Pharmacy PRACTICE

continuing education lesson

Gastroesophageal reflux disease: a review

1.5 CEUs

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Objectives

Upon successful completion of this lesson, you should be able to:

1. describe the incidence, etiology and symptoms of gastroesophageal reflux disease (GERD)
2. identify the classification system for GERD and the various tests used to diagnose this condition
3. describe common lifestyle modifications to help reduce GERD symptoms
4. discuss various over-the-counter and prescription drug treatment options for GERD
5. describe the role of the pharmacist in the management of GERD

Heartburn, the hallmark symptom of gastroesophageal reflux disease (GERD), is suffered by one-third of healthy individuals at least once a month, while at least five per cent of the population suffers from it daily.[1,2] GERD is a chronic, relapsing disease that causes significant morbidity in the lives of the individuals who suffer from it, as well as significant costs to the healthcare system.[1] The terms "hiatus hernia" and "reflux esophagitis" have been replaced by the term GERD, which includes all patients with reflux.

For many years, GERD has been recognized as a disease with a wide spectrum, ranging from mild reflux to severe esophagitis and Barrett's esophagus. Treatments range from over-the-counter (OTC) products to prescription medications, and antireflux surgery. Many patients choose to self-medicate with a variety of OTC products; others need immediate medical attention and high-dose acid suppressive therapy.[3] This lesson will provide a step-wise approach to the diagnosis and treatment of GERD in adult patients.

Epidemiology

GERD affects both children and adults. Its true prevalence rate and incidence are not clear because not all patients seek medical attention.[4] Secondly, many patients present with atypical signs and symptoms, which makes accurate diagnosis difficult. Thirdly, many epidemiological studies are hampered by inconsistent definitions used for the disease.[5] Some prevalence studies used questionnaires to assess reflux symptoms, while others used physiological criteria such as 24-hour pH probe data and endoscopy results. Despite the shortcomings, several epidemiological studies provide the following facts about GERD in the Western population:

- About seven per cent of Canadians seen by primary care physicians have functional dyspepsia, which refers to upper abdominal discomfort.[6]
- About 25 per cent of pregnant women experience heartburn on a regular basis.[7]
- A survey of healthy hospital employees in the U.S. found that seven per cent experienced heartburn daily, and 14 per cent experienced it weekly.[8]
- An endoscopy study in 355 otherwise healthy individuals found that 13.8 per cent had abnormal endoscopic findings (e.g., mucosal friability and erythema) and 8.5 per cent had erosive esophagitis.[9]

Pathophysiology

While the actual cause of GERD is unknown, it is well established that the pathophysiology involves contact of noxious substances in the esophagus, also referred to as the "offensive force."[10] Substances in the gastric refluxate that cause damage to the mucosa include hydrochloric acid, pepsin and, less likely, conjugated and unconjugated bile salts and the pancreatic enzymes tripsin and lipase.[11] Interestingly, patients with GERD do not necessarily produce

Instructions

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2. Indicate if you are already registered as an annual CE Club Member or if you would like to become a member.
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more acid or pepsin compared to healthy subjects.[7,11] This suggests that GERD may be attributed to a breakdown of the defensive system against damage by acid in the esophagus.

Defence system

The major components of the antireflux barrier are the lower esophageal sphincter (LES) and the diaphragm. The role of the diaphragm is to support the LES by physically encircling it and providing mechanical support during bending, stooping and running.[11] The LES is comprised of circular smooth muscle rings located two to three centimeters from the distal end of the esophagus. It remains contracted at rest and relaxes upon swallowing. Mechanisms that lead to an impaired "defence system" and regurgitation in GERD involve one or more of the following:[11,12]

- Incompetent LES
- Increased abdominal pressure due to gastric distension, delayed gastric emptying or gastric inflammation
- Increased frequency of transient LES relaxation
- Abnormal peristalsis
- Decreased tissue resistance against mucosal damage

