, and its metabolites are

excreted gradually over days to weeks. Its major use is to prevent chemotherapy-related emesis. **Tachycardia**, **conjunctival congestion,** and **orthostatic hypotension** are the autonomic side effects associated.

Nabilone is a related **THC analog** approved for clinical use in the USA. It acts on cannabinoid receptors in the central nervous system. It should be avoided in emotionally disturbed patients and those with **concomitant alcoholism** or use of psychotropic drugs. It can affect driving and the ability to perform hazardous tasks. The elimination half-life for the parent compound is two hours and that for the metabolites is 35 hours. A good part is excreted via bile after undergoing metabolism by direct enzymatic oxidation.

ANTIULCER DRUGS

INTRODUCTION An Ulcer is Erosion in the lining of the stomach or the first part of the small intestine, an area called the duodenum. Ulcers damage the mucosa of the alimentary tract, which extends through the muscularis mucosa into the sub mucosa or deeper. The ulcers may exist in the lower part of food pipe (oesophagus), in the stomach or in the initial part of the intestine (duodenum).

Ulcers that form in the stomach are called gastric ulcers ; in the duodenum, they are called duodenal ulcers . Both types are referred to as peptic ulcers . About 10% of all adults are affected with Peptic ulcers at some time in their life. The incidence of Peptic ulcers is more common in males as compared to females. Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (Advil) can also cause ulcers . Open Sore (Ulceration) the white Part in the upper Lining of the Stomach.

PHYSIOLOGY OF GASTRIC ACID SECRETION Gastric acid secretion is a complex, continuous process in which multiple central and peripheral factors contribute to a common endpoint: the secretion of H + by parietal cells. Neuronal (acetylcholine, ACh), paracrine (histamine), and endocrine (gastrin) factors all regulate acid secretion . Their specific receptors (M 3 , H 2 , and CCK 2 receptors, respectively) are on the basolateral membrane of parietal cells in the body and fundus of the stomach.

The H 2 receptor is a GPCR that activates the G s - adenylcyclase -cyclic AMP-PKA pathway. ACh and gastrin signal through GPCRs that couple to the G q -PLC-IP 3 -Ca 2+ pathway in parietal cells. In parietal cells, the cyclic AMP and the Ca 2+ -dependent pathways activate H + ,K + - ATPase (the proton pump), which exchanges hydrogen and potassium ions across the parietal cell membrane.

Mucosal Protective Agents

Sucralfate

- **Mechanism of Action:**
  - Sucralfate is a salt of sucrose complexed to sulfated aluminum hydroxide
  - In acidic solutions it forms a viscous, tenacious paste that binds selectively to ulcers or erosions for up to 6 hrs

        - The negatively charged sucrose sulfate binds to positively charged proteins in the base of ulcers or erosions, forming a physical barrier that restricts further caustic damage.
    - Indications:
        - Duodenal ulcer.
    - **Pharmacokinetics:**
        - Less than 3% of intact drug gets absorbed into the body. The remainder gets excreted in the feces.
    - **Side Effects:**
        - Constipation & **black** stool
    - **Major drug interactions:**
        - don't take with H2 blockers or antacids**,** which reduce the acidic environment required for activation of sucralfate.

Bismuth subsalicate

- **Mechanism of Action:**
    - Like sucralfate, bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin
    - It may also stimulate prostaglandin, mucus & bicarbonate secretion
    - Has some antimicrobial effects (e.g. against *H. pylori*) (mechanism is unclear)(Vakil, 2016)
    - Binds enterotoxins (useful in preventing or treating traveler's diarrhea)
    - It reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin & chloride secretion
- **Indications:**
    - Treatment of dyspepsia & acute diarrhea
    - Prevention of traveler's diarrhea
- **Side Effects:**
    - **Black** stool

H2 Antihistamines

Cimetidine

- **Drug Class:** H2 Antagonist
- **Mechanism of Action:**

- Competitive antagonist at the H2 receptor.
- Blocks H2 receptors in parietal cells which suppresses basal and meal-stimulated acid secretion in a dose-dependent manner
- Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

- **Indications:**
  - Short-Term Treatment of Active Duodenal Ulcer
  - Maintenance Therapy for Duodenal Ulcer Patients at Reduced Dosage after Healing of Active Ulcer
  - Short-Term Treatment of Active Benign Gastric Ulcer
  - Erosive Gastroesophageal Reflux Disease (GERD) (Oral Solution Only)
  - Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients (Injection Only)
  - The Treatment of Pathological Hypersecretory Conditions: (i.e., Zollinger-Ellison Syndrome).
- **Side Effects:**
  - H2 blockers are extremely safe drugs, with side effects in less than 3% of patients (headaches, diarrhea, fatigue).
  - Mental status changes may occur with i.v. administration in elderly.
  - Endocrine effects: cimetidine inhibits the binding of dihydrotestosterone to androgen receptors & inhibits metabolism of estradiol, both of which can alter the androgen/estrogen balance in men & increase prolactin levels. With chronic use may cause gynecomastia or impotence in men & galactorrhea in women. Drug-induced gynecomastia is not seen with other H2 blockers, but can be caused by other drugs (Bowman et al, 2012).
- **Major drug interactions:**
  - **Cimetidine** inhibits multiple forms of cytochrome P450 (CYP1A2, CYP2C9, CYP2D6 & CYP3A4). Hence the half-lives of drugs metabolized by these pathways may be prolonged. Examples: warfarin, theophylline, phenytoin, lidocaine, quinidine, propranolol, metoprolol, tricyclic antidepressants, benzodiazepines, calcium channel blockers, sulfonylureas, and ethanol.
  - Ranitidine binds 4-10 times less avidly to cytP450 than cimetidine.
  - H2 blockers also compete with drugs for renal tubular secretion via P-glycoprotein (e.g. procainamide).

Prostaglandins

Misoprostol

- **Drug Class:** Prostaglandin analog (synthetic)
- **Mechanism of Action**
  - A methyl analog of PGE-1
  - It is believed to stimulate mucus & bicarbonate secretion & enhance mucosal blood flow, thereby helping protect the stomach by forming a protective barrier against acid
  - It also binds to prostaglandin receptors on parietal cells, reducing histamine-stimulated cAMP production & causing modest inhibition of acid secretion
- **Indications:**
  - Prevention of NSAID (including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with history of ulcer
- **Contraindications:**
  - Contraindicated, because of its abortifacient property, in women who are pregnant. Women of childbearing potential should be told that they must not be pregnant when misoprostol therapy is initiated, and that they must use an effective contraception method while taking misoprostol.

Side Effects:

- Diarrhea
- Increased uterine contractions

Proton Pump Inhibitors

Proton Pump Inhibitors (PPIs)- drugs ending in "prazole"

- **Drug Names:**
  - Omeprazole
  - Esomeprazole
- **Mechanism of Action:**
  - Proton pump inhibitors are administered as <u>inactive pro-drugs</u> & are given as acid-resistant enteric-coated formulations.

- They form covalent disulfide bonds with the H/K ATPase, which causes irreversible inactivation.
- PPIs produce a synergistic effect with antibiotics against *H. pylori* by increasing gastric pH. When the pH of the microenvironment surrounding *H. pylori* is made less acidic, there is increased *H. pylori* replication, which increases bacterial susceptibility to the inhibitory effects of antibiotics such as amoxicillin & clarithromycin. In lower (more acidic) pH environments, *H. pylori* converts to a "nonreplication state", where it is phenotypically insensitive to antibiotics (antibacterial MIC values are increased) (Wu et al, 2012).

- **Indications:**
  - Gastroesophageal Reflux Disease (GERD)
  - Peptic ulcer disease
  - Nonulcer dyspepsia (a pain in the upper middle part of your stomach)
  - Stress induced gastritis
  - Gastrin-secreting tumors (Zollinger-Ellison syndrome)
- **Pharmacokinetics:**
  - Administer on an empty stomach 1 hr before a meal to achieve maximal effective concentrations when proton pump secretion will be maximal.
  - Not all pumps are inactivated with the first dose & up to 3-4 days of treatment are needed to reach the maximal acid-inhibiting potential
  - acid inhibition lasts for up to 24 hours due to the irreversible effect on the proton pump; up to 18 hours are required for new synthesis of H/K ATPase.
- **Side Effects:**
  1. Increased risk of hip fractures with long term use in >50 yo patients. Possible mechanisms include:
     - pH-induced changes in Ca absorption from the GI tract
     - PPI effects on osteoclast proton pump transporters
  2. A 30% increase in hospital-acquired pneumonia (Herzig et al., 2009). Approximately 70% of hospitalized patients are taking PPIs. In has been speculated that this side effect may be due to an effect of PPIs on white blood cell physiology (more research is needed).
- **Major drug interactions:**

- PPIs inhibit the metabolism of warfarin, diazepam & phenytoin (via competitive P-450 metabolism)

Antacids

Calcium, Magnesium & Na Bicarbonate

- **Drug Types:**
  - Calcium carbonate
  - Magnesium hydroxide
  - Sodium bicarbonate
  - Aluminum hydroxide
- **Mechanism of Action:**
  - Weak bases that react with gastric HCl to form water & a salt, thereby lowering the acidity in the stomach.
- **Indications:**
  - Dyspepsia & acid-peptic disorders
- **Pharmacokinetics:**
  - Effective for a few hours after administration
- **Side Effects:**
  - Al & Mg are often combined because formulations containing Al alone cause constipation, and formulations containing Mg alone can cause an osmotic diarrhea
- **Drug interactions:**
  - may affect the absorption of other medications by binding the drug, or by altering a drug's pH-dependent solubility (e.g. tetracyclines, flouroquinolone, itraconazole, iron).

