Pharmacotherapy I

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Suggested Readings

- Chapter 32: Gastroesophageal Reflux Disease

Learning Objectives

- Explain pathophysiology and etiologies of GERD
- Identify typical, atypical, and alarm symptoms of GERD
- List foods and medications that can worsen GERD
- Counsel on lifestyle modifications and
- medications for GERD
- Recommend appropriate therapy for a patient with GERD
- Monitor a patient receiving GERD therapy

Common Abbreviations

GERD – Gastroesophageal reflux disease

H2RAs – Histamine type-2 receptor antagonists, AKA "H2 blockers"

LES – lower esophageal sphincter

PPIs – proton pump inhibitors

Sx – symptoms

Introduction

Heartburn: burning feeling begins in substernal area (lower chest) or stomach & spreads up to neck and sometimes the back

Postprandial heartburn: occurs within 2hrs after eating or when bending over or lying down

Nocturnal heartburn: occurs during sleep and usually awakens person

Dyspepsia (bad digestion): consistent or recurrent discomfort inupper abdominal area (epigastrium)

Mainly self-treat

Need to distinguish between who can be self-treated & who need to be evaluated by PCP

Other Definitions

Episodic heartburn – heartburn of low frequency or severity

Esophagitis – inflammation of the lining of the esophagus

Erosive esophagitis – erosion of the squamous epithelium of the esophagus

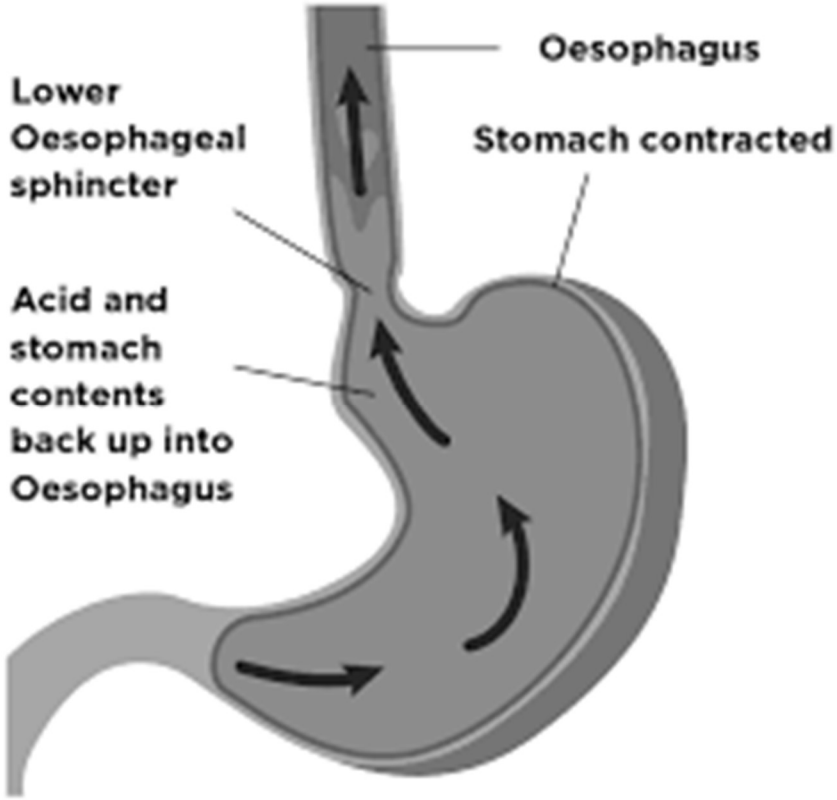
Nonerosive reflux disease (NERD) – GERD symptoms without erosions

Anatomy and Physiology of the Upper Gastrointestinal System

Esophagus: from pharynx to stomach and closed at both ends by upper and LES

Lower esophageal sphincter (LES): lower end of esophagus, prevents reflux, pass food into stomach, regulates belching

- At rest: LES contracts to prohibit passage of stomach contents into esophagus
- Swallowing: LES relaxes for food to pass into stomach



Definition of GERD

- Symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity or lung."