Role of *Helicobacter pylori*

Helicobacter pylori, a gram-negative bacteria found in the stomach, is a major pathogen in duodenal and gastric ulcers. Its role in GERD is controversial for several reasons. First, studies have found that the incidence of *H. pylori* infection in subjects with GERD is no different from that seen in healthy patients.[13] Secondly, the eradication of *H. pylori* in patients with dyspepsia has no impact on their symptoms of pain. In fact, it has been suggested that *H. pylori* eradication may actually result in aggravation of GERD symptoms in some patients.[13,14] At this time, there is no evidence to support benefit of *H. pylori* eradication in patients with GERD. Routine testing and eradication of the organism, if present, is not recommended due to a lack of benefit in patients with GERD.[15]

TABLE 1 Symptoms of GERD

Typical symptoms	Atypical symptoms	Alarm symptoms
Heartburn	Cough	Dysphagia
Regurgitation	Hoarseness	Gastrointestinal bleeding
Dyspepsia	Recurrent sore throat	Weight loss
"Sour stomach"	Laryngitis	Sensation of choking
	Substernal discomfort	Atypical non-cardiac chest pain
	Shortness of breath	

Diagnosis

The term "gastroesophageal reflux disease" encompasses both the manifestations of reflux symptoms and endoscopic findings. A good history and thorough physical exam are important steps in determining the initial diagnosis. Symptoms of GERD are divided into typical or atypical symptoms, as shown in Table 1. The "alarm symptoms" point to severe disease or carcinoma, and require thorough and immediate investigation.

Heartburn, the most common symptom of GERD, occurs after eating, when lying down or even when bending. About one-third of the patients with GERD experience regurgitation.[1,7] Often the effortless return of gastric contents into the pharynx may result in hoarseness, laryngitis, coughing or wheezing. It has been reported that up to 50 per cent of patients with GERD-induced asthma symptoms did not experience heartburn but had other atypical symptoms.[12] Respiratory symptoms may be induced by aspiration of gastric contents into the lungs, which sets off a vagal reflex that produces bronchoconstriction.[12] Finally, reflux-induced chest pain is a common cause of non-cardiac chest pain.

A thorough evaluation is required to rule out cardiac or respiratory diseases before the atypical symptoms are related to GERD. Differential diagnosis for GERD includes gallstones, irritable bowel syndrome and peptic ulcer disease.[7,12]

GERD is classified according to endoscopic and pathological findings as follows:

1. *Non-erosive reflux disease (NERD):* These patients have mild to severe symptoms of GERD but have negative endoscopic findings.[10]

2. *Erosive esophagitis (EE):* Erosion and exudative findings are the type of mucosal damage found during endoscopy in these patients. Their symptoms range from moderate to severe, and progressive damage can occur to the mucosa without treatment. A typical grading system used to describe damage seen during endoscopy is as follows: Grade 1 is mild, with edema and redness; Grades 2 and 3 include progression from linear to confluent erosions within the esophageal mucosa; and Grade 4 includes deep ulcerations with strictures and the presence of columnar epithelium. Grades 2 and 3 damage is seen in patients with EE.

3. *Barrett's esophagus:* This develops when the squamous epithelium is replaced by intestinal columnar cells. This is Grade 4 damage as described above.

4. *Esophageal adenocarcinoma:* The incidence of this is rare in the general population. Patients with Barrett's esophagus are at very high risk of developing esophageal carcinoma.[7] This diagnosis is made by taking a biopsy during an endoscopy and examining the specimen under the microscope.

CE Faculty

This month

Gastroesophageal reflux disease: a review

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Reviewers

All lessons are reviewed by three pharmacists for accuracy, currency and relevance to current pharmacy practice.

