

TREATMENT AND MANAGEMENT OF ANXIETY AND GASTROINTESTINAL DISORDERS

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Disclosures

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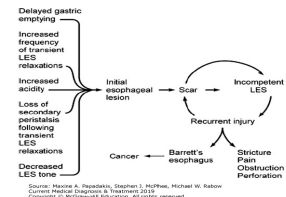
Esophageal disease: Gastroesophageal Reflux Disease (GERD)

- GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms or complications.
- It affects 20% of adults.
- **The two most common symptoms are heartburn and regurgitation.**
- However, other symptoms of GERD include:
 - Dyspepsia (indigestion),
 - Dysphagia (difficulty swallowing),
 - belching,
 - chest pain,
 - cough, and
 - hoarseness.
- Although most patients have mild disease, esophageal mucosal damage (reflux esophagitis) develops in up to one-third and more serious complications develop in a few others.
- Several factors may contribute to GERD

Esophageal disease: Gastroesophageal Reflux Disease (GERD)

Causes:

- Incompetent lower esophageal sphincter
- Hiatal hernia
- Highly acid stomach contents
- Poor esophageal peristalsis
- Delayed gastric emptying



GERD Symptoms

- The typical symptom is heartburn.
 - most often occurs 30–60 minutes after meals and upon reclining.
- Patients often report relief from taking antacids or baking soda.
- When this symptom is dominant, the diagnosis is established with a high degree of reliability.



GERD

- Major concern is chronic (many years) irritation of squamous epithelium of esophagus
- Epithelium undergoes metaplasia, may become dysplastic
- May lead to adenocarcinoma in severe cases



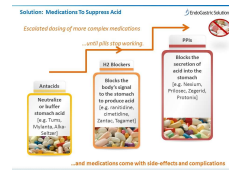
GERD Tx: Lifestyle Modifications

- Avoid lying down within 3 h after meals
- Avoid acidic foods (citrus, tomatoes, spicy foods)
- Avoid foods that precipitate reflux (fatty foods, chocolate, peppermint, alcohol)
- Weight loss, smaller meals



GERD Tx: Medications

- Patients with infrequent heartburn (less than once weekly) may be treated on demand with antacids or oral H₂-receptor antagonists.
- Antacids provide rapid relief of heartburn; however, their duration of action is less than 2 hours.
- All oral H₂-receptor antagonists are available in OTC formulations:
 - Cimetidine (Tagamet®) 200 mg,
 - Ranitidine (Zantac®) and nizatidine (Axid®) 75mg,
 - Famotidine (Pepcid®) 10 mg—
 - all of which are half of the typical prescription strength



Antacids

- Chemical bases which bind and neutralize the stomach acid (e.g. Sodium bicarbonate, calcium carbonate, magnesium hydroxide or aluminum hydroxide)
- Inexpensive
- Effective quickly. Only last 1-2 hours
- Low side effects
 - Aluminum hydroxide tends to cause constipation, whereas magnesium hydroxide tends to produce diarrhea
- Alka-seltzer, Maalox, Rolaids, Tums, Mylanta

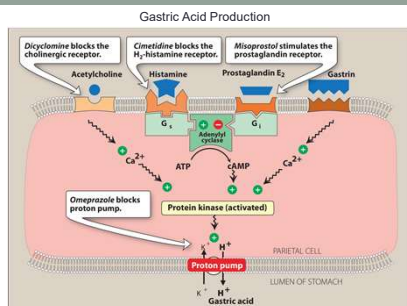
ANTACIDS
 Aluminum hydroxide *ALUMOHISTOL*
 Calcium carbonate *TUMS*
 Magnesium hydroxide *MILK OF MAGNESIA*
 Sodium bicarbonate *ALKA-SALT*

Mucosal protective agents

- prevent mucosal injury, reduce inflammation, and heal existing ulcers.
- **Sucralfate**: complex of aluminum hydroxide and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa.
 - stimulates prostaglandin, mucus and bicarbonate release,
 - Requires an acidic pH for activation, not compatible with PPIs, H₂ antagonists, or antacids.
- **Bismuth subsalicylate**: antimicrobial actions, inhibit the activity of pepsin, increase secretion of mucus.