GERD/Heartburn Pathophysiology

Abnormal reflux of gastric contents into esophagus causing symptoms and/or esophageal mucosal damage

Retrograde flow of gastric contents into esophagus

Signs and symptoms

- Esophagus, oropharynx, larynx, & respiratory damage
- (ex: esophageal erosions, ulcers, esophagitis)

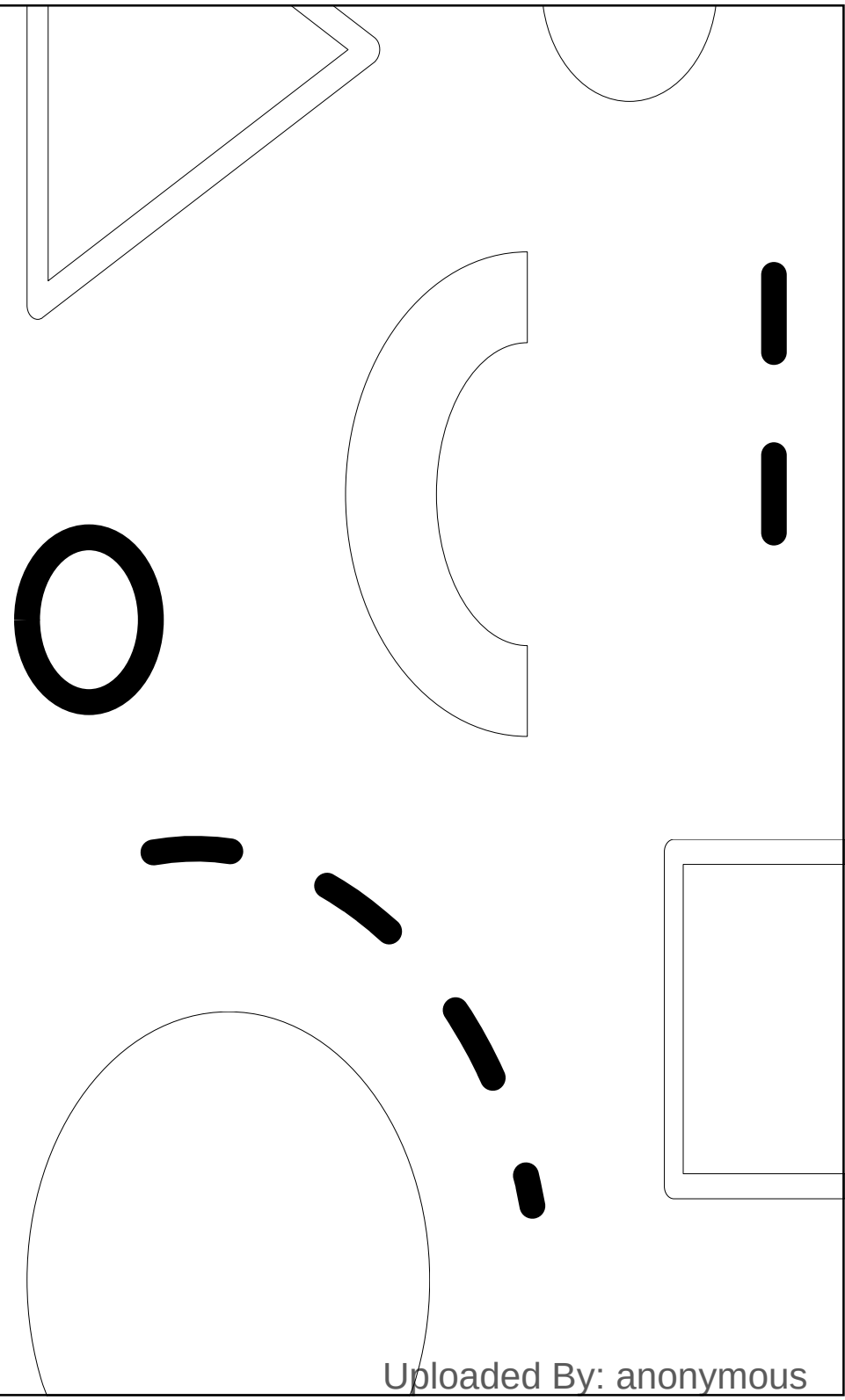
Case Presentation

- AA is a 35 YO WM who comes to your pharmacy Complaining severe heartburn 3 to 4 times per week.
- He wants to know what you recommend for heartburn.

- What questions would you want to ask this patient?

Pathophysiology

- Common disorder (10-20%)
- Reflux of gastric contents
- Defective lower esophageal sphincter (LES)
- Defective mucosal defense
- Delayed gastric emptying
- Composition of reflux
- Gastric acid
- Pepsin



What Foods Can Exacerbate GERD?