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TABLE 2 Stepwise approach to empiric therapy with acid suppressants[7,16,17]

GERD symptoms	Description of therapy*	Notes
Any symptoms of GERD	• Lifestyle modifications (see Table 3) • Avoid drugs that worsen symptoms, if possible (see Table 4)	Continue throughout course of therapy.
Empiric therapy for mild and intermittent heartburn	Antacids for two weeks *With or without* OTC H_2RA products for two weeks	Use either or both for symptom relief. Seek medical attention if no relief in two weeks.
Empiric therapy for "typical" symptoms of GERD	Mild GERD: Standard H_2RA dose X 6-12 weeks Moderate-severe GERD: PPI X 4-8 weeks	Treat recurrences on an as-needed basis.
For patients who • failed standard H_2RA therapy • have "atypical" or severe symptoms • have erosive disease	High-dose H_2RA X 8-12 weeks *Or* PPI X 8-12 weeks High doses required for Barrett's esophagus	Maintenance therapy may be warranted; endoscopy or other investigation is warranted; surgery may be warranted.

H_2RA=Histamine$_2$ receptor antagonists (cimetidine, famotidine, nizatidine and ranitidine)
PPI=Proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole)
** Refer to Tables 6 and 7 for doses of H_2RAs and PPIs.*

Diagnostic tests for GERD

Patients who present with prolonged or atypical symptoms of GERD are usually referred for further invasive tests to confirm or rule out the diagnosis of GERD. Sometimes, invasive tests are used to follow the progress in severe disease, after a period of treatment. The following is a brief explanation of the various types of tests used in GERD.

Barium swallow

This test involves X-ray imaging of the chest after a barium "milk shake" is swallowed. The barium coats the throat and esophagus and reveals signs of thickening of esophageal folds, as well as the presence and shape of hiatus hernia, ulcerations and strictures. This test will not detect mucosal inflammation or presence of Barrett's epithelial changes.

Esophageal manometry

A multi-lumen tube is passed into the stomach and pressures are measured at various points within the esophagus as the tube is pulled out. This test is used to evaluate the peristalsis of the esophagus (i.e., esophageal clearance), and the function of the lower esophageal sphincter. It can also be used to place an ambulatory pH probe (for a 24-hour pH test).

24-hour ambulatory pH monitoring

An electrode pH probe is placed intranasally down to an area just above the lower esophageal sphincter. Patients keep a diary of pH and symptoms for 24 hours. This test provides useful correlative information about reflux patterns, symptomatology and acidity. Studies have shown that GERD symptoms are related to the degree and duration of esophageal acid exposure (pH <4).[11] Patients with more severe disease have a longer esophageal acid (pH <4) exposure time than those with milder disease.[7]

Endoscopy

Endoscopy involves passing a probe from the mouth down the esophagus to visualize and obtain biopsies. It provides information about the extent of esophagitis, presence of Barrett's esophagus or neoplasm. Endoscopy is indicated in those with alarm or atypical symptoms, or those who have persistent symptoms despite adequate treatment.

"PPI trial"

Also known as the omeprazole test, this is one- or two-week empiric therapy with a proton pump inhibitor. This trial is given to patients to empirically diagnose GERD. If treatment provides symptom relief, then GERD is a likely diagnosis. The PPI trial is often used prior to endoscopy, or in patients with negative endoscopy results.[15]

Treatment of GERD

Desired outcomes

The immediate desired outcomes of treating GERD are to eliminate symptoms and decrease the frequency of recurrence. The long-term goals are to heal the injured mucosa and prevent further damage.

Treatment approach

Pharmacological therapy is mainly directed towards neutralizing or reducing acid production. Some patients will benefit from therapy targeted toward increasing LES function and improving gastric emptying. Studies show that patients with mild and intermittent symptoms benefit significantly with lifestyle modifications, OTC acid suppressive therapy and antacids. Patients with regular and more severe symptoms require standard dose or high-dose acid suppressive therapy. A smaller percentage of this population (i.e., with regular/severe symptoms) will require surgical interventions when conservative treatment fails. Table 2 describes a typical approach to empiric therapy.