MUCOSAL PROTECTIVE AGENTS

Bismuth subsalicylate *PEPTO-BISMOL*
Sucralfate *CARAFATE*



H₂ Blockers (H₂ Antagonists) (-tidine)

- Block the action of histamine on parietal cells, thereby decreasing the production of acid by these cells (basal and meal-stimulated)
- Relieve symptoms within 45-60 minutes**
- Longer duration of action (6-10 hours) & more effective than antacids
 - Cimetidine (Tagamet)
 - Famotidine (Pepcid) (20 to 50x more potent than cimetidine)
 - Ranitidine (Zantac) (longer acting and is 5-10x more potent than cimetidine)
 - Nizatidine (Axid)
- H₂ antagonists are extremely safe drugs.
- Adverse effects occur in less than 3% of patients and include diarrhea, headache, fatigue, myalgias, and constipation.

H₂ - HISTAMINE RECEPTOR BLOCKERS
Cimetidine *TAGAMET*
Famotidine *PEPCID*
Nizatidine *AXID*
Ranitidine *ZANTAC*

Proton Pump Inhibitors (PPI) (-azole)

- Inhibitors of the H⁺/K⁺-ATPase proton pump
- the final step in the secretion of gastric acid
- Omeprazole (OTC), dexlansoprazole, esomeprazole, lansoprazole (OTC), pantoprazole, and rabeprazole.
- Prodrug, enteric coating
- Preferred drugs for stress ulcer, GERD treatment
- reduce the risk of bleeding from an ulcer caused by aspirin and other NSAIDs
- 30 to 60 minutes before meal

PROTON PUMP INHIBITORS (PPIs)

Dexlansoprazole **DEXILANT**

Esomeprazole **NEXIUM**

Lansoprazole **PREVACID**

Omeprazole **PRLOSEC**

Pantoprazole **PROTONIX**

Rabeprazole **ACIPHEX**



GERD Tx: Medications

- Patients with troublesome reflux symptoms and patients with known complications of GERD should be treated with a once-daily oral proton pump inhibitor:
 - omeprazole or rabeprazole, 20 mg; omeprazole, 40 mg with sodium bicarbonate; lansoprazole, 30 mg; dexlansoprazole, 60 mg; esomeprazole or pantoprazole, 40 mg)
 - taken 30 minutes before breakfast for 4–8 weeks
- Once-daily proton pump inhibitors achieve adequate control of heartburn in 80–90% of patients, complete heartburn resolution in over 50%, and healing of erosive esophagitis (when present) in over 80%.

Treatment of Gastric Ulcers: NSAID use

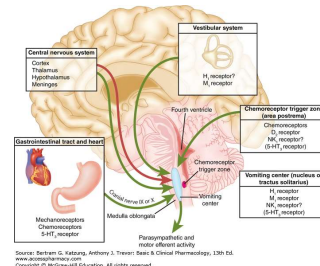
- COX-2 inhibitors such as celecoxib (Celebrex) are less likely to cause ulcers than aspirin
- Proton pump inhibitors (e.g. Prevacid® or Prilosec®) help to offset the risk of NSAID-related stomach ulcers
 - patients should be treated with concomitant proton pump inhibitors once daily, which results in ulcer healing rates of approximately 80% at 8 weeks in patients continuing to take NSAIDs

Tx of Gastric Ulcers: excess stomach acid

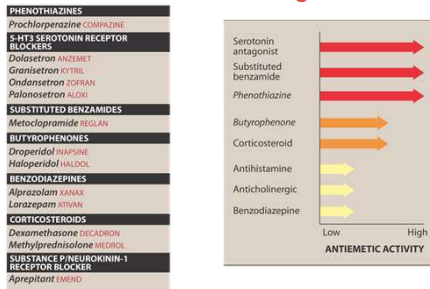
- Proton pump inhibitors (e.g. Prevacid® or Prilosec®) are highly effective here, even over durations of 10 years or more
- Healing of duodenal ulcers with proton pump inhibitors qd is usual after 4 wk; for gastric ulcers after 8 wk
- H₂ inhibitors (e.g. Zantac® and Tagamet®) are less often used for this purpose, since less effective