Decrease LES pressure

- Carbonated beverages
- Chocolate
- Tobacco

Increase acid exposure

- Chocolate
- ETOH
- Fatty foods
- Tobacco Others

Acidic foods

- Citrus, Orange
- Tomatoes

Caffeine, Coffee

Spearmint/Peppermint

Tight-fitting clothes

What Medications Can Worsen GERD?

Decrease LES pressure

- Anticholinergics
- Barbiturates
- Calcium channel blockers
- Estrogen
- Progesterone
- Nitrates
- Nicotine
- Theophylline

Direct mucosal irritant

- Aspirin
- Bisphosphonates
- Iron
- NSAIDs , ASA
- Potassium chloride

Clinical Presentation

Typical symptoms – heartburn (hallmark), regurgitation, non-cardiac chest pain

- Occurs within 1 hour of meal, lying down, stress, bend over, exercise (cycling, sit-ups), emotional stress

Atypical symptoms – dyspepsia, epigastric pain, nausea, bloating, belching

Extraesophageal symptoms – asthma, chronic cough, laryngitis, Hoarseness,

Dental erosions

Severity of symptoms does not always correlate with severity of tissue injury

Alarm Symptoms

Constant pain

Dysphagia Difficulty swallowing

- could be severe erosive esophagitis,

Odynophagia Pain on swallowing

- Due to ulcerative esophagitis, esophageal cancer, pills (tetracycline, ASA,
- NSAID, bisphosphonate, KCL, vitamin C), infection

Unexplained Weight loss

Choking

Patients Who Should Be Referred

- Any of alarm symptoms
- Heartburn or dyspepsia on recommended doses of OTC PPI, H2RA
- Heartburn or dyspepsia continues after 2 weeks on OTC PPI, H2RA
- Heartburn and dyspepsia when taking RX PPI, H2RA
- Under PCP care for epigastric pain
- Symptoms > 3 months
- Higher than recommended OTC doses for GERD
- Concurrent use of H2RA and PPI
- HB and dyspepsia that is severe and/or long-lasting
- Nocturnal heartburn
- Chronic hoarseness, wheezing, coughing, or choking
- Chest pain with sweating, pain radiating to shoulder, arm, neck, or jaw and shortness of breath
- Adults > 45 YO with new-onset dyspepsia

Diagnosis of GERD

Typical symptoms – empiric trial of therapy

- Mild, episodic symptoms (heartburn, regurgitation)
  - Most likely do not need invasive esophageal evaluation
  - Medication trial and lifestyle modifications → respond → GERD

Further work-up

- Non-responders to empiric medication
- Require continuous chronic therapy to relieve symptoms
- Alarm symptoms

Endoscopy (pictures)

PillCam

Ambulatory pH monitoring

Manometry (pressure) – preop eval only

Endoscopy

Visualize esophageal mucosa, biopsy

Technique of choice to diagnose Barrett's esophagus and GERD complications

Need biopsy to confirm Barrett's epithelium diagnosis and evaluate for dysplasia

Detects esophagitis, Barrett's esophagus (since need biopsy), ulcers, erosions

Specific but not very sensitive (50% for GERD)→ in mild GERD mucosa may appear normal but biopsy may have different result

- Symptoms do not predict erosive esophagitis →esophagus

may be normal in ½ patients with GERD (normal endoscopy does not exclude GERD)

Diagnosis

PillCam ESO

- Camera-containing capsule swallowed to see esophageal mucosa by endoscopy (esophagus images downloaded through sensors on chest)
- Less invasive
- Less than 15 minutes to perform in office
- Capsule eliminated in stool and cannot obtain biopsy