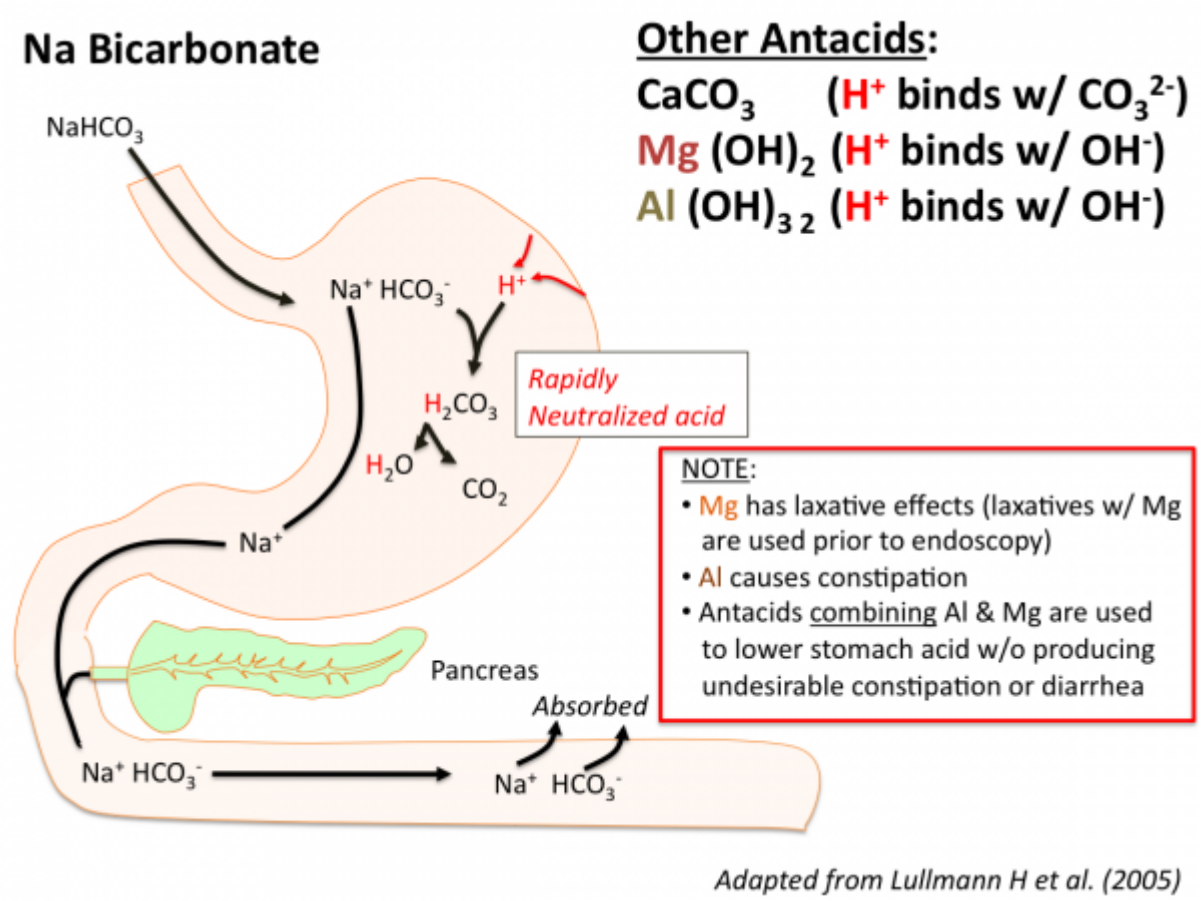

Figure: Antacids for rapid acid neutralization. Each compound in solution dissociates into a metal ion (Na, Ca, Mg, Al) and an acid binding group. The pancreas secretes bicarbonate in the duodenum, wich can precipitate Ca and Al so that they are largely excreted in the feces (not shown). Many antacids combine both Al and Mg, ions which counteract each others action to prevent unwanted constipation or diarrhea (a potential board question!). Al by itself produces constipation due to an astringent action, and $Mg(OH)_2$ produces diarrhea by an osmotic mechanism. Since food has a buffering effect, antacids should be taken between meals (e.g. 1 hour before, or 3 hours after, and at bedtime).

H2 blockers

H2 blockers reduce the amount of acid made by your stomach. They are used in conditions where it is helpful to reduce stomach acid. For example, to help with acid reflux which causes heartburn. Most people who take H2 blockers do not develop any side-effects.

H2 blockers are a group of medicines that reduce the amount of acid produced by the cells in the lining of the stomach. They are also called 'histamine H2-receptor antagonists' but are

commonly called H2 blockers. They include cimetidine, famotidine, nizatidine and ranitidine, and have various different brand names.

Your stomach normally produces acid to help with the digestion of food and to kill germs (bacteria). This acid is corrosive so your body produces a natural mucous barrier which protects the lining of the stomach from being worn away (eroded)

In some people this barrier may have broken down allowing the acid to damage the stomach, causing an ulcer. In others there may be a problem with the muscular band at the top of the stomach (the sphincter) that keeps the stomach tightly closed. This may allow the acid to escape and irritate the gullet (oesophagus). This is called 'acid reflux', which can cause heartburn and/or inflammation of the gullet (oesophagitis).

The letter H in their name stands for histamine. Histamine is a chemical naturally produced by certain cells in the body, including cells in the lining of the stomach, called the enterochromaffin-like cells (ECL cells). Histamine released from ECL cells then stimulates the acid-making cells (parietal cells) in the lining of the stomach to release acid. What H2 blockers do is stop the acid-making cells in the stomach lining from responding to histamine. This reduces the amount of acid produced by your stomach.

By decreasing the amount of acid, H2 blockers can help to reduce acid reflux-related symptoms such as heartburn. This can also help to heal ulcers found in the stomach or in part of the gut (the duodenum).

H2 blockers are commonly used:

- To reduce acid reflux which may cause heartburn or inflammation of the gullet (oesophagitis). These conditions are sometimes called gastro-oesophageal reflux disease (GORD).
- To treat ulcers in the stomach and in part of the gut (the duodenum).
- To help heal ulcers associated with anti-inflammatory medication called non-steroidal anti-inflammatory drugs (NSAIDs).
- In other conditions where it is helpful to reduce acid in the stomach.

At one time they were used as one part of a treatment to get rid of *Helicobacter pylori*, a germ (bacterium) found in the stomach, which can cause ulcers. However, proton pump inhibitors are now preferred for this use.

Side-effects of H2 blockers

Most people who take H2 blockers do not have any side-effects. However, side-effects occur in a small number of users. The most common side-effects are diarrhoea, headache, dizziness, rash and tiredness. For a full list of side-effects and possible interactions associated with your medicine, consult the leaflet that comes with your medication.

Biological and circadian rhythms, application of chronotherapy in various disease like CVS

Cardiovascular disease is the leading cause of death worldwide. Available therapies have had only limited success improving long-term survival of patients. In recent years there have been a flurry of studies demonstrating time-of-day variations in drug toxicity and efficacy, daily cardiovascular gene and protein expression and there are reports of new pharmacological compounds targeting the circadian mechanism. These have led to novel opportunities to investigate and apply the important field of chronobiology on clinical cardiology, and medicine in general.

The underlying foundation for cardiovascular chronotherapy stems from observations that biological processes in humans (and other mammals) exhibit 24-h daily rhythms, and these are controlled by molecular circadian clocks in the brain, heart, and other organs. There are many excellent reviews on the circadian system. Cardiovascular physiology appears to follow a rhythm as well; heart rate (HR), blood pressure (BP), and cardiac contractility all peak in the wake hours and reach a nadir during sleep. Indeed, many cardiovascular functions that oscillate over the 24-h period are influenced by the circadian clock mechanism as well as daily fluctuations in the neurohormonal milieu. Timing of onset of cardiac pathologies also follows a rhythm, and sudden cardiac death. These time-of-day variations in cardiovascular physiology and pathophysiology have led to a growing clinical appreciation that endogenous circadian rhythms may be an important factor to consider in treating disease. Here, we review the current knowledge regarding therapeutic applications of circadian rhythms for the cardiovascular system specifically (1) timing of therapy (chronotherapy), (2) circadian biomarkers (chronobiomarkers), and (3) how modifiers of the circadian clock mechanism may be useful in the treatment of heart disease.

Chronotherapy

Rationale

Chronotherapy is an important therapeutic application of circadian rhythms for the cardiovascular system. The rationale for chronotherapy is that it offers translational benefit by considering factors such as the underlying circadian rhythms in drug pharmacology, specifically pharmacokinetics (i.e., drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (i.e., affinity and specificity for target receptor binding, downstream intracellular signaling). Chronotherapy also takes into account the patients' underlying

physiology and disease pathology. That the majority of the best-selling drugs and World Health Organization essential medicines target the products of circadian genes provides a mechanistic basis for understanding chronotherapy and provides further support for the clinical application of chronotherapy. Specific examples applied to the treatment of cardiovascular disease are discussed in further detail below. We also created a blog featuring published chronotherapy studies for cardiovascular and other diseases[1].

Chronotherapy Decreases Adverse Cardiovascular Remodeling

In our recent pre-clinical study in mice, we showed that chronotherapy can have direct benefits on the heart in cardiovascular disease models. Mice with pressure-overload induced cardiac hypertrophy were administered the short-acting angiotensin converting enzyme inhibitor (ACEi) captopril at either sleep-time or wake-time. We found that only sleep-time administration improves cardiac function, and reduces cardiac remodeling, as compared to wake-time captopril and placebo-treated animals. Mechanistically, captopril given at sleep-time appears to target the peak in the renin-angiotensin-system gene profiles in the heart. Thus this study demonstrates the direct beneficial effects of chronotherapy for cardiac hypertrophy in the murine model. The important clinical implications are that ACEis given at bedtime can benefit myocardial remodeling in hypertensive patients, or after MI, or in congestive heart failure. Indeed, clinically, ACEis are one of the most commonly prescribed drugs given to hypertensive patients and also for ischemic heart disease

Chronotherapy Benefits Daily BP and HR Rhythms

Diurnal BP rhythms are an important part of healthy cardiovascular physiology, and thus are also a key target for chronotherapeutic strategies. Indeed, it is well-known that daily BP profiles are characterized by a dramatic BP surge that occurs around the time of wakening, followed by a progressive fall (~10%) to reach a nadir during sleep. Conversely, loss of the nocturnal BP fall (non-dipper profile) adversely affects the heart and chronotherapy to improve the nocturnal BP profile is beneficial. There are many studies that take a chronotherapeutic approach to regulate 24-h BP profiles in hypertensive patients. This includes treatment with ACEis, angiotensin receptor blockers (ARBs), β-blockers, acetylsalicylic acid (aspirin), and combination therapies at specific times of day or night. Intriguingly, HR also exhibits a rhythm that peaks in the day and is lowest at night.The effects of chronotherapy on HR are not as well investigated as with BP profiles, however, several studies have indicated a time-of-day influence of β-blockers on HR. (1) In healthy subjects, the β-blocker propanolol exhibits a significantly faster time to peak effect on HR if taken in the morning (8 A.M.) as compared to

late at night 2 A.M. (2) The suppressive effect of propranolol on the rise in HR during exercise is significantly greater if the drug is taken in the morning versus at night. (3) In patients with stable coronary disease, myocardial ischemic episodes associated with HR increases are more likely to occur during the day time than at night; propranolol reduces the proportion of these daily HR-related episodes. (4) In hypertensive patients, the β-blocker bisoprolol reduces the 24-h ambulatory HR if the drug is taken in the morning. (5) Lastly, experimental studies in rodents help confirm that HR is differentially influenced by some β-blockers depending on the time of drug application; propanolol causes a near maximum decrease in HR when given in the light period (rodent sleep time) as compared to the dark period (rodent wake time; . Collectively these findings illustrate the importance of maintaining daily BP and HR profiles, and the clinical applicability of chronotherapy to benefit cardiovascular physiology.

Aspirin Chronotherapy and Timing of Acute Cardiovascular Events

In an exciting recent chronotherapy study, it was found that evening administration of low-dose aspirin reduces morning platelet reactivity, via COX-1 dependent pathways, as compared with taking aspirin upon awakening. This finding is consistent with earlier reports of a circadian rhythm in platelet surface markers, and in platelet aggregability. Collectively these studies are clinically important because acute cardiovascular events (e.g., MI) are most likely to occur in the early morning hours vs. other times of day or night, and platelet reactivity likely contributes to this early morning peak. Thus it is postulated that aspirin chronotherapy taken at bedtime instead of on awakening, as a preventative measure in healthy subjects and by patients with cardiovascular disease, can reduce the incidence of adverse cardiac events during the high-risk morning hours. That daily low-dose aspirin reduces the peak frequency of MIs in the morning and overall risk across the 24-h cycle, provides further support for this notion.