Antiemetic drugs

- Nausea and vomiting may be manifestations of a wide variety of conditions, including:
 - adverse effects from medications;
 - systemic disorders or infections;
 - pregnancy;
 - vestibular dysfunction;
 - central nervous system infection or increased pressure;
 - peritonitis;
 - hepatobiliary disorders;
 - radiation or chemotherapy; and
 - gastrointestinal obstruction, dysmotility, or infections.
- 4 main vomiting centers



Antiemetic drugs



Antiemetic drugs

- Selective 5-HT₃-receptor antagonists have potent antiemetic properties
 - mediated in part through central 5-HT₃-receptor blockade in the vomiting center and chemoreceptor trigger zone but mainly through blockade of peripheral 5-HT₃ receptors on extrinsic intestinal vagal and spinal afferent nerves.
 - The anti-emetic action of these agents is restricted to emesis attributable to vagal stimulation (eg, postoperative) and chemotherapy; other emetic stimuli such as motion sickness are poorly controlled.
- Ondansetron (Zofran[®]), granisetron, dolasetron, and palonosetron
 - administered once daily by oral or intravenous routes
 - most commonly reported adverse effects are headache, dizziness, and constipation

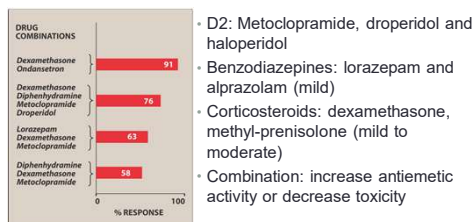
Antiemetic drugs

- Phenothiazines:
 - Phenothiazines are antipsychotic agents that can be used for their potent antiemetic and sedative properties
 - The antiemetic properties of phenothiazines are mediated through inhibition of dopamine and muscarinic receptors
 - Ex. Prochlorperazine (Compro[®])
- Substituted benzamides:
 - primary mechanism of antiemetic action is believed to be dopamine-receptor blockade
 - include metoclopramide (Reglan[®]) and trimethoprim
- H₁ antihistamines & anticholinergic agents:
 - these drugs have weak antiemetic activity, although they are particularly useful for the prevention or treatment of motion sickness
 - Scopolamine, meclizine (Travel Sickness[®])

Antiemetic drugs

- Benzodiazepines
 - are used before the initiation of chemotherapy to reduce anticipatory vomiting or vomiting caused by anxiety
 - such as lorazepam (Ativan[®]) or diazepam (Valium[®])
- Cannabinoids:
 - Dronabinol is Δ⁹-tetrahydrocannabinol (THC), the major psychoactive chemical in marijuana
 - used medically as an appetite stimulant and as an antiemetic, but the mechanisms for these effects are not understood

Antiemetic Combinations



- D₂: Metoclopramide, droperidol and haloperidol
- Benzodiazepines: lorazepam and alprazolam (mild)
- Corticosteroids: dexamethasone, methyl-prenisolone (mild to moderate)
- Combination: increase antiemetic activity or decrease toxicity

Antidiarrheals

ANTIMOTILITY AGENTS	
Diphenoxylate + atropine	LOMOTIL
Loperamide	IMODIUM A-D
ADSORBENTS	
Aluminum hydroxide	ALTERNAGEL
Methylcellulose	CITRUCEL
AGENTS THAT MODIFY FLUID AND ELECTROLYTE TRANSPORT	
Bismuth subsalicylate	PEPTO-BISMOL

- Diarrhea: ↑ motility of the GIT and ↓ absorption of fluid
- Antidiarrheal agents may be used safely in patients with mild to moderate acute diarrhea.
 - They should be discontinued in patients whose diarrhea is worsening despite therapy.
- Antidiarrheals are also used to control chronic diarrhea caused by such conditions as IBS or inflammatory bowel disease (IBD).