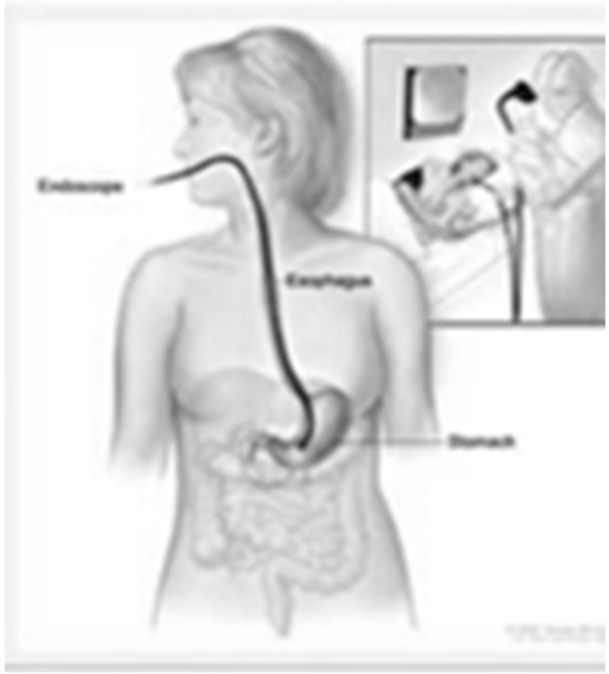
PPI test

- Empiric use for therapeutic trial
- Especially useful: symptoms but no esophageal erosions, peptic

ulcers, cancer

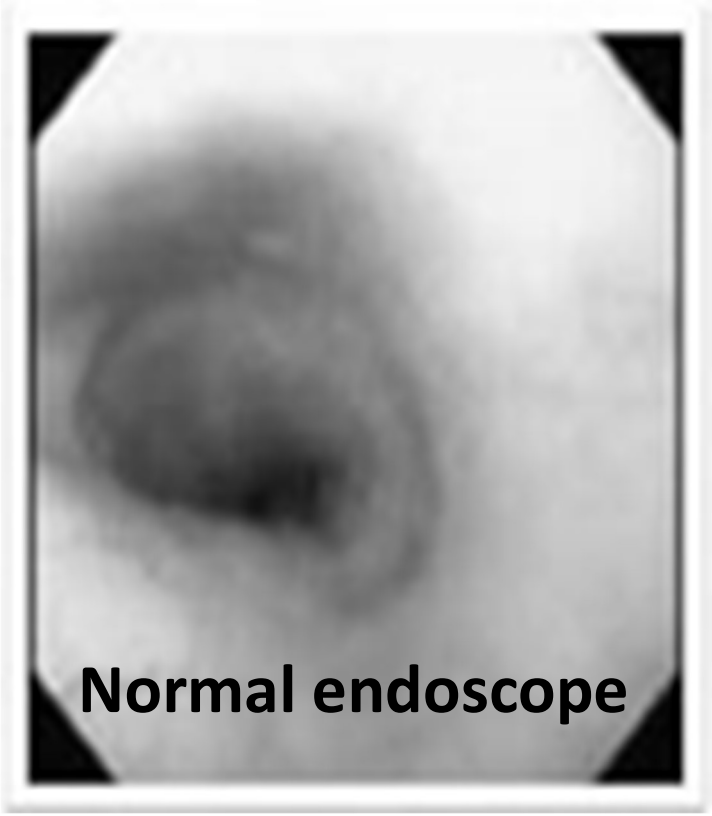
- Problems: no standard dose or duration

Diagnosis of GERD



- Endoscopy
- Telemetry pH Monitor

Endoscopy



Goals of Treatment

Reduce or alleviate	• Reduce or alleviate symptoms
Decrease	• Decrease recurrence of reflux
Promote	• Promote healing of injured mucosa
Prevent	• Prevent complications • Barrett's esophagus Esophageal strictures Esophageal cancer

Approaches to Treatment

Lifestyle modifications

Patient-directed OTC therapy

Rx acid-suppressive therapy

Antireflux surgery

Choose based on severity of symptoms

Case Presentation

- AA is a 35 YO WM who comes to your pharmacy Complaining severe heartburn 3 to 4 times per week.
- He wants to know what you recommend for heartburn.

- What lifestyle modifications might you recommend for CP to help with his GERD symptoms?