Lifestyle modifications

All patients experiencing symptoms of GERD should follow common lifestyle changes (see Table 3). Well-designed trials measuring the effects of lifestyle modifications in patients with GERD are lacking. However, many experts estimate that about 10-20 per cent of patients will notice a significant benefit with lifestyle changes alone.[7,8,16] Patients should be advised to maintain these changes throughout the course of GERD therapy regardless of the therapeutic modalities used.

Advise patients to start with changes in eating habits, as these are easier to implement and have immediate, even if temporary, relief. The major (and probably more difficult) lifestyle changes include smoking cessation, avoidance of alcohol and weight loss. Smoking lowers lower esophageal sphincter pressure and aggravates reflux symptoms.[7] Weight reduction, if overweight, has been found to help GERD symptoms simply because of reduction in abdominal pressure and improved dietary habits.[12,16]

Lastly, it is important to review patients' profiles to see if they are taking any drugs that promote reflux or that are known to irritate gastric mucosa (see Table 4). Drugs that cause an irritant effect should be taken with a glass of water if they cannot be avoided.

Antacids

The effectiveness of antacids in GERD depends on their neutralizing capacity on the acid secretions. Antacids raise the pH of the gastric contents above 4 and thereby inhibit the conversion of pepsinogen to pepsin. Neutralization of gastric acid also increases LES pressure, and helps to reduce the frequency of reflux. Evidence from randomized trials shows antacids to be

superior over placebo; however, endoscopic data and data on long-term efficacy are lacking.[7,18] Antacids can be used as needed for symptom relief and are fast-acting. The disadvantage is that they are short-acting (two to three hours) and require frequent large doses.

Antacids come in single compounds such as aluminum hydroxide, calcium carbonate or magnesium hydroxide. They also come in combinations that include alginic acid. Alginic acid forms a highly viscous solution and serves as a barrier for reflux, as it floats on the surface of the gastric contents. Antacids with alginic acid as combination products are more effective than the single component alone.[7] Table 5 shows examples of common regimens used.

Antacids have few side effects but may cause acid-base disturbances or alterations in mineral metabolism. The pharmacist should provide the following advice when counselling patients on the use of antacids:[7,15]

- Antacids and alginic acid products are appropriate for temporary relief of mild symptoms.
- Patients with diabetes should be advised to use sugarless products.
- Aluminum-containing antacids bind to phosphate in the gut and may lead to bone demineralization with long-term use.
- Aluminum-containing antacids may cause constipation. Magnesium-containing products may cause diarrhea. Use combination products to avoid these side effects.
- Both aluminum and magnesium accumulate in patients with renal failure. Avoid in these patients.
- Sodium bicarbonate-containing antacids should be avoided in patients with renal failure, congestive heart failure or hypertension, and in patients on a sodium-restricted diet.
- Antacids increase gastric as well as urinary pH and react with many compounds to form insoluble complexes. Hence, space antacids two hours before or six hours after taking any of the following medications:
  - Tetracycline
  - Ferrous sulfate (space as much as possible)
  - Isoniazid
  - Sulfonylureas
  - Fluoroquinolones
- Large doses of antacids interfere with the absorption of phenytoin, digoxin and histamine$_2$ receptor antagonists (H_2RA), among others. Monitor the levels of phenytoin and digoxin if antacids are used concomitantly.
- Space antacids two hours before or after the use of cimetidine, nizatidine or ranitidine, as antacids significantly reduce their absorption by up to 35 per cent.[20] Famotidine may be taken with antacids as its absorption has been found to be less affected.[21]

TABLE 3 Lifestyle modifications for GERD[7,8,16,18]