It is worth noting that several factors important for thrombosis and fibrinolysis in MI, in addition to platelet reactivity and cycling, also exhibit daily rhythms and could provide additional targets for chronotherapy for treatment of acute cardiovascular events. These factors include plasminogen activator inhibitor-1 (PAI-1 a key inhibitor of fibrinolysis; , tissue factor pathway inhibitor and factor VII, and plasma fibrinogen. Moreover, several experimental rodent studies mechanistically link these coagulation pathways directly to the circadian clock mechanism. That is, transcription of the anti-coagulant factor thrombomodulin is regulated by the mechanism factors CLOCK and BMAL2 heterodimers, and PAI-1 transcription is regulated by CLOCK and BMAL proteins. Endothelial responses to vascular injury also appear to be regulated by the clock mechanism. In terms of clinical translation, time-of-day variation in the

efficacy of thrombolytic therapy in MI has been reported, which shows a marked early morning resistance and significantly better results later in the day. Taken together, these and earlier studies provide support for cardiovascular chronotherapy to limit the pathogenesis and improve treatment following the onset of acute cardiovascular events.

Nocturnal Hemodialysis (NHD) Benefits Cardiovascular Disease

Cardiovascular disease is a significant cause of death in patients with end-stage renal disease, and left ventricular hypertrophy contributes to the high mortality rates in patients given conventional daytime hemodialysis (CHD) treatment. Intriguingly, NHD, renal replacement therapy during sleep) offers better BP control and is accompanied by regression of left ventricular hypertrophy, as compared to patients given conventional daytime therapy. In addition to decreasing the nighttime BP, NHD also decreases 24-h mean arterial BP compared to CHD. These findings of a chronotherapeutic benefit are further corroborated by a randomized controlled clinical trial demonstrating that frequent NHD improves systemic BP and reduces left ventricular mass compared with CHD. Mechanistically, the beneficial effects of NHD are associated with changes in myocardial mechanics in patients, and experimentally correlated with unique cardiac gene expression signatures in rodent studies *in vivo* . These studies demonstrate chronotherapeutic benefit for the heart, in patients with end-stage renal disease, by chronotherapeutically converting from CHD to NHD treatment.

Nocturnal Therapy for Obstructive Sleep Apnea Benefits the Heart

Obstructive sleep apnea (OSA) is a common sleep disorder, with cardiovascular consequences (e.g., through increased sympathetic activation, etc. OSA is a target for chronotherapy, as several studies have revealed that sleep time treatment with continuous positive airway pressure (CPAP) attenuates some of the adverse effects on the cardiovascular system. For example, CPAP therapy decreases the risk of non-fatal and fatal adverse cardiovascular events in severe OSA patients (apnea-hypopnea index >30 h) as compared to untreated patients, as demonstrated in a 10 years long term follow-up study.In another study, it was shown that CPAP therapy improves ejection fraction, lowers systolic BP, and reduces HR in heart failure patients with OSA Also, CPAP treatment decreases cardiovascular-related deaths in OSA patients, as compared to an untreated OSA group, as was demonstrated over a follow-up period of 7.5 years. Thus these studies underscore the notion that time-of-day therapies, such as nocturnal CPAP treatment, benefits cardiovascular physiology, and reduces pathophysiology in patients with OSA.

Biological and circadian rhythms, application of chronotherapy in various disease like asthma

Asthma and the circadian rhythm

It is characteristic of asthma that symptoms worsen overnight, particularly in the early hours of the morning. Nocturnal symptoms in asthma are common and are an important indicator for escalation of treatment. An extensive body of research has demonstrated that nocturnal symptoms of cough and dyspnea are accompanied by circadian variations in airway inflammation and physiologic variables, including airflow limitation and airways hyperresponsiveness.

Circadian variation in asthma symptoms

Asthma is a disease with a strong circadian rhythm. Symptoms of asthma frequently show exacerbation in the early hours of the morning, at around 4 am. Sudden death in asthma also tends to occur at this time. In a survey of 7,729 patients with asthma, 74% awoke at least once per week with asthma symptoms, 64% reported nocturnal asthma symptoms at least three times per week, and approximately 40% of patients experienced symptoms nightly.

Circadian variation in lung physiology

Physiological parameters of airway resistance, forced expiratory volume in 1 second (FEV1), and peak expiratory flow rate (PEFR) are commonly measured in respiratory clinics and as outcome measures in drug trials. Both FEV1 and PEFR vary in a circadian manner in healthy individuals with a nadir at approximately 4 am. However, in asthma, the amplitude of the circadian rhythm of both FEV1 and PEFR is greatly magnified.

Circadian variation in airway inflammation

Kraft et al performed bronchoscopy and transbronchial biopsy in subjects with nocturnal or nonnocturnal asthma at 4 pm (the peak of lung function) and 4 am (when airflow limitation was at its worst). In tissue from subjects with nocturnal asthma, there was a circadian variation in the number of alveolar eosinophils, with significantly more present at 4 am versus 4 pm. Increases in alveolar eosinophils in subjects with nocturnal asthma correlated with nocturnal decrease in FEV1. Circadian variation in tissue macrophages was also observed in alveolar tissue from subjects with nocturnal asthma.26 Although patients with nocturnal asthma typically meet criteria for moderate or severe persistent asthma, circadian changes in lung function can be seen in patients with milder asthma. In 2004, Kelly et al investigated circadian

changes in airway inflammation in patients with mild atopic asthma (mean FEV1 of 93%±4% of predicted value). In this patient population, bronchoalveolar lavage fluid contained increased numbers of macrophages, neutrophils, and CD4+ T lymphocytes at 4 am versus 4 pm. Additionally, the percentage of CD4+ T lymphocytes in the 4 am lavage fluid was inversely correlated with 4 am FEV1.

How are circadian rhythms regulated?

The suprachiasmatic nucleus of the mammalian brain serves as a central source of timing information to permit peripheral clocks to "track" day and night, as they lack light input. Both central and peripheral clocks use the same molecular machinery to "time" the day. Interlocking repressing and activating transcriptional and translational feedback loops culminate in the approximately 24-hour rhythmic expression and activity of a set of core clock genes in each organ. CLOCK and BMAL1 promote the transcription of period (PER1/2) and cryptochrome (CRY1/2) genes. As protein levels increase, PER and CRY associate and translocate into the nucleus directly, repressing CLOCK/BMAL1, thereby inhibiting their own transcription. Enzymatic degradation of PERIOD and CRYPTOCHROME proteins provides a delay mechanism prior to the onset of the next transcriptional cycle. The expression of positive factors, CLOCK and BMAL1, and negative factors, PER and CRY, are in antiphase to one another, providing circadian timing at the molecular level. Outputs from the molecular clock are generated through transcription or repression of target genes. BMAL1 is regulated by rhythmic interaction with REV-ERBα. REV-ERBα, a nuclear hormone receptor and core clock gene, is a critical regulator of inflammation and metabolism. REV-ERB
function can be regulated by small-molecule ligands and thus represents an exciting option for manipulation of the clock in disease states.

What is known about the peripheral lung clock?

Work in our laboratory has demonstrated the presence of a local clock within the lung and specifically localized this clock to the Clara cell in the bronchial epithelium of mice.30 It has also been shown that disruption of circadian rhythms in mice, to mimic chronic jet lag or shift work, causes an alteration in lung mechanics and clock gene expression in the lung in a sexually dimorphic manner.31 Sukumaran et al conducted a genome-wide analysis of diurnal/nocturnal patterns in mRNA expression from lungs of rats kept in a tightly controlled 12:12 hour light–dark cycle. Cyclic oscillations in the expression of genes associated with extracellular matrix, cytoskeleton, cell cycle, and apoptosis were observed, suggesting that the repair and turnover of these components in lung are directly or indirectly clock controlled. Many of the growth

factor ligands and receptors involved in the direct regulation of these processes and the maintenance of the homeostasis in lung also showed circadian-like oscillations in expression. In addition, many genes involved in processing of proteins, ranging from posttranslational modification to ubiquitin-mediated proteosomal degradation, also showed circadian oscillations in expression in lung. Genes coding for inflammatory molecules, including chemokine ligands (eg, Cxcl12) showed circadian-like oscillations in expression in lung, suggesting that the molecular clock can regulate the immune response in the organ. Furthermore, genes that are involved in the metabolism of xenobiotics showed circadian-like oscillations in expression in lung.

Immune clock

Circadian variations in immune parameters such as lymphocyte proliferation, antigen presentation, and cytokine gene expression have been described. Recently, an association between the molecular circadian clock, immunity, and inflammation has been recognized. Importantly, the macrophage clockwork provides temporal gating of systemic responses to endotoxin, and, we have identified REV-ERBα as a key link between the clock and immune function.33 Furthermore, toll-like receptor 9 (TLR9) expression and function have been recently shown to be modulated by core circadian molecular clock components. In a vaccination model using TLR9 ligand as adjuvant, mice immunized at the time of enhanced TLR9 responsiveness presented weeks later with an improved adaptive immune response. In a TLR9-dependent mouse model of sepsis, disease severity was dependent on the timing of sepsis induction, coinciding with the daily changes in TLR9 expression and function.34 Therefore, the timing of an attack on the lung immune system by an allergen or virus might significantly affect the ability of the lung to mount an adequate immune response.

What is the significance of circadian variation in asthma

The marked circadian variability in symptoms, airway physiology, and inflammation that occurs in asthma on a day-to-day basis suggests that the molecular clock plays an important role in the mechanisms that drive them. It is possible that, if the molecular clock is indeed responsible for “gating” the immune response within the lung, then chronic airway inflammation, typical of asthma, might be caused through disruption of essential clock regulation. This intriguing possibility merits further experimental and clinical study, and suggests that novel therapies targeting clock function may have important benefits in asthma management.

Chronotherapy in asthma

Chronotherapy may be accomplished by synchronizing drug concentrations to rhythms in disease activity, thus increasing efficacy as well as reducing adverse effects. The effectiveness of chronotherapy for asthma is most frequently determined by its effects on the morning dip in the lung function measurements of PEFR or FEV1. When there is poor management of asthma, the morning PEFR is markedly lower than the evening PEFR. Most of the drugs that are currently used chronotherapeutically are administered once at night with the goal of preventing chronic airway inflammation or the onset of airflow limitation. Once-daily dosing also has the added benefit of improving patient adherence and promoting self-management of asthma. However, both PEFR and FEV1 reflect airway symptoms at a particular point in time. The inflammatory process that leads to this symptomology will have been triggered many hours earlier, with the transcription of pro-inflammatory genes and the subsequent stimulation of the immune system. Knowledge of the circadian rhythm of inflammatory biomarkers in the blood or sputum might allow us to narrow the chronotherapeutic window even further in the future.

Current asthma treatment guidelines

Current treatment guidelines do not reflect chronotherapy, phenotype, or endotype; rather they provide a linear treatment algorithm, based on asthma symptoms ICSs, with or without long-acting beta agonists (LABAs), continue to be the mainstay of pharmacological treatment for mild-to-moderate asthma. Severe asthma is defined as asthma that requires treatment with high-dose ICSs plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy. Although the majority of asthma is effectively treated with existing medications, a substantial subset exists that remains difficult to treat.