Antidiarrheals

- Antidiarrheal drugs: antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport
- Opioid agonists:
 - opioids have significant constipating effects
 - Loperamide (Imodium A-D) & diphenoxylate: analogs of meperidine and have opioid-like actions on the gut
- Bismuth subsalicylate, used for traveler's diarrhea, decreases fluid secretion in the bowel

LAXATIVES

- The overwhelming majority of people do not need laxatives; yet they are self-prescribed by a large portion of the population.
- For most people, intermittent constipation is best prevented with a high-fiber diet, adequate fluid intake, regular exercise, and the heeding of nature's call

IRRITANTS and STIMULANTS	
<i>Bisacodyl</i>	CORRECTOL, DULCOLAX
<i>Castor oil</i>	
<i>Senna</i>	EX-LAX, SENOKOT
BULK LAXATIVES	
<i>Methylcellulose</i>	CITRUCEL
<i>Psyllium</i>	METAMUCIL, FIBERALL
SALINE and OSMOTIC LAXATIVES	
<i>Magnesium citrate</i>	CITROMA
<i>Magnesium hydroxide</i>	MILK OF MAGNESIA
<i>Polyethylene glycol</i>	MIRILAX, GOLYTELY
<i>MOVIPREP</i>	NULYTELY, TRILYTELY
<i>Lactulose</i>	CONSTULOSE, ENULOSE, GENERLAC, KRISTULOSE
STOOL SOFTENERS	
<i>Docusate</i>	COLACE, CORRECTOL, DOCU-SOFT, DULCOLAX
LUBRICANT LAXATIVES	
<i>Glycerin suppositories</i>	FLEET, COLACE
<i>Mineral oil</i>	
CHLORIDE CHANNEL ACTIVATORS	
<i>Lubiprostone</i>	AMITIZA

Laxatives

- Stimulant/Irritants:
 - Stimulant laxatives (cathartics) induce bowel movements through a number of poorly understood mechanisms. These include direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.
 - Castor oil increases peristalsis
 - Senna: stimulant laxative, causes water and electrolyte secretion into the bowel.
 - Bisacodyl: a potent stimulant of the colon
- Bulk laxatives:
 - Bulk-forming laxatives are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis
 - methylcellulose, psyllium seeds, and bran
- Saline and osmotic laxatives:
 - The colon can neither concentrate nor dilute fecal fluid: fecal water is isotonic throughout the colon. Osmotic laxatives are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.
 - magnesium citrate, magnesium hydroxide, and sodium phosphate, polyethylene glycol (PEG)

Laxatives

- Stool softeners:
 - agents soften stool material, permitting water and lipids to penetrate. They may be administered orally or rectally
 - docusate sodium, docusate calcium, and docusate potassium
- Lubricant laxatives:
 - Mineral oil and glycerin suppositories act by facilitating the passage of hard stools
- Chloride channel activators:
 - Lubiprostone, currently the only agent in this class, works by activating chloride channels to increase fluid secretion in the intestinal lumen
 - treatment of chronic constipation
 - do not appear to show tolerance or dependency

Anxiety Disorders

- Essentials of Diagnosis:
 - Persistent excessive anxiety or chronic fear and associated behavioral disturbances.
 - Somatic symptoms referable to the autonomic nervous system or to a specific organ system (eg, dyspnea, palpitations, paresthesias).
 - Not limited to an adjustment disorder.
 - Not a result of physical disorders, other psychiatric conditions (eg, schizophrenia), or drug abuse (eg, cocaine).

Anxiety

- The psychologic, behavioral, and physiologic responses that characterize anxiety can take many forms.
- Typically, the psychic awareness of anxiety is accompanied by enhanced vigilance, motor tension, and autonomic hyperactivity.
- Anxiety is often secondary to organic disease states—acute myocardial infarction, angina pectoris, gastrointestinal ulcers, etc—which themselves require specific therapy.