- Avoid tight-fitting clothes
- Elevate head of the bed by four to eight inches
- Weight loss (for obese patients)
- Dietary changes
  - Eat smaller meals more frequently
  - Decrease dietary fat
  - Do not eat within three hours of bedtime
  - Avoid foods with irritant effect (citrus fruits and juice, tomato-based juice and sauces, coffee, pepper, spicy foods)
  - Avoid foods that reduce LES pressure (chocolate, spearmint and peppermint)
- Stop smoking
- Avoid alcohol

LES=lower esophageal sphincter

TABLE 4 Drugs that promote reflux*[,7,16,18]

- If possible,** avoid drugs that promote reflux by either reducing the LES tone or gastric emptying:
  - Anticholinergics (e.g., phenothiazines, tricyclic antidepressants)
  - Theophylline preparations
  - Calcium channel blockers
  - Beta-agonists
- If possible,** avoid drugs that have an irritant effect on esophageal mucosa:
  - Tetracycline
  - Quinidine
  - Potassium supplements
  - Iron salts
  - ASA
  - NSAIDs
  - Bisphosphonates

** This is not a complete list. Other drugs may require precautions in patients with GERD.*
*** If these drugs cannot be avoided, they should be taken with a full glass of water.*
ASA=acetylsalicylic acid
NSAIDs=nonsteroidal anti-inflammatory drugs

TABLE 5 Common antacid regimens[7,12,19]

Antacid	Typical dose (administered as needed, PC and HS)
Magnesium hydroxide 70 mg/mL	30 mL
Aluminum hydroxide 64 mg/mL	30 mL
Magnesium hydroxide 40 mg/mL + aluminum hydroxide 40 mg/mL	30 mL
Aluminum hydroxide 20 mg/mL + sodium alginate 50 mg/mL	30 mL
Magnesium carbonate 40 mg + alginic acid 200 mg	2 tablets
Magaldrate 96 mg/mL	30 mL
Calcium carbonate (e.g., chewable 500 mg; chewable ultra 1000 mg)	1 or 2 regular tablets or 1 ultra tablet

PC=after meals; HS=at bedtime

Histamine$_2$ receptor antagonists

H_2RAs competitively inhibit histamine at H_2 receptor sites in gastric parietal cells, thereby reducing gastric acid secretion. The first H_2RA, cimetidine, has been available for the treatment of peptic ulcer disease in Canada since 1977. These drugs have been used as a group for the treatment of GERD since the 1980s. Randomized, placebo-controlled trials have shown that about 70 per cent of patients with heartburn experience relief after a few weeks of therapy with an H_2RA.[1,22] Other studies have shown that H_2RAs are effective for mild but not moderate or severe GERD, or endoscopically defined erosive esophagitis.[23,24]

TABLE 6 H_2RAs: Common doses, side effects and interactions*

Drug & dosage range[7,15,18]	Side effects[c]	Drug interactions[c,d]
Cimetidine[a,b] *Symptomatic relief:* 200 mg OD-BID *Standard dose:* 400 mg BID *High dose:* 400 mg QID or 800 mg BID	• Mild, transient diarrhea, skin rash and hives • CNS effects (1-10%) (headache, fatigue, confusion); elderly have higher risk of CNS & other side effects • Prolonged use associated with gynecomastia: weak androgenic potential • Transient increase in LFTs, SCr • Consult monograph for detailed explanation	• Inhibition of CYP450: accumulation of warfarin, phenytoin, theophylline. Monitor for increased serum levels and toxicity of these drugs. • May potentiate therapeutic effect of benzodiazepines, beta-blockers, calcium channel blockers, carbamazepine, cisapride,[e] clozapine, sulfonylureas, paroxetine, propafenone, quinidine, tricyclic antidepressants. • Decreased absorption of azoles (e.g., ketoconazole, itraconazole and fluconazole). Increase the dose of the azole or consider an alternative.
Famotidine[a,b] *Symptomatic relief:* 10 mg OD-BID *Standard dose:* 20 mg BID *High dose:* 40 mg BID	• Uncommon: diarrhea, constipation • CNS side effects (1-5%)	• Little or no effect on CYP 450. • Decreased absorption of azoles (requires acidic environment). Increase the dose of the azole or consider an alternative.
Nizatidine[b] *Symptomatic relief:* 75-150 mg OD *Standard dose:* 150 mg BID *High dose:* 150 mg QID	• CNS side effects: dizziness (10%), headache (up to 16%) • Rash, pruritis • Rare: elevation of LFTs	• Weak inhibitor of CYP 3A4; no significant interactions. • Decreased absorption of azoles. Increase the dose of the azole or consider an alternative.
Ranitidine[a,b] *Symptomatic relief:* 75 mg OD-BID *Standard dose:* 150 mg BID *High dose:* 150 mg QID	• Mild diarrhea, skin rash, hives • Rare CNS side effects	• Minor effect on CYP 2C19, 2D6. • No significant drug interactions. • Decreased absorption of azoles. Increase the dose of the azole or consider an alternative.