Current and emerging chronotherapies for asthma

β_2-adrenergic agonist medication

β2-agonists (BAs) primarily cause relaxation of airway smooth muscle, to increase airway caliber and relieve bronchoconstriction. However, BAs also have an anti-inflammatory action.Plasma epinephrine shows a circadian rhythm with the lowest level at 4 am and the highest level at 4 pm in both healthy subjects and patients with asthma.38 Both the BAs, procaterol and fenoterol, have been reported to strongly induce hPer1 mRNA expression in human bronchial epithelial cells in vitro. BAs are predominantly inhaled and can be short-acting BA (SABA) with a duration of around 4 hours, or LABA effective for 12–24 hours. SABAs are prescribed as "reliever" medications for immediate relief from bronchoconstriction. The majority of LABAs are inhaled as aerosols (the advantage being

delivery directly to the target area with fewer systemic side effects). LABAs can also be administered orally as tablets and as a transdermal preparation in the form of patches

LABA tablet formulation

Terbutaline (Bricanyl Depot, AB Draco, Lund, Sweden) is a LABA tablet formulation that was one of the first to be assessed in chronotherapy trials. Daily doses were administered to asthmatics in synchrony with biological need defined in terms of the circadian rhythm of lung function (PEFR, FEV1). Five milligrams was administered in the morning (8 am) when the lung function was beginning to improve to its best level in the afternoon. Ten milligrams was administered in the evening (8 pm) when lung function was beginning its decline to its worst level in the early hours of the morning. This chronotherapeutic strategy significantly increased the 24-hour mean PEFR and FEV1 and almost completely averted their characteristic nocturnal decline.

Bambuterol , is a prodrug of terbutaline and exerts a bronchodilator effect for 24 hours. A chronotherapeutic trial of bambuterol investigated once-daily dosing with 20 mg in the morning, versus the evening, versus placebo. Evening dosing resulted in a considerably higher morning FEV1 and PEFR. Overall, evening dosing was more advantageous because it improved FEV1 throughout the 24 hours to a greater extent than morning dosing (although nonstatistically significant due to small sample size). Neither of the bambuterol treatment regimens was associated with any cardiovascular or nervous system adverse effects.

LABA inhaler medication

Formoterol (Novartis, Basel, Switzerland) and salmeterol (GlaxoSmithKline plc, London, UK, and USA) are aerosol LABA medications, with few adverse effects. Both medications have duration of action of about 12 hours, although formoterol may have a more rapid onset of affect.Formoterol and salmeterol are similar in chemical structure, except that salmeterol possesses an elongated side chain that binds the molecule firmly to the β2-adrenoceptor, allowing it to repeatedly excite the receptor. Overall, the results of many large-scale studies demonstrate that twice-daily, 12-hour interval dosing of 50 μg salmeterol, compared to the dosing of 180–200 μg albuterol four times daily, results in better control of overnight and morning PEFR and FEV1, reduces daytime and nighttime asthma frequency, lowers patient dependence on BA aerosol rescue medication, and improves nighttime sleep. However, the chronotherapy of LABA has not been extensively investigated, and it would be interesting to

investigate the chronobiological effects of nighttime versus morning once-daily dosing with these agents.

Indacaterol and vilanterol are ultra-LABAs that act for 24 hours. Data so far suggest that a single morning dose of indacaterol significantly improves the 24-hour trough FEV1, compared with twice-daily formoterol and placebo. A study to investigate the effect of time of day of dosing (morning or evening) on lung function following administration of fluticasone furoate/vilanterol 100/25 μg, showed no significant differences between morning or evening dosing in patients with persistent asthma. This suggests that the timing of dosing with ultra-LABAs is not important. However, any circadian effects of these long-acting drugs may well be masked.

Anticholinergic agents

Cholinergic tone from vagal nerves in the parasympathetic system increases at night and may cause bronchoconstriction and mucus secretion. It has been suggested that the vagal nerve is one of the dominant pathways for conveying circadian signals from the suprachiasmatic nucleus master clock to the peripheral clock in the respiratory tract.58 Inhaled muscarinic antagonists are classified according to their duration of action. Short-acting muscarinic antagonists (SAMAs) include ipratropium bromide and long-acting muscarinic antagonists (LAMAs) include tiotropium, aclidinium, and glycopyrronium. However, inhaled anticholinergic agents demonstrate inconsistent results in patients with nocturnal asthma. It has been postulated that the failure of traditional equal-interval, equal-dose regimens to impact airway caliber and protect against asthma overnight could be due to less than adequate dosing of this class of medications late in the day and/or at bedtime. In fact, several studies have shown that, if a sufficiently large dose of early generation anticholinergic medication was administered late at night or very early in the morning, there was attenuation of the nocturnal decline in peak expiratory flow (PEF) in nocturnal asthmatics.

Of the LAMAs, tiotropium is the most widely studied in asthma. Tiotropium is an anticholinergic medication that dissociates slowly from the muscarinic M3 receptor, found on bronchial smooth muscle. It therefore has a prolonged duration of action of more than 24 hours. It can be inhaled as a dry powder (Handihaler®, Boehringer Ingelheim, Ingleheim am Rhine, Germany) or as a fine particle mist (Respimat®, Boehringer Ingelheim, Ingleheim am Rhine, Germany). Tiotropium has been shown to be an effective asthma treatment in patients inadequately controlled on ICSs alone or in combination with a LABA. Tiotropium showed no significant differences in effect on airway caliber when administered once daily in the morning

versus evening. However, the long duration of action of this high-affinity medication may mask possible circadian time-dependent effects.

Systemic corticosteroids

Oral steroids are used as a short-term "burst" at step 5 of the British Thoracic Society (BTS)/SIGN (Scottish Intercollegiate Guidelines Network) guidelines to control acute deterioration in asthma control. However, many patients with severe asthma are controlled on long-term "maintenance" oral corticosteroids and will be affected by the many adverse side effects.

Chronotherapeutic studies investigating the use of synthetic steroids must take into account the pronounced endogenous circadian variation in cortisol levels. Cortisol is highest in the morning and lowest during night. In a study to investigate how the time of administration of synthetic steroid affects the endogenous circadian rhythm of cortisol secretion, administration of synthetic methylprednisolone by infusion between 8 am and 4 pm resulted in no adrenal suppression; however, infusion between 12 am and 4 am resulted in very severe adrenocortical suppression. Infusion during 4 pm and 8 pm and also between 4 am and 8 am resulted in moderate adrenocortical suppression.

Beam et al conducted a double-blinded, placebo-controlled, crossover protocol to study the effect of either 50 mg prednisolone or placebo given at 8 am, 3 pm, or 8 pm on FEV1 in patients with uncontrolled nocturnal asthma. Surprisingly, the 50 mg prednisolone dose attenuated the nocturnal decline in FEV1 only when ingested at 3 pm.

The ingestion of 50 mg prednisolone at 8 am or 8 pm was ineffective.65 These results are consistent with other studies,66 suggesting that synthetic corticosteroids administered at 3 pm are more effective in nocturnal asthma and cause less disruption to endogenous circadian cortisol rhythm. In future, more lengthy clinical trials are required in this area.

Inhaled corticosteroids

ICSs are the mainstay of asthma treatment and are used at step 2 in the BTS asthma guidelines. ICSs are very effective in controlling asthma symptoms in asthmatic patients of all ages and severity.The advantage of inhaled therapy is that corticosteroid is delivered specifically to the target area. However, this is dependent on the ability of the subject to correctly use the inhaler device; deposition of the ICS in the oropharynx will lead to increased systemic absorption and the development of associated side effects. ICSs inhibit inflammatory cytokines and reduce airway hyperresponsiveness. ICSs reduce mast cells, T lymphocytes, and eosinophils in the bronchial epithelium and submucosa.

Several studies have investigated the chronotherapy of ICSs. In one study, triamcinolone acetate aerosol when given to asthmatics at 3 pm (800 μg) was found to be at least equivalent compared to the conventional four-times-a-day (200 μg) treatment schedule.71 In a second study, Pincus et al compared four-times-a-day triamcinolone acetate (800 μg/day) with single 8 am or 5.30 pm once-daily dosing regimens in moderately severe nocturnal asthmatics. Both the four-times-a-day and the 5.30 pm dosing regimens improved the morning and evening PEF in a comparable manner, but not the single 8 am dose. Furthermore, there were no differences in systemic effects, including adreno-cortical suppression, between treatment groups. These results are consistent with chronotherapeutic studies investigating oral corticosteroids.

Ciclesonide (Alvesco, Teijin Pharma Ltd, Tokyo, Japan) is a novel ICS administered once daily at night by a metered-dose inhaler. Dosing with ciclesonide once daily in the morning or evening significantly improves PEF and FEV1 without causing adrenocortical suppression; however, the evening dosing regimen best improved the morning PEF. Once-daily ciclesonide (160 μg dose) has been shown to be as effective as twice-daily (88 μg dose) fluticasone in improving airway caliber, controlling asthma symptoms, and reducing reliance on rescue medication.

Theophyllines

Theophyllines, although relatively weak bronchodilators, possess significant anti-inflammatory effects. In asthmatic patients, theophylline inhibits the late response to allergen, increases CD8+ cells in peripheral blood, and decreases T lymphocytes in the airways.Sustained release theophyllines can be added at step 3 of the BTS/SIGN guidelines35 if there has been no response to LABA.

Both the kinetics and the adverse effects of theophyllines vary depending on whether the drug is taken in the morning or evening. The chronotherapy of theophylline entails the purposeful delivery of medication in unequal amounts during 24 hours so that an elevated concentration is achieved during the nighttime, when the risk of asthma is greatest, and a reduced concentration is achieved during the daytime, when the risk of asthma is lowest. Euphyllin was developed in the 1980s as a sustained release, asymmetric morning–evening dosed theophylline preparation.78 However, the asymmetric dosing schedule reduces patient adherence, and so once-daily preparations were developed. Euphylong and Uniphyl (Purdue Frederick, Stamford, CT, USA)/Uniphyllin (Mundipharma, Limburg, Germany) are dosed at night with the intention of achieving peak concentration overnight/early morning when the drop in PEF is the greatest. When once-daily dosing in the evening (chronotherapy) is

compared to twice-daily and round-the-clock dosing in asthmatic patients with a nocturnal dip on PEF, once-daily evening administration was more effective for increasing the serum theophylline concentration at the time when lung function was worse, and this regimen improved both symptoms and PEF.

Leukotriene receptor antagonists

Leukotrienes are formed by the degradation of arachidonic acid by 5′-lipoxygenase. They are pro-inflammatory and bronchoconstrictor mediators. The leukotriene receptor antagonists (montelukast, pranlukast, and zafirlukast) and the 5-lipoxygenase inhibitor zileuton are a new class of anti-inflammatory drugs that reduce leukocyte traffic and modulate airway inflammation and bronchial hyperresponsiveness.80–82 Leukotriene receptor antagonists are used at step 3 of the BTS/SIGN guidelines35 as add-on therapy. Montelukast is recommended for ingestion once daily in the evening; however, it is not marketed as a A double-blind study showed that montelukast better improved FEV1 when dosed in the evening than morning,82 and a second study confirmed this and also showed that even once-daily, low-dose (10 mg) evening montelukast dosing improves asthma.Zileuton was initially formulated to be taken four times a day; however, an extended-release tablet is now available with twice-daily dosing. Zileuton therapy is monitored because of the risk of hepatic toxicity. Future chronotherapy trials for Zileuton could potentially provide a therapeutic window, by changing the delivery time to coincide with a key pathway, which would negate the need for steady state levels of Zileuton throughout the day, and may reduce the risk of side effects.