Lifestyle Modifications

Lose weight	Elevate head of bed (nocturnal GERD)	Don't eat before bed (nocturnal GERD)	Avoid fatty foods
Avoid peppermint	Avoid spicy foods	Eat small meals	Minimize caffeine
Avoid meds that can worsen GERD	Limit ETOH (not recommended)	May be some benefit in select patients	Do not lie down after meal

Patient-Directed OTC Therapy

For mild, intermittent symptoms

Further evaluation required

- Duration of symptoms > 2 weeks
- Alarm symptoms

Options

- Antacids
- OTC H2RAs
- OTC PPIs

Antacids

- Use for treatment of mild symptoms
- Provide immediate relief
- Decrease the activation of pepsinogen
- Neutralize gastric fluid
- Dose PC and HS
- May be combined with other therapy

Antacids

Types of antacids

- Aluminum
- Magnesium (Phillips Milk of Magnesiaâ)
- Al-Mg combination (Maaloxâ, Mylantaâ)
- Calcium carbonate (Tumsâ)
- Alginic acid (Gavisconâ)

Considerations

- Adverse effects
  - Constipation (Al)
  - Diarrhea (Mg)
  - Bone issues (Al)

Calcium content

Drug interactions

- Tetracycline
- Iron
- Quinolones

Frequent dosing

H2-Receptor Antagonists (H2RAs)

Inhibit gastric acid secretion by antagonizing histamine receptors

Slower onset, but longer duration of action as compared to antacids

Have similar efficacy at equivalent doses

Achieve relief of sx in ~ 60%

Less effective than PPIs

Available OTC

PPIs - Considerations

- Formulation – delayed-release cap or tab to prevent degradation in stomach acid
- For patients unable to swallow pills/caps
- Slow metabolizers - omeprazole, esomeprazole
- Drug interactions

PPI	Suspension	ODT	IV
Esomeprazole	X		X
Lansoprazole	X	X	X
Omeprazole	X		
Pantoprazole	X		X

H2-Receptor Antagonists (H2RAs)

Cimetidine

- Rx: Tagamet generic formulations
- OTC: Tagamet HB 200

Famotidine

- Rx: Pepcid
- OTC: Pepcid AC, Pepcid AC Maximum Strength, Pepcid Complete (famotidine + Ca and Mg antacid)

Nizatidine (Axidâ)

Ranitidine (off the market)

- Rx: Zantac
- Zantac 75 (store brand) or Zantac 150

H2-Receptor Antagonists (H2RAs)

OTC Dosing

Intermittent, mild heartburn

Take up to twice daily

- Cimetidine 200 mg
- Famotidine 10 mg
- Famotidine 20 mg
- Ranitidine 75 mg

Rx Dosing

- Symptomatic relief - mild to moderate GERD

Take twice daily

- Cimetidine 400 mg
- Famotidine 20 mg
- Nizatidine 150 mg
- Ranitidine 150 mg

Continue for 6-12 weeks

Higher doses may be needed for severe sx

H2RAs - Considerations

- Select based on PK considerations, adverse effects, and cost
- Generally well tolerated – headache, dizziness, constipation, diarrhea
- Renal dosing
- Cimetidine - gynecomastia
- Cimetidine – drug interactions (inhibits CYP1A2, CYP2C9, CYP2D6, CYP3A4)
  - Warfarin, phenytoin, nifedipine

Proton Pump Inhibitors (PPIs)

Inhibit H+/K+ ATPase enzyme pump

Preferred for symptom relief and healing of erosive esophagitis (8-week course)

Relief of symptoms in ~ 80-85%

Available OTC

- Omeprazole magnesium 20 mg (Prilosec OTC)
- Lansoprazole 15 mg (Prevacid24HR)
- Esomeprazole 20 mg (Nexium24HR)
- Omeprazole + sodium bicarbonate (Zegerid OTC)
- Should not be taken for more than 14 days without notifying a healthcare provider

Dosing of Rx PPIs

Take on

- Take on empty stomach 30-60 min before meal
  - Esomeprazole (Nexium®) 20 mg daily
  - Lansoprazole (Prevacid®) 30 mg daily
  - Omeprazole (Prilosec®) 20 mg daily
  - Pantoprazole (Protonix®) 40 mg daily
  - Rabeprazole (Aciphex®) 20 mg daily

Take

- Take before first meal of the day

Breakfast

- Before breakfast and before dinner if BID

Dosing of Rx PPIs

May be taken without regard to meals

- Dexlansoprazole (Dexilant®) 30 mg daily

May be administered at bedtime

- Omeprazole-sodium bicarbonate

Partial responders to PPIs

- Adjust timing of dosage (take on empty stomach or HS)
- Twice daily dosing (esp. nighttime symptoms)
- Add H2RA at bedtime (nighttime symptoms) - tachyphylaxis

Switch to another PPI ??