** The above list includes common side effects and drug interactions and is not all-inclusive.*
a Dosage adjustment required in renal failure. Consult individual monographs for dosage adjustments.
b Available as OTC product.
c Nonprescription drug reference for health professionals. Ottawa: Canadian Pharmacists Association; 2001.
d Adapted from: Hansten PD, Horn JR. Drug interactions analysis and management. Vancouver, WA: Applied Therapeutics; 1997.
e Cisapride has been removed from the market; available on Special Access Programme only.
CNS=central nervous system; LFTs= liver function tests; SCr= serum creatinine

As a class, the H_2RAs are recommended for initial therapy of mild GERD. Patients with meal-related heartburn may benefit by using an OTC H_2RA product. Compared to antacids, the H_2RAs provide a more manageable, less cumbersome dosing schedule. Patients seeking to use OTC H_2RAs should be appropriately counselled about dosing, drug interactions and side effects (see Table 6).

All four OTC H_2RAs are available in approximately one-half of their prescription doses: nizatidine 75 mg, cimetidine 100 mg and 200 mg, famotidine 10 mg and ranitidine 75 mg. The latter two products are commonly available on the pharmacy shelves. Patients with meal-related symptoms should be advised to take either of these drugs prior to a meal once, or at the most twice, daily. Pharmacists should pay attention to dosing adjustments for patients with renal impairment. Patients who have only nocturnal symptoms should be advised to take the H_2RA prior to bedtime. An adequate trial period involves daily use of an OTC product for two weeks along with lifestyle changes. Patients with insufficient relief of symptoms should be referred to the physician for further investigation (after two weeks, or earlier depending on their symptoms).

Studies show that the healing rates with H_2RAs depend on the severity of the disease, the dose of the H_2RA (standard versus high) and duration of therapy. In a study involving patients with endoscopically defined mild (Grade 1) esophagitis, the healing rate with high-dose cimetidine (400 mg QID) for 12 weeks was 80 per cent, compared to only 46 per cent in patients with severe (Grade 3) esophagitis.[25] Significantly higher doses of H_2RA were required (famotidine 40 mg BID, nizatidine 150 mg TID) in clinical trials to show improved endoscopic healing rates (76-81%) when used for prolonged duration (e.g., 12 weeks).[26,27] There is limited information about the long-term safety of such high doses of H_2RAs. Therefore, it is prudent to recommend standard doses to begin with (see Table 6). Short courses of higher doses may be attempted in carefully assessed patients with close medical supervision.