Anxiety

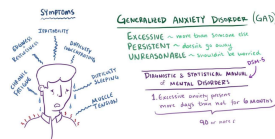
- Another class of secondary anxiety states (situational anxiety) results from circumstances that may have to be dealt with only once or a few times, including anticipation of frightening medical or dental procedures and family illness or other stressful event.
- Even though situational anxiety tends to be self-limiting, the short-term use of sedative-hypnotics may be appropriate for the treatment of this and certain disease-associated anxiety states.
- Similarly, the use of a sedative-hypnotic as premedication prior to surgery or some unpleasant medical procedure is rational and proper

Anxiety Disorders

- General findings:
 - The principal components of anxiety are psychological (tension, fears, difficulty in concentration, apprehension) and
 - somatic (tachycardia, hyperventilation, shortness of breath, palpitations, tremor, sweating).
 - Fatigue and sleep disturbances are common
 - Anxiety can become self-generating, since the symptoms reinforce the reaction, causing it to spiral

Anxiety Disorders

- **Generalized Anxiety Disorder:**
 - chronic in many patients with over half of patients having the disorder for longer than 2 years
 - 7% of women and 4% of men
 - anxiety symptoms of apprehension, worry, irritability, difficulty in concentrating, insomnia, or somatic complaints are present more days than not for at least 6 months.



Anxiety Disorders

- **Generalized Anxiety Disorder:**
 - Manifestations can include:
 - cardiac (eg, tachycardia, increased blood pressure),
 - gastrointestinal (eg, increased acidity, nausea, epigastric pain), and
 - neurologic (eg, headache, near-syncope) systems.



Anxiety Disorders

- **Panic Disorder:**
 - Recurrent, unpredictable episodes of intense surges of anxiety accompanied by marked physiologic manifestations
 - diagnosed when panic attacks are accompanied by a chronic fear of the recurrence of an attack or a maladaptive change in behavior to try to avoid potential triggers of the panic attack.



Anxiety Disorders

- **Panic Disorder:**
 - The symptoms of a panic attack can be remembered with the mnemonic: **STUDENTS FEAR the 3 Cs: Sweating, Trembling, Unsteadiness/dizziness, Derealization/depersonalization, Elevated heart rate (tachycardia), Nausea, Tingling, Shortness of breath, FEAR of dying, FEAR of losing control, FEAR of going crazy, 3 Cs - Choking, Chest pain, Chills.**



Anxiety Disorders

➤ Panic Disorder:

- Panic disorder tends to be familial, with onset usually under age 25;
- it affects 3–5% of the population, and the female-to-male ratio is 2:1.
- The premenstrual period is one of heightened vulnerability.
- Patients frequently undergo emergency medical evaluations (eg, for “heart attacks” or “hypoglycemia”) before the correct diagnosis is made.

Anxiety Disorders

➤ Panic Disorder:

- Patients who have recurrent panic disorder often become demoralized, hypochondriacal, agoraphobic, and depressed.
- These individuals are at increased risk for major depression and the suicide attempts associated with that disorder.
- Alcohol abuse (in about 20%) results from self-treatment and is frequently combined with dependence on sedatives.

Anxiety Disorders

➤ Phobias:

- Phobias are fears of a specific object or situation (eg, spiders, height) that are out of proportion to the danger posed, and they tend to be chronic.