Non-responders - refer

PPIs – Drug Interactions

Drugs with pH-dependent absorption (all) – ketoconazole, iron salts, protease inhibitor (atazanavir)

Clopidogrel – converted to active metabolite via CYP 2C19; omeprazole, esomeprazole inhibit 2C19; recent meta-analyses do not support an increased risk of CV events

Omeprazole

Inhibits 2C19 and 2C9	warfarin, diazepam, phenytoin

Case Presentation

- AA is a 35 YO WM who comes to your pharmacy Complaining severe heartburn 3 to 4 times per week.
- He wants to know what you recommend for heartburn.

- Based on this patient's presentation, what initial pharmacotherapy would you recommend?

Other Therapies for GERD

Antireflux surgery

- For patients responsive to, but unable to tolerate acid suppressive therapy
- For patients with symptoms despite PPI

Promotility agents

- Metoclopramide – not recommended unless documented gastroparesis

Sucralfate – not recommended; may be used in pregnant patients

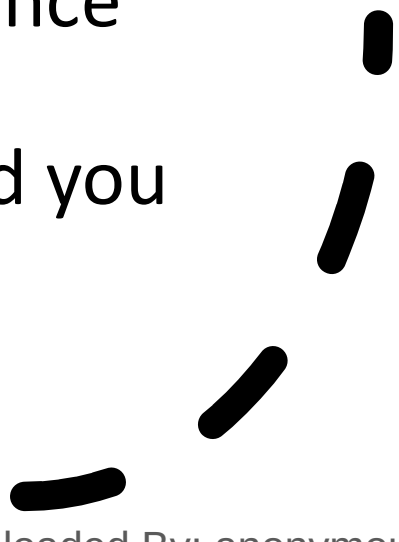
Baclofen – consider for those with symptoms on optimal PPI therapy

Maintenance Therapy

- Required by majority of patients
- PPIs are preferred therapy
- Titrate to lowest effective dose
- Consequences of acid suppression:
- Increased incidence of C. diff colitis
  - Increased risk of hip fracture – use caution in patients with other fracture risk factors
  - Increased incidence of community-acquired pneumonia (short- term usage)
  - Vitamin B12 deficiency
  - Hypomagnesemia

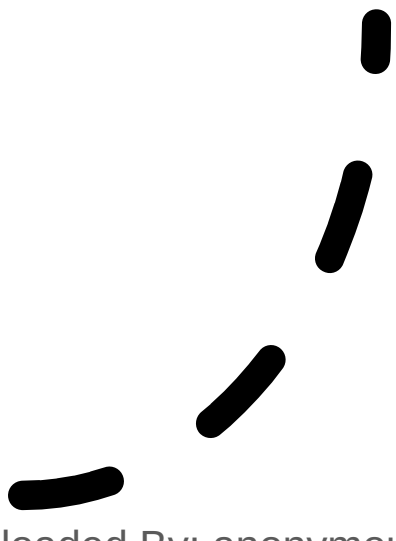
Case Presentation

- AA is a 35 YO WM who comes to your pharmacy Complaining severe heartburn 3 to 4 times per week.
- He wants to know what you recommend for heartburn.
- Would this patient be a candidate for maintenance therapy? If so, what pharmacotherapy would you recommend?



Case Presentation – Part 5

- You were so helpful that 2 weeks later CP comes in with his wife. She is having terrible heartburn, too! What can you recommend?



Special Populations

Pregnancy

- OTC antacids (esp. those with calcium) – first line
- H2RAs: ranitidine or cimetidine (pregnancy category B)
- PPIs: All pregnancy category B, except omeprazole pregnancy category C (use still supported)
- Sucralfate – pregnancy category B

Pediatrics

- Smaller feedings, thickened feedings
- H2RAs: ranitidine, famotidine
- PPIs: omeprazole

Elderly - PPIs preferred

Special populations

Pediatrics

Smaller feeding, thickened feedings

H2R2

Famotidine

Ranitidine

PPI

Take Home Message

The common symptoms include heartburn, acid brash, regurgitation, chest pain, and dysphagia

Lifestyle modifications – as appropriate

Mild, intermittent heart burn

- OTC antacids, H2RAs, or PPIs as needed

Mild symptomatic GERD

- Trial of once-daily PPI (or BID H2RA)

Moderate to severe GERD/ erosive esophagitis

- PPI preferred

Maintenance therapy

- PPI preferred