Proton pump inhibitors

Proton pump inhibitors (PPIs) work on the surface of gastric parietal cells to inhibit H^+/K^+ adenosine triphosphate enzymes and prevent the transport of the H^+ ion in exchange for K^+. This occurs at the final step of acid production and results in profound acid suppression. Comparative studies show PPIs have at least 30 per cent higher response rates than H_2RAs in severe erosive and severe non-erosive GERD.[28-30]

There are five PPIs available on the market (see Table 7). All have short half-lives and a long duration of action, due to sustained acid suppression caused in the parietal cells. They are

generally well tolerated; side effects including headache, somnolence, dizziness, diarrhea, constipation or nausea occur in less than five per cent of the population. All PPIs are metabolized by CYP 3A4 and CYP 2C19 in different degrees. Pantoprazole, lansoprazole and rabeprazole have not been involved in clinically significant CYP enzyme system interactions, unlike omeprazole.[1,7,15] There is insufficient experience regarding interactions with esomeprazole.

There is a growing body of evidence supporting the use of PPIs in severe GERD. A meta-analysis compared endoscopic outcomes and symptom relief with the use of various H_2RAs and PPIs in patients with Grades 2 to 4 esophagitis. PPIs showed consistently faster healing rates within two weeks (PPI 63.4% vs H_2RA 30%).[31] The overall healing rate for PPIs was 83.6 per cent ± 11.4 per cent irrespective of dose, drug or duration, and 51.9 per cent ± 17.1 per cent for H_2RAs at standard or higher doses. Similar findings were reported in a systematic review of 30 randomized controlled trials with endoscopic healing as the outcome measure. Healing was faster and more extensive with PPIs compared to H_2RAs at four weeks and eight weeks (relative risk [RR] 2.0, 95% confidence interval 1.7-2.5 at four weeks, and RR 1.7, 95% confidence interval 1.5-2.0 at eight weeks).[32] These reviews substantiate the superiority of PPIs over H_2RAs in patients with severe, erosive GERD.

Today, PPIs are commonly prescribed for the treatment of GERD. There has been some debate about whether one PPI is superior over another. A systematic review of 32 studies showed that there were some differences. In head-to-head trials, two PPIs (esomeprazole and lansoprazole) showed superiority over omeprazole for speed of symptom relief.[34] However, after one to two weeks, all five agents had similar efficacy for maintaining symptom control. In terms of healing rates, one study showed that after eight weeks of treatment, esomeprazole 40 mg had superior healing rates compared to esomeprazole 20 mg and omeprazole 20 mg (94%, 90% and 87%, respectively, p <0.05).[35] Many clinicians have questioned the clinical significance of these findings.[34] Others have simply pointed out that the 40 mg dose of esomeprazole (the S isomer of omeprazole) is effectively a higher dose and unfair comparator to 20 mg esomeprazole and 20 mg omeprazole.[36]

According to most guidelines, the choice of PPI depends on cost and convenience, as they are all found to be highly efficacious in GERD. Higher doses of PPI may be required (e.g., omeprazole 40-60 mg or lansoprazole 30-60 mg daily) in the initial treatment of esophageal ulcers in patients with complicated GERD. Most other patients with moderate to severe uncomplicated GERD will achieve good results with standard doses of any PPI.[1,15,34]

There have been some concerns about long-term use of PPIs. PPIs cause an increase in gastrin production in the antral-G cells, which may cause hypertrophy of the gastric mucosa. However, there have been no reports of PPI-associated gastric carcinoma after a decade of PPI use in the U.S., Europe and Australia.[1] The second concern is possible overgrowth of bacteria due to profound acid suppression, which can predispose a patient to severe infections. This concern has not been substantiated. Nevertheless, a risk-benefit assessment has to be done with the long-term use of PPIs. The benefit with continuous use of PPIs in patients with chronic or complicated GERD may override the risks.