Chronopharmaceutical technologies for the treatment of asthma

Novel technologies have been developed to allow medications to be taken at a convenient time of day (to help improve compliance) but allow the release of drug to be delayed to coincide with the “morning dip” in PEFR.

Biological and circadian rhythms, application of chronotherapy in various disease like Diabetes

Chronopharmacology is the study of how the effects of drugs vary with biological timing and endogenous periodicities. The goal is to improve our understanding of periodic and thus predictable (e.g. circadian) changes in both desired effects (Chrono effectiveness) and tolerance (Chrono tolerance) of medications.1 Many functions of the human body vary day by day and these type of variations cause the changes in both in disease state and in normal state.

Cardiovascular functions such as heart rate and blood pressure show 24 hours variation. The incidence of cardiovascular diseases such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation since most of these disorders can induce fatal or severe outcomes. It is the most important to elucidate the precise mechanism of the onset of this disease. The dependence of our body functions in the certain diseased state depends on the circadian rhythm. The science dealing with the phenomenon of biological rhythmicity in living organism is called chronobiology. The branch dealing with the pharmacological aspects of chronobiology is termed as Chronopharmacology which may be subdivided into chronotherapy, chronopharmacokinetics and Chrono toxicity.

In the management of diabetes, the target is to maintain the patient in normoglycemia.

Chronopharmacological aspects are highly relevant in the management of diabetes mellitus since time of day, patient activities and timing of medication may impact on the risk of occurrence of peaks and troughs in blood glucose levels. It is well known that shift workers have increased diabetes and obesity, worse glucose control, and higher rates of cardiovascular disease and mortality. Changing the clocks back in spring is associated with increased myocardial infarctions. Supporting these observations are short-term experimental studies showing that misalignment of behavioral and circadian cycles results in adverse cardiometabolic endpoints including higher arterial blood pressure, glucose, insulin, ghrelin, cortisol, and catecholamines. Genetic studies point to molecular mechanisms based on highly conserved controllers of periodicity or Zeitgeber. These molecular clocks are located in the central nervous system and in peripheral tissue, communicating with each other and responding to a great number of inputs presumably designed to maintain homeostasis of the entire organism relative to changing environments.6-7 In type, I diabetes the circadian rhythms of insulin and its action are of physiological interest and clinical importance. So, insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show its cyclic rhythmicity of 8-30 min which can show the optimal action. The modulators of insulin release

and action are secreted in a circadian pattern and impress the mode of insulin release. So difference between maximum and minimum plasma insulin concentration has short-term rhythmicity and complex secondary circadian rhythm is variable early-morning and late afternoon insulin resistance.

Circadian Rhythm

An approximately 24-hour cycle of biological processes in plants and animals. In humans, the circadian "clock" is found in the suprachiasmatic nucleus, a cluster of cells located in a part of the brain called the hypothalamus. The circadian rhythm influences sleeping, eating, heart rate, blood pressure, body temperature, the levels of certain hormones, and the immune system. Levels of both insulin and the counterregulatory hormones, which work against the action of insulin, are influenced by a circadian rhythm. The counterregulatory hormones, which include glucagon, epinephrine (also known as adrenaline), growth hormone, and cortisol, raise blood glucose levels when needed. In the middle of the night, there is a surge in the amount of growth hormone the body releases, followed by a surge in cortisol, which increases blood glucose production by the liver. In people who don't have diabetes, these processes are offset by increased insulin secretion by the pancreas, so blood glucose levels remain relatively stable.

However, in people with Type 1 diabetes, whose pancreases don't make insulin, and in people with Type 2 diabetes, whose livers may not respond to insulin well enough to stop glucose production, changes in blood glucose levels during sleep can have a powerful effect on morning blood glucose levels. Blood glucose levels typically rise between 4 am and 8 am, an event dubbed the "dawn phenomenon." Some of the more common of these disorders include "jet lag" syndrome, consisting of certain conditions called circadian rhythm disorders can disrupt a person's wake-sleep cycle. Excessive sleepiness and lack of daytime alertness in travelers who cross time zones, shift-work sleep disorder, which occurs in people who work night shifts or rotating shifts, and delayed sleep phase syndrome, in which people fall asleep very late and wake up very late. Research findings suggest that not getting enough sleep or having poor quality of sleep can disrupt blood glucose control in people with diabetes

Chronopharmacology further deals with11

- Chronotherapeutics
- Chronokinetic
- Chronesthesy
- Chronergy
- Chronotoxicity

Chronotherapeutics: Knowledge of day-night and other prediction in time variations in the symptoms intensity and risk of acute exacerbation of disease coupled with evidence of circadian rhythms in the kinetics, effects and safety of medications constitutes the rationale for new pharmacologic approach to treatment. It deals with increase of the efficiency and safety of medications by proportioning their concentrations during the 24 hrs in synchrony with biological rhythm determinants of disease.

Chronopharmacokinetics: It deals with the study of temporary changes in absorption (A), distribution (D), metabolism (M), excretion (E) and thus takes into account the influence of time of administration on these different steps. Temporal changes in drug absorption from GIT occurs due to circadian variations in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow, plasma protein binding and drug distribution and drug metabolism (temporal variations in enzyme).

Chronesthesy: It deals with circadian or other systemic changes in the susceptibility and sensitivity of the target system to a drug.

Chronergy: It deals with rhythmic difference in effects of drug on the organism as a whole which includes both desired and undesired effects.

Chrono toxicology: It is an aspect of chromodynamics; it refers specifically to dosing time i.e rhythm – dependent differences in the manifestations and severity of adverse effects and thus intolerance of patients to medication.

Circadian rhythms, insulin action, and glucose homeostasis.

Accumulating evidence supports a role for the circadian clock in the development of metabolic disease. We discuss the influence of the circadian clock on glucose homeostasis, intermediary factors in this relationship, and potential therapies for the prevention or attenuation of metabolic disease associated with circadian misalignment. Murine studies with tissue-specific deletion of core clock genes in key metabolic tissues confirm a mechanistic relationship between the circadian clock and the development of metabolic disease. Circadian misalignment increases insulin resistance and decreases pancreatic function.13 Clock gene polymorphisms or altered expression of clock genes induced by circadian misalignment appear to play a role in the development of obesity and diabetes in humans. Circadian disruption caused by exposure to light at night is associated with lower nocturnal melatonin, which in turn seems to affect glucose metabolism. Potential therapies for circadian misalignment include entraining the central pacemaker with timed light exposure and/or melatonin and restricting food intake to the biological day.

Circadian Clock Controls Sugar Metabolism

Humans' 24-hour circadian clock plays a leading role in glucose tolerance. Researchers in Boston have found that, because of body's circadian rhythm, human glucose tolerance is reduced during the evening hours, even when "day" and "night" times are experimentally reversed. "In a prior [human] study, we found that when behavior cycles of feeding and sleeping are not in normal alignment with the internal body clock, that this negatively affects the regulation of blood sugar and especially glucose tolerance," said neuroscientist Frank Scheer from the Division of Sleep and Circadian Disorders at the Brigham and Women's Hospital in Boston. People who work night shifts are more prone to type 2 diabetes and obesity.

In an attempt to understand the independent effects of eating and sleeping behaviors versus the circadian clock on glucose tolerance, Scheer and his colleagues mimicked night-shift work in 14 healthy individuals under controlled laboratory conditions. Participants spent eight days on a typical day-shift schedule, eating breakfast at 8:00 a.m., dinner at 8:00 p.m., and sleeping during the night. Several weeks later, the same individuals had their days reversed: they then ate breakfast at 8:00 p.m., had dinner at 8:00 a.m., and slept during the day. "We showed that glucose levels after identical meals were 17 percent higher [indicating lower glucose tolerance] in the evening than in the morning, independent of when a participant had slept or had their meals".

Circadian Variation of the Blood Glucose, Plasma Insulin and Human Growth Hormone Levels in Response to an Oral Glucose Load in Normal Subjects

Circadian variations in blood glucose, plasma insulin and human growth hormone response were studied in six healthy males who received 100 gm. oral glucose loads at 6 a.m., noon, 6 p.m., and midnight. The tests were conducted at seven day intervals, and each was preceded by a ten hour fast. During the three days before each test the subjects received meals containing no less than 300 gm. carbohydrate per day. Blood samples were drawn at 0, 15, 30, 60, 90, 120, and 180 minutes. A clear circadian variation occurred in the blood glucose levels, with lower values in the morning and higher values at 6 p.m. and midnight. The insulin profiles showed a trend toward lower afternoon and night values, with a noon peak. The afternoon insulin-glucose ratios were significantly lower. HGH values were inconsistent and tended toward higher afternoon and night basal levels. The results confirm the existence of a circadian variation in the blood glucose response to oral glucose loads in healthy men. This might in turn result from a circadian variation in the insulin response, probably secondary to changes in the pancreatic β cell sensitivity to glucose. This basic mechanism is believed to sustain the conditioning influence of other hormones, HGH being one of them

Circadian Clock Controls Insulin and Blood Sugar in Pancreas

A new Northwestern Medicine study has pinpointed thousands of genetic pathways an internal body clock takes to dictate how and when our pancreas must produce insulin and control blood sugar, findings that could eventually lead to new therapies for children and adults with diabetes. The body's circadian clocks coordinate behaviors like eating and sleeping, as well as physiological activity like metabolism, with the Earth's 24-hour light-dark cycle. There's a master clock in the brain, as well as peripheral clocks located in individual organs. When genetics, environment or behavior disrupt the synchrony of these clocks, metabolic disorders can develop.

Blood Glucose and the Circadian Rhythm

Endocrinologists and other health professionals who work with diabetic patients have long been aware that blood glucose levels vary with the time of day, even independently of eating habits and insulin use. Many people with diabetes experience what is known as a dawn phenomenon, in which the liver releases large amounts of glucose into the bloodstream just before dawn. The blood sugar can be as much as is contained in two cans of regular soda. This can cause problems for people with diabetes that is difficult to manage. In addition, diabetics are advised not to eat high carb meals late at night, as this often causes higher blood glucose levels than the same foods would cause at other times of the day.

Chronotherapy of diabetes

Both insulin secretion by pancreatic cells and insulin sensitivity in the insulin target organs exhibit daily rhythmicity, which may be involved in maintaining homeostasis of glucose metabolism. Because these rhythms are impaired in patients with diabetes, the correction of these abnormalities is necessary for effective treatment.

At present, there are few studies showing chronotherapy of insulin sensitizers (thiazolidinediones and biguanides). On the other hand, several classes of medications which are used for the treatment of impaired insulin secretion, including glinides and rapid- and long-acting insulin analogs, have the merit of chronotherapeutic approach. These medications are useful not only for improving glycemic control but for the risk reduction of prolonged hypoglycemia and body weight gain.