Anxiety Disorders

➤ Phobias:

- Social Phobias are global or specific; in the former, all social situations are poorly tolerated, while the latter group includes performance anxiety (eg, fear of public speaking).
- Agoraphobia is frequently associated with severe panic attacks, and it often develops in early adult life, making a normal lifestyle difficult
 - intense fear about common situations, such as being in open spaces (eg, marketplaces), enclosed spaces (eg, theaters), standing in line, or being alone outside of their homes

Generalized Anxiety Disorders: Management

- Behavior therapy (individual, group, family)
- Cognitive behavioural therapy is the first-line psychotherapy in treatment of panic disorder, GAD, and phobias when erroneous beliefs need correction. These approaches share a common cognitive component of examining the thoughts associated with the fear and behavioral technique of exposing the individual to the feared object or situation
- Medical therapy:
 - benzodiazepines (e.g. Xanax®, Valium®, Ativan®) are helpful minor tranquilizers
 - Antidepressants are the first-line medications for sustained treatment of GAD, having the advantage of not causing physiologic dependency problems

Anxiety Management: Sedative-Hypnotics (Benzodiazepines)

- Clinical uses of sedative-hypnotics.
 - For relief of anxiety
 - For insomnia
 - For sedation and amnesia before and during medical and surgical procedures
 - For treatment of epilepsy and seizure states
 - As a component of balanced anesthesia (intravenous administration)
 - For control of ethanol or other sedative-hypnotic withdrawal states
 - For muscle relaxation in specific neuromuscular disorders
 - As diagnostic aids or for treatment in psychiatry

Anxiety Management: Sedative-Hypnotics (Benzodiazepines)

- Excessive or unreasonable anxiety about life circumstances (generalized anxiety disorder, GAD), panic disorders, and agoraphobia are amenable to drug therapy, sometimes in conjunction with psychotherapy.
- The benzodiazepines continue to be widely used for the management of acute anxiety states and for rapid control of panic attacks.
- They are also used, though less commonly, in the long-term management of GAD and panic disorders.
- Anxiety symptoms may be relieved by many benzodiazepines
- Disadvantages of the benzodiazepines include the risk of dependence, depression of CNS functions, and amnesic effects.

Benzodiazepines: Commonly Prescribed

	Onset (hours)	Action Duration	Half-Life (hours)	Potency	Equivalent Doses (mg)
flurazepam	1	Long	* 40-250	low	15-30
chlordiazepoxide	1.5	Long	* 36-200	low	10-25
diazepam	1	Long	* 36-200	low	5-10
clorazepate	1	Long	* 36-200	low	7.5-15
clonazepam	1	Long	18-50	high	0.25-0.5
temazepam	0.5	Intermediate	8-22	low	30
lorazepam	2	Intermediate	10-20	high	1
oxazepam	3	Short	4-15	low	15-20
alprazolam	1	Short	6-12	high	0.5
triazolam	0.5	Short	2-5	high	0.25-0.5

* active metabolites.

Benzodiazepines

- Oral benzodiazepines are used for insomnia, anxiety, alcohol withdrawal states, muscle spasm due to a variety of causes, including tetanus and cerebral spasticity.
- Injectable preparations are used for rapid tranquillisation in psychosis, anaesthesia and sedation for minor surgery and invasive investigations
- Dependence is a risk. Commonly there is a kind of psychological dependence based on the fact that the treatment works to reduce patients' anxiety or sleep disturbance, and therefore they are unwilling to stop. If they do stop, there can be *relapse*, where original symptoms return.

Benzodiazepines

- benzodiazepines affect memory and balance.
- Hazards with car driving or operating machinery can arise from sedation, amnesia and impaired psychomotor function.
- Amnesia for events subsequent to administration occurs with high doses given i.v., e.g. for endoscopy, dental surgery (with local anaesthetic), cardioversion.
- Paradoxical behavior effects and perceptual disorders, e.g. hallucinations occur occasionally.
- Headache, giddiness, alimentary tract upsets, skin rashes and reduced libido can occur.

Benzodiazepines: Drug Interactions

- The principal *pharmacodynamic* interaction of concern is exacerbation of *sedation* with other centrally depressant drugs, H₁-receptor antihistamines, antipsychotics, opioids, alcohol and general anaesthetics.
- All are likely to exacerbate breathing difficulties where this is already compromised, e.g. in obstructive sleep apnoea.
- Unexpected *hypotension* may occur with any co-prescribed antihypertensive drug, and vasodilators, e.g. nitrates.