Recently, we showed that circadian clock is impaired in patients with type 2 diabetes. Because the association between clock gene expression and glucose tolerance is also detected in subjects without diabetes, favorable lifestyles (e.g. awake time, bedtime, drinking) to maintain circadian clock function are important for the prevention of type 2 diabetes. However, lifestyles which may affect the biological clock are common. Because it is difficult to alter such a lifestyle in modern societies, a therapeutic agent for the correction of the impaired clock is stronglydesired.

Drug for constipation

What is Constipation?

Constipation is the term used to describe difficulty or infrequency in passing feces (poo). When people are constipated, they have difficulty emptying their bowels or strain when they go to the toilet.

Most people empty their bowels at least once a day or every other day. Constipation is generally defined as having less bowel movements per normal per week.

What Causes Constipation?

Our bowel is the part of our gastrointestinal tract that removes solid waste (poo) left over from the food we eat from our body. When we pass feces it is called having a bowel movement or motion.

Constipation can either occur from a lack of fiber or fluid in the diet, or if the movements of the bowel slow down, due to disease, medications, hormones, or trauma, causing a longer transit for feces through the bowel.

What are the signs and symptoms of constipation?

Signs and symptoms of constipation may include rectal bleeding and/or anal fissures that are caused by hard or small stools, lower abdominal discomfort, and straining to have a bowel movement.

Call you doctor or other health care professional for treatment for constipation if you have a sudden onset if symptoms that come on suddenly that are severe pain that worsens and are associated with other worrisome symptoms such as suddenly losing weight, or is not responding to simple, safe and effective treatments.

What exams, tests, and procedures cause constipation?

Tests to diagnose the cause of constipation may include a medical history, physical examination, blood tests, abdominal X-rays, barium enema, colonic transit studies, defecography, anorectal motility studies, and colonic motility studies.

What are the goals for constipation therapy? Is there a special diet plan for it? How is it cured?

The goal of therapy for constipation is one bowel movement every two to three days without straining. Treatment may include foods high in fiber, non-stimulant laxatives, stimulant laxatives, enemas, suppositories, biofeedback training, prescription medications, and surgery. Stimulant laxatives, including herbal products, should be used as a last resort because they might damage the colon and worsen constipation.

Mild cases of constipation can often be treated using OTC medications, which are called laxatives. These include:

- bulk-forming laxatives
- lubricants
- osmotic laxatives
- stimulant laxatives
- stool softeners
- combination medications

Each type of laxative works in a slightly different way to relieve constipation. The main types of laxatives are listed below. All of these laxatives are available as generics, and most are available as brand-name products as well.

When looking for an OTC laxative, it's helpful to be familiar with the generic name of the medication.

This is because with brand-name products, the manufacturer may sell different products containing different laxatives under the same brand name. These products may differ in how fast they work and what side effects they may cause.

Bulk-forming laxatives

Bulk-forming laxatives are also known as fiber supplements.

They work by pulling fluid into the intestines to make the stool softer and bulkier. This can help to produce muscle contractions in the intestines, which means the muscles tighten or squeeze. The contractions push the stool through your system.

Bulk-forming laxatives may take a few days to work, but they are safe for long-term use.

Types of bulk-forming laxatives include:

- psyllium (Metamucil, Konsyl)
- calcium polycarbophil (FiberCon)
- methylcellulose fiber (Citrucel)

Bulk-forming laxatives often come in the form of powder or granules that you mix with water or other liquid and take by mouth.

However, bulk-forming laxatives also come in a number of other forms, such as:

- liquid
- tablets
- packets
- wafers

All forms of bulk-forming laxatives should be taken with plenty of water or other liquid. This helps to avoid fecal impaction, which is when stool becomes stuck in the intestine.

The more common side effects of bulk-forming laxatives are bloating or abdominal pain.

Shop for bulk-forming laxatives online.

Lubricants

Lubricant laxatives coat the stool to allow it to pass more easily through your intestines. These laxatives may begin working within 6 to 8 hours of when you take them.

Lubricant laxatives should not be used long term. Long-term use could lead to dependence, which means you would need lubricant laxatives to pass stool. In addition, long-term use could make you deficient in certain vitamins, including vitamins A, D, E, and K.

Mineral oil is the most common lubricant laxative.

It comes as an enema that's available as a generic and as the brand-name product Fleet Mineral Oil Enema. Mineral oil also comes as a liquid you take by mouth. You can find the liquid as a generic called a "mineral oil lubricant laxative solution."

The more common side effects of lubricant laxatives include stomach pain and cramping. These lubricants may also make your body absorb less of certain medications and vitamins. Ask your doctor if this effect is a concern for you.

Shop for lubricant laxatives online.

Osmotic laxatives

Osmotic laxatives help keep water within the intestines, which softens stool and can cause more frequent bowel movements.

Some of these products are also known as saline laxatives, including:

- magnesium hydroxide
- magnesium citrate
- sodium phosphate

Osmotic laxatives come as:

- enemas
- suppositories
- forms you take by mouth

These laxatives act quickly. The oral forms may work within 30 minutes. The suppositories and enemas may work even faster.

Osmotic laxatives include:

- magnesium hydroxide (Phillips Milk of Magnesia)
- magnesium citrate (Citroma)
- polyethylene glycol (MiraLAX)
- sodium phosphate* (Fleet Saline Enema)
- glycerin (Fleet Glycerin Suppository)

Osmotic laxatives are generally safe to use long term, but you should be sure to drink plenty of water to avoid becoming dehydrated. Also, some people have reported that osmotic laxatives stop working if used too often.

The more common side effects of osmotic laxatives include:

- stomach cramping
- diarrhea

In some cases, the diarrhea can result in dehydration.

Shop for osmotic laxatives online.

Stimulant laxatives

Stimulant laxatives trigger the muscles in your intestines to contract, which moves the stool through the intestines. Typically, oral stimulant laxatives work within 6 to 10 hours.

Stimulant laxatives come as:

- oral liquids
- capsules

- enemas
- suppositories

Types of stimulant laxatives include:

- bisacodyl (Dulcolax)
- senna/sennoside (Senokot)

One of the more common side effects of stimulant laxatives is stomach cramping. In fact, these products are more likely than other laxatives to cause this effect.

You shouldn't use stimulant laxatives as a long-term treatment. Your body may become tolerant to this type of medication. If that happens, your constipation will worsen when you stop taking the laxative.

Shop for stimulant laxatives online.

Stool softeners

Stool softeners add water and fats into the stool, creating softer bowel movements. These products are often recommended to prevent straining during bowel movements, which might be important if you've recently had surgery or given birth.

Typically, stool softeners take 1 to 3 days to take effect. Docusate (Colace, DulcoEase, Surfak) is a commonly used stool softener.

It comes in the following forms:

- tablet
- capsule
- liquid
- enema
- suppository

Stool softeners have few side effects and are safe for long-term use.

Shop for stool softeners online.

Combination medications

Sometimes, two different OTC laxatives are combined into one product.

Most combination products contain a:

- stool softener
- stimulant laxative

An example of a common combination product is docusate-sodium-senna (Senokot-S and Peri-Colace).

Shop for combination stool softener and stimulant laxatives online.

Type	Generic and brand names	Forms	How fast?	Safe to use long-term?	Available as a generic?
bulk-forming	psyllium (Metamucil, Konsyl), calcium polycarbophil (FiberCon), methylcellulose fiber (Citrucel)	powder, granules, liquid, tablet, packet, wafer	a few days	yes	yes
lubricant	mineral oil (Fleet Mineral Oil Enema)	enema, oral liquid	6 to 8 hours	no	yes
osmotic	magnesium hydroxide (Phillips Milk of Magnesia), magnesium citrate, polyethylene glycol (Miralax), sodium phosphate	enema, suppository, oral liquid	30 minutes or less	yes	yes

	(Fleet Saline Enema), glycerin (Fleet Glycerin Suppository)				
stimulant	bisacodyl (Dulcolax), senna/sennoside (Senokot)	enema, suppository, oral liquid or capsule	6 to 10 hours	no	yes
stool softener	docusate (Colace, DulcoEase, Surfak)	Enema, suppository, oral tablet, capsule, or liquid	1 to 3 days	yes	yes

Prescription medications for constipation

If you try OTC products and they don't resolve your constipation, talk to your doctor. They may recommend a prescription medication. These medications are generally safe for long-term use.

Prescription constipation medications are typically recommended for people with:

- chronic constipation
- irritable bowel syndrome with constipation (IBS-C)

Some are also recommended for people with opioid-induced constipation.

These medications aren't meant to provide immediate relief. They don't necessarily lead to a bowel movement within minutes to hours, as many of the OTC laxatives do. Instead, when you take a prescription product daily, your number of weekly bowel movements should increase.

Most people taking these medications have a bowel movement within the first 24 hours, with more frequent bowel movements seen within the first week or two of treatment.

The only types of prescription constipation medications available in the United States are:

- linaclotide
- plecanatide
- lubiprostone
- methylnaltrexone
- naloxegol
- naldemedine

Linaclotide (Linzess) and plecanatide (Trulance)

Linaclotide (Linzess) and plecanatide (Trulance) regulate the amount of fluid in the intestines. They also speed up the movement of stool through the intestines. Both of these drugs are used to treat chronic constipation. Linaclotide is also used to treat IBS-C.

Both products are only available as brand-name medications, which means they don't have generic forms. Trulance comes as an oral tablet, and Linzess comes as an oral capsule.

Common side effects of these medications include:

- diarrhea
- gas
- bloating
- abdominal pain

Diarrhea may be severe and require you to stop using the medication.

These medications should not be used in children under age 18 years. Use is recommended for adults age 18 and over.

Lubiprostone (Amitiza)

Lubiprostone (Amitiza) helps increase fluid secretion in the intestines, which helps pass stool through the intestines.

Lubiprostone is used to treat:

- chronic constipation
- IBS-C
- opioid-induced constipation

This medication comes as a capsule you take by mouth.

Common side effects include:

- diarrhea
- nausea
- abdominal pain

Methylnaltrexone (Relistor)

Methylnaltrexone (Relistor) works by blocking certain effects of opioids to treat opioid-induced constipation.

Opioids work by binding to pain receptors in your brain. However, they may also bind to receptors in your gut or intestines. When this happens, it can cause constipation.

Methylnaltrexone blocks opioids from binding to the receptors in your gut or intestines. However, it does not block opioids from binding to pain receptors in your brain. This action helps relieve constipation while still allowing for pain relief.

Methylnaltrexone comes as a tablet you take by mouth and as an injectable form.

Common side effects include:

- nausea
- diarrhea
- abdominal pain

Naloxegol (Movantik)

Naloxegol (Movantik) works in the same way as methylnaltrexone to treat opioid-induced constipation. It blocks certain effects of opioids that can cause constipation without blocking their pain-relieving effects.

Naloxegol comes as a tablet you take by mouth.

Common side effects include:

- diarrhea
- nausea
- abdominal pain

Naldemedine (Symproic)

Naldemedine (Symproic) also works in the same way as methylnaltrexone and naloxegol in treating opioid-induced constipation by blocking opioid effects in your gut and intestines without blocking the pain relief.

If you've been taking opioids for less than 4 weeks, it may be less effective.

Naldemedine comes as a tablet you take by mouth.

Common side effects include:

- abdominal pain
- diarrhea
- nausea
- gastroenteritis

Generic name	Brand name	Forms	How fast?	Safe to use long-term?	Available as a generic?

linaclotide	Linzess	oral capsule	within 24 hours for most people	yes	no
plecanatide	Trulance	oral tablet	within 24 hours for most people	yes	no
lubiprostone	Amitiza	oral capsule	within 24 hours for most people	yes	no
methylnaltrexone	Relistor	oral tablet, injection	within 24 hours for most people	yes	no
naloxegol	Movantik	oral tablet	within 24 hours for most people	yes	no

Irritable Bowel Syndrome

What is IBS?

Irritable bowel syndrome is a gastrointestinal disorder characterized by the presence of a cluster of symptoms and signs in adults or children that include cramping, abdominal pain, increased gas, altered bowel habits, food intolerance, and bloating (distention).

Irritable bowel syndrome is a "functional" disorder. This term refers to the changes in the functioning of the digestive system that results in the collection of symptoms referred to as IBS, meaning that it is a problem with the movement (motility) rather than any damage to the tissues of the digestive system.

In the past, irritable bowel syndrome was also called spastic colon or bowel, functional bowel disease, mucous colitis, or nervous colon.

What are the signs and symptoms of IBS?

Irritable bowel syndrome is characterized mostly by abdominal pain and cramping. Other symptoms and signs include:

- Diarrhea: IBS with diarrhea (IBS-D) can come with sudden urges to have bowel movements and loose stools.
- Constipation: IBS with constipation (IBS-C) can be accompanied by straining during bowel movements and infrequent stools.
- Increased gas
- Abdominal swelling or bloating
- Abdominal pain or discomfort
- Cramping pain after eating certain foods
- Nausea
- Mucousy or foamy stool
- Unexplained weight loss

- Loss of appetite

While not technically a symptom, nearly 70% of people with IBS also experience indigestion.

Symptoms are often relieved by bowel movements. Women with IBS may have more symptoms during their menstrual periods.

What causes IBS?

The exact cause of irritable bowel syndrome is unknown. It is believed to be due to a number of factors, including alteration in the gastrointestinal (GI) tract motility, abnormal nervous system signals, increased sensitivity to pain, and food intolerances. The following are risk factors thought to cause IBS:

1. Abnormal movements of the colon and small intestines (too fast or slow, or too strong)
2. Hypersensitivity to pain from a full bowel or gas
3. Food sensitivities, possibly caused by poor absorption of sugars or acids in food
4. Gastroenteritis ("stomach flu" or "stomach bug"), a viral or bacterial infection of the stomach and intestines, may trigger IBS symptoms
5. Psychological conditions such as anxiety or depression are observed in many people with IBS, though these conditions have not been found to be a direct cause of IBS.
6. Reproductive hormones or neurotransmitters may be off-balance in people with IBS.
7. Small intestinal bacterial overgrowth (SIBO)
8. Genetics is thought to be a possible cause of IBS, but so far, this hereditary link has not been proven.

Diagnosis

There's no test to definitively diagnose IBS. Your doctor is likely to start with a complete medical history, physical exam and tests to rule out other conditions. If you have IBS with diarrhea, you likely will be tested for gluten intolerance (celiac disease).

After other conditions have been ruled out, your doctor is likely to use one of these sets of diagnostic criteria for IBS:

- **Rome criteria.** These criteria include abdominal pain and discomfort lasting on average at least one day a week in the last three months, associated with at least two of these factors: Pain and discomfort are related to defecation, the frequency of defecation is altered, or stool consistency is altered.
- **Manning criteria.** These criteria focus on pain relieved by passing stool and on having incomplete bowel movements, mucus in the stool and changes in stool consistency. The more symptoms you have, the greater the likelihood of IBS.
- **Type of IBS.** For the purpose of treatment, IBS can be divided into three types, based on your symptoms: constipation-predominant, diarrhea-predominant or mixed.

Your doctor will also likely assess whether you have other signs or symptoms that might suggest another, more serious, condition. These signs and symptoms include:

- Onset of signs and symptoms after age 50
- Weight loss
- Rectal bleeding
- Fever
- Nausea or recurrent vomiting
- Abdominal pain, especially if it's not completely relieved by a bowel movement, or occurs at night
- Diarrhea that is persistent or awakens you from sleep
- Anemia related to low iron

If you have these signs or symptoms, or if an initial treatment for IBS doesn't work, you'll likely need additional tests.

Additional tests

Your doctor may recommend several tests, including stool studies to check for infection or problems with your intestine's ability to take in the nutrients from food (malabsorption). You may also have a number of other tests to rule out other causes for your symptoms.

Imaging tests can include:

- **Flexible sigmoidoscopy.** Your doctor examines the lower part of the colon (sigmoid) with a flexible, lighted tube (sigmoidoscope).
- **Colonoscopy.** Your doctor uses a small, flexible tube to examine the entire length of the colon.
- **X-ray or CT scan.** These tests produce images of your abdomen and pelvis that might allow your doctor to rule out other causes of your symptoms, especially if you have abdominal pain. Your doctor might fill your large intestine with a liquid (barium) to make any problems more visible on X-ray. This barium test is sometimes called a lower GI series.

Laboratory tests can include:

- **Lactose intolerance tests.** Lactase is an enzyme you need to digest the sugar found in dairy products. If you don't produce lactase, you may have problems similar to those caused by IBS, including abdominal pain, gas and diarrhea. Your doctor may order a breath test or ask you to remove milk and milk products from your diet for several weeks.
- **Breath test for bacterial overgrowth.** A breath test also can determine if you have bacterial overgrowth in your small intestine. Bacterial overgrowth is more common among people who have had bowel surgery or who have diabetes or some other disease that slows down digestion.
- **Upper endoscopy.** A long, flexible tube is inserted down your throat and into the tube connecting your mouth and stomach (esophagus). A camera on the end of the tube allows the doctor to inspect your upper digestive tract and obtain a tissue sample (biopsy) from your small intestine and fluid to look for overgrowth of bacteria. Your doctor might recommend endoscopy if celiac disease is suspected.
- **Stool tests.** Your stool might be examined for bacteria or parasites, or a digestive liquid produced in your liver (bile acid), if you have chronic diarrhea.

reatment

Treatment of IBS focuses on relieving symptoms so that you can live as normally as possible.

Mild signs and symptoms can often be controlled by managing stress and by making changes in your diet and lifestyle. Try to:

- Avoid foods that trigger your symptoms
- Eat high-fiber foods
- Drink plenty of fluids

- Exercise regularly
- Get enough sleep

Your doctor might suggest that you eliminate from your diet:

- **High-gas foods.** If you experience bloating or gas, you might avoid items such as carbonated and alcoholic beverages, caffeine, raw fruit, and certain vegetables, such as cabbage, broccoli and cauliflower.
- **Gluten.** Research shows that some people with IBS report improvement in diarrhea symptoms if they stop eating gluten (wheat, barley and rye) even if they don't have celiac disease.
- **FODMAPs.** Some people are sensitive to certain carbohydrates such as fructose, fructans, lactose and others, known as FODMAPs — fermentable oligo-, di-, and monosaccharides and polyols. FODMAPs are found in certain grains, vegetables, fruits and dairy products. Your IBS symptoms might ease if you follow a strict low-FODMAP diet and then reintroduce foods one at a time.

A dietitian can help you with these diet changes.

If your problems are moderate or severe, your doctor might suggest counseling — especially if you have depression or if stress tends to worsen your symptoms.

In addition, based on your symptoms your doctor might suggest medications such as:

- **Fiber supplements.** Taking a supplement such as psyllium (Metamucil) with fluids may help control constipation.
- **Laxatives.** If fiber doesn't help symptoms, your doctor may prescribe magnesium hydroxide oral (Phillips' Milk of Magnesia) or polyethylene glycol (Miralax).
- **Anti-diarrheal medications.** Over-the-counter medications, such as loperamide (Imodium), can help control diarrhea. Your doctor might also prescribe a bile acid binder, such as cholestyramine (Prevalite), colestipol (Colestid) or colesevelam (Welchol). Bile acid binders can cause bloating.
- **Anticholinergic medications.** Medications such as dicyclomine (Bentyl) can help relieve painful bowel spasms. They are sometimes prescribed for people who have bouts of diarrhea. These medications are generally safe but can cause constipation, dry mouth and blurred vision.
- **Tricyclic antidepressants.** This type of medication can help relieve depression as well as inhibit the activity of neurons that control the intestines to help reduce pain. If you

have diarrhea and abdominal pain without depression, your doctor may suggest a lower than normal dose of imipramine (Tofranil), desipramine (Norpramine) or nortriptyline (Pamelor). Side effects — which might be reduced if you take the medication at bedtime — can include drowsiness, blurred vision, dizziness and dry mouth.

- **SSRI antidepressants.** Selective serotonin reuptake inhibitor (SSRI) antidepressants, such as fluoxetine (Prozac, Sarafem) or paroxetine (Paxil), may help if you're depressed and have pain and constipation.
- **Pain medications.** Pregabalin (Lyrica) or gabapentin (Neurontin) might ease severe pain or bloating.

Medications specifically for IBS

Medications approved for certain people with IBS include:

- **Alosetron (Lotronex).** Alosetron is designed to relax the colon and slow the movement of waste through the lower bowel. Alosetron can be prescribed only by doctors enrolled in a special program, is intended for severe cases of diarrhea-predominant IBS in women who haven't responded to other treatments, and isn't approved for use by men. It has been linked to rare but important side effects, so it should only be considered when other treatments aren't successful.
- **Eluxadoline (Viberzi).** Eluxadoline can ease diarrhea by reducing muscle contractions and fluid secretion in the intestine, and increasing muscle tone in the rectum. Side effects can include nausea, abdominal pain and mild constipation. Eluxadoline has also been associated with pancreatitis, which can be serious and more common in certain individuals.
- **Rifaximin (Xifaxan).** This antibiotic can decrease bacterial overgrowth and diarrhea.
- **Lubiprostone (Amitiza).** Lubiprostone can increase fluid secretion in your small intestine to help with the passage of stool. It's approved for women who have IBS with constipation, and is generally prescribed only for women with severe symptoms that haven't responded to other treatments.
- **Linaclotide (Linzess).** Linaclotide also can increase fluid secretion in your small intestine to help you pass stool. Linaclotide can cause diarrhea, but taking the medication 30 to 60 minutes before eating might help.

Potential future treatments

Researchers are investigating new treatments for IBS. Serum-derived bovine immunoglobulin/protein isolate (SBI), a nutritional therapy, has shown some promise as a treatment for IBS with diarrhea.

Studies also show that, in people who have IBS with diarrhea, a specially coated tablet that slowly releases peppermint oil in the small intestine (enteric-coated peppermint oil) eases bloating, urgency, abdominal pain and pain while passing stool. It isn't clear how enteric-coated peppermint oil might affect IBS, so ask your doctor before using it.

Lifestyle and home remedies

Simple changes in your diet and lifestyle often provide relief from IBS. Your body will need time to respond to these changes. Try to:

- **Experiment with fiber.** Fiber helps reduce constipation but also can worsen gas and cramping. Try slowly increasing the amount of fiber in your diet over a period of weeks with foods such as whole grains, fruits, vegetables and beans. A fiber supplement might cause less gas and bloating than fiber-rich foods.
- **Avoid problem foods.** Eliminate foods that trigger your symptoms.
- **Eat at regular times.** Don't skip meals, and try to eat at about the same time each day to help regulate bowel function. If you have diarrhea, you may find that eating small, frequent meals makes you feel better. But if you're constipated, eating larger amounts of high-fiber foods may help move food through your intestines.
- **Exercise regularly.** Exercise helps relieve depression and stress, stimulates normal contractions of your intestines, and can help you feel better about yourself. Ask your doctor about an exercise program.

Alternative medicine

The role of alternative therapies in relieving IBS symptoms is unclear. Ask your doctor before starting any of these treatments. Alternative therapies include:

- **Hypnosis.** A trained professional teaches you how to enter a relaxed state and then guides you in relaxing your abdominal muscles. Hypnosis may reduce abdominal pain and bloating. Several studies support the long-term effectiveness of hypnosis for IBS.

- **Mindfulness training.** Mindfulness is the act of being intensely aware of what you're sensing and feeling at every moment, without interpretation or judgment. Research indicates that mindfulness can ease symptoms of IBS.
- **Acupuncture.** Researchers have found that acupuncture may help improve symptoms for people with IBS.
- **Peppermint.** Peppermint is a natural antispasmodic that relaxes smooth muscles in the intestines. It might provide short-term relief of IBS symptoms, but study results have been inconsistent.
- **Probiotics.** Probiotics are "good" bacteria that normally live in your intestines and are found in certain foods, such as yogurt, and in dietary supplements. Recent studies suggest that certain probiotics may relieve IBS symptoms, such as abdominal pain, bloating and diarrhea.
- **Stress reduction.** Yoga or meditation can help relieve stress. You can take classes or practice at home using books or videos.

Prokinetic Drugs

Prokinetic drugs increase the movement of ingested material through the GI tract. They are useful in the treatment of motility disorders, because they induce coordinated motility patterns. Unfortunately, some prokinetic drugs may produce a number of serious adverse effects that complicate their use.

The enteric nervous system of the GI tract can function independently of the CNS to control bowel function. Because there are no nerve fibers that actually penetrate the intestinal epithelium, the enteric nervous system uses enteroendocrine cells such as the enterochromaffin cells as sensory transducers. More than 95% of the body's serotonin is located in the GI tract, and >90% of that store is in the enterochromaffin cells scattered in the enteric epithelium from the stomach to the colon. The remaining serotonin is located in the enteric nervous system, where 5-HT acts as a neurotransmitter. From the enterochromaffin cells, serotonin is secreted into the lamina propria in high concentrations, which overflow into the portal circulation and intestinal lumen. The effect of serotonin on intestinal activity is coordinated by 5-HT receptor subtypes. The 5-HT1P receptor initiates peristaltic and secretory reflexes, and so far no drugs have been developed to target this specific receptor. The 5-HT3 receptor activates extrinsic sensory nerves and is responsible for the sensation of nausea and induction of vomiting from visceral hypersensitivity. Therefore, specific 5-HT3 antagonists such as ondansetron and granisetron are very effective for treatment of vomiting seen with chemotherapy. Stimulation of the 5-HT4 receptor increases the presynaptic release of acetylcholine and calcitonin gene-related peptide, thereby enhancing neurotransmission. This enhancement promotes propulsive peristaltic and secretory reflexes. Specific 5-HT4 agonists such as cisapride enhance neurotransmission and depend on natural stimuli to evoke peristaltic and secretory reflexes. This makes these drugs very well tolerated, because they do not induce perpetual or excessive motility. It is also the reason for the limitations of these drugs, because they are not effective if enteric nerves have degenerated or become nonfunctional (as in cats with end-stage megacolon).

Metoclopramide is a central dopaminergic antagonist and peripheral 5-HT3 receptor antagonist and 5-HT4 receptor agonist with GI and CNS effects. In the upper GI tract, metoclopramide increases both acetylcholine release from neurons and cholinergic receptor sensitivity to acetylcholine. Metoclopramide stimulates and coordinates esophageal, gastric, pyloric, and duodenal motor activity. It increases lower esophageal sphincter tone and stimulates gastric contractions, while relaxing the pylorus and duodenum. Inadequate cholinergic activity is incriminated in many GI motility disorders; therefore, metoclopramide should be most effective in diseases in which normal motility is diminished or impaired. Metoclopramide speeds gastric emptying of liquids but may slow the emptying of solids. It is effective in treating postoperative ileus in dogs, which is characterized by decreased GI myoelectric activity and motility. Metoclopramide has little or no effect on colonic motility.

Metoclopramide is primarily indicated for relief of vomiting associated with chemotherapy in dogs, as an antiemetic for dogs with parvoviral enteritis, and for treatment of gastroesophageal reflux and postoperative ileus. GI obstruction, such as intussusception in puppies with parvoviral enteritis, must be excluded before initiating metoclopramide therapy. Its prokinetic action is negated by narcotic analgesics and anticholinergic drugs, such as atropine. Drugs that dissolve or are absorbed in the stomach, such as digoxin, may have reduced absorption. Bioavailability may be increased for drugs absorbed in the small intestine. Because of accelerated food absorption, metoclopramide therapy may increase the insulin dose required in animals with diabetes.

Metoclopramide readily crosses the blood-brain barrier, where dopamine antagonism at the CRTZ produces an antiemetic effect. However, dopamine antagonism in the striatum causes adverse effects known collectively as extrapyramidal signs, which include involuntary muscle spasms, motor restlessness, and inappropriate aggression. Concurrent use of phenothiazine and butyrophenone tranquilizers should be avoided, because they also have central antidopaminergic activity, which increases the potential for extrapyramidal reactions. If recognized in time, the extrapyramidal signs can be reversed by restoring an appropriate dopamine:acetylcholine balance with the anticholinergic action of an antihistamine, such as diphenhydramine hydrochloride given IV at a dosage of 1 mg/kg.

Cisapride is chemically related to metoclopramide, but unlike metoclopramide, it does not cross the blood-brain barrier or have antidopaminergic effects. Therefore, it does not have antiemetic action or cause extrapyramidal effects (extreme CNS stimulation). Cisapride is a serotonin 5-HT4 agonist with some 5-HT3 antagonist activity, so it enhances the release of acetylcholine from postganglionic nerve endings of the myenteric plexus and antagonizes the inhibitory action of serotonin (5-HT3) on the myenteric plexus, resulting in increased GI motility and increased heart rate. Cisapride is more potent and has broader prokinetic activity than metoclopramide, increasing the motility of the colon, as well as that of the esophagus, stomach, and small intestine. Cisapride is especially useful in animals that experience neurologic effects from metoclopramide. Cisapride is very useful in managing gastric stasis, idiopathic constipation, and postoperative ileus in dogs and cats. Cisapride may be especially useful in managing chronic constipation in cats with megacolon; in many cases, it alleviates or delays the need for subtotal colectomy. Cisapride is also useful in managing cats with hairball problems and in dogs with idiopathic megaesophagus that continue to regurgitate frequently despite a carefully managed, elevated feeding program. In comparative studies of GI motility in people and animals, cisapride is clearly superior to other treatments.

Initially, the only adverse effects reported in people were increased defecation, headache, abdominal pain, and cramping and flatulence; cisapride appeared to be well tolerated in animals. As cisapride became widely used in management of gastroesophageal reflux in people, cases of heart rhythm disorders and deaths were reported to the FDA. These cardiac problems in

people were highly associated with concurrent drug therapy or specific underlying conditions. In veterinary medicine, adverse reactions to clinical use of cisapride have not been reported. Cisapride for animals can only be obtained through compounding veterinary pharmacies.

Domperidone is a peripheral dopamine receptor antagonist that has been marketed outside the USA since 1978. It is available in Canada as a 10-mg tablet. Currently, it is available in the USA only as an investigational new drug (1% oral domperidone gel) to treat agalactia in mares due to fescue toxicosis. Domperidone regulates the motility of gastric and small-intestinal smooth muscle and has some effect on esophageal motility. It appears to have very little physiologic effect in the colon. It has antiemetic activity from dopaminergic blockade in the CRTZ. But because very little domperidone crosses the blood-brain barrier, reports of extrapyramidal reactions are rare; however, if a reaction occurs, the treatment is the same as for reactions to metoclopramide. Domperidone failed to enhance gastric emptying in healthy dogs in one study. In other studies, however, domperidone was superior to metoclopramidein stimulating antral contractions in dogs but not cats, and it improved antroduodenal coordination in dogs. Because of its favorable safety profile, domperidone appears to be an attractive alternative to metoclopramide.

Macrolide antibiotics, including erythromycin and clarithromycin, are motilin receptor agonists. They also appear to stimulate cholinergic and noncholinergic neuronal pathways to stimulate motility. At microbially ineffective doses, some macrolide antibiotics stimulate migrating motility complexes and antegrade peristalsis in the proximal GI tract. Erythromycin has been effective in the treatment of gastroparesis in human patients in whom metoclopramide or domperidone was ineffective. Erythromycin increases the gastric emptying rate in healthy dogs, but large food chunks may enter the small intestine and be inadequately digested. Erythromycin induces contractions from the stomach to the terminal ileum and proximal colon, but the colon contractions do not appear to result in propulsive motility. Therefore, erythromycin is unlikely to benefit patients with colonic motility disorders.

Human pharmacokinetic studies indicate that erythromycin suspension is the ideal dosage form for administration of erythromycinas a prokinetic agent. Other macrolide antibiotics have prokinetic activity with fewer adverse effects than erythromycin and may be suitable for use in small animals. Both erythromycin and clarithromycin are metabolized by the hepatic cytochrome P450 enzyme system and inhibit the hepatic metabolism of other drugs, including theophylline, cyclosporine, and cisapride. Nonantibiotic derivatives of erythromycin are being developed as prokinetic agents.

Ranitidine and **nizatidine** are histamine H_2-receptor antagonists that are prokinetics in addition to inhibiting gastric acid secretion in dogs and rats. Their prokinetic activity is due to acetylcholinesterase inhibition, with the greatest activity in the proximal GI tract. Cimetidine and famotidine are not acetylcholinesterase inhibitors and do not have

prokinetic effects. Ranitidine and nizatidinestimulate GI motility by increasing the amount of acetylcholinesterase available to bind smooth muscle muscarinic cholinergic receptors. They also stimulate colonic smooth muscle contraction in cats through a cholinergic mechanism.

Ranitidine causes less interference with cytochrome P450 metabolism of other drugs than does cimetidine, and nizatidine does not affect hepatic microsomal enzyme activity, so both drugs have a wide margin of safety.

IV **lidocaine** is used in the treatment of postoperative ileus in people and has been shown to be useful in treating ileus and proximal duodenitis-jejunitis in horses. It is thought to suppress firing of primary afferent neurons, as well as to have anti-inflammatory properties and direct stimulatory effects on smooth muscle. It is also thought to suppress the primary afferent neurons from firing, as well as have anti-inflammatory properties and direct stimulatory effects on smooth muscle. Most horses respond within 12 hr of starting an infusion.