TABLE 7 Proton pump inhibitors: doses and interactions*

PPI	Dose[7,15,18]	Interactions[c,15]
Esomeprazole[a]	Symptomatic: 20-40 mg OD Maintenance: 20 mg OD	• Reduces absorption of drugs that depend on gastric pH for bioavailability (e.g., ketoconazole, iron salts).
Lansoprazole[a]	Symptomatic: 15-30 mg OD *Note:* Short-term (4-8 week) use of 30 mg BID has been studied Maintenance: 15 mg OD	• Reduces bioavailability of azoles (e.g., ketoconazole) and indinavir. • May increase bioavailability of digoxin; monitor levels.
Omeprazole[a]	Symptomatic: 20 mg OD *Note:* Short-term (4-8 week) use of 20 mg BID or TID has been studied[29] Maintenance: 20 mg OD	• Inhibits metabolism of carbamazepine, cyclosporine, phenytoin, warfarin, benzodiazepines. • Reduces bioavailability of azoles (e.g., ketoconazole) and indinavir. • May increase bioavailability of digoxin; monitor levels.
Pantoprazole[b]	Symptomatic: 40 mg OD[d] Maintenance: 40 mg OD	• Reduces absorption of drugs that depend on gastric pH for bioavailability (e.g., ketoconazole, iron salts).
Rabeprazole[a]	Symptomatic: 10-20 mg OD to BID Maintenance: 20 mg OD	• May increase bioavailability of digoxin. Monitor levels.

** The above list includes common drug interactions and is not all-inclusive.*
a Dosage adjustment necessary in severe hepatic failure.
b Patients who have difficulty swallowing may open capsules and sprinkle intact pellets or granules of certain products (lansoprazole, omeprazole) in applesauce to then be swallowed.
c Information from product monographs in Compendium of Pharmaceuticals and Specialties, 2004.
d No difference in four- and eight-week healing rate was found between 40 mg and 80 mg doses of pantoprazole in GERD.[33]

TABLE 8 Prokinetic agents

Drug & dose	Therapeutic effect	Side effects[7,18]
Bethanechol 25 mg QID	Cholinergic agonist	• Diarrhea, cramping, fatigue, blurred vision.
Metoclopramide 10 mg BID-TID	Smooth muscle stimulant, inhibits dopamine receptors	• Galactorrhea, menstrual dysfunction, lethargy, extrapyramidal side effects, tardive dyskinesia.
Cisapride 10 mg QID (Withdrawn from the market)	Stimulates acetylcholine release, increasing LES pressure	• Fatal cardiac arrhythmias when used in combination with select drugs. • Available on Special Access Programme only.

LES=lower esophageal sphincter

Prokinetic agents

Table 8 summarizes information about prokinetic agents. The rationale for using prokinetic agents in GERD comes from physiological evi-

dence suggesting that GERD may result from dysfunction of the LES.[14] However, a review from the Cochrane database showed that efficacy of prokinetics was similar to that of H_2RAs in controlling symptoms and promoting endoscopic healing of GERD.[22] In general, prokinetic agents have more side effects and limited efficacy compared to conventional acid suppressive therapy. For example, bethanechol's cholinergic action potentiates esophageal peristalsis and LES pressure, but also results in an increase in gastric acid secretion.[1,7] This limits its use in GERD.

Combination treatment may benefit some patients. One study showed that metoclopramide combined with an H_2RA was more effective than the H_2RA alone at healing esophagitis.[37] However, metoclopramide has many central nervous system (CNS) side effects, the most problematic of which is tardive dykinesia.[18] Cisapride has been studied extensively for the treatment of GERD and was found to have similar efficacy to H_2RAs. However, a pH monitoring study failed to show a decrease in reflux compared to controls.[38,39] Cisapride was withdrawn from the market in the autumn of 2000 due to reports of fatal cardiac dysrhythmias associated with the combination of cisapride and other agents metabolized by the cytochrome P450 system.

Other agents being studied for a possible role in GERD include tegaserod, domperidone and erythromycin. Currently, acid suppressive therapy remains the mainstay of therapy for GERD.[1,12,18]

Surgical interventions

Antireflux surgery may be recommended in patients with physical defects with any major component of the antireflux barrier: the lower esophageal sphincter and the position of the esophagus in relation to the diaphragm. Such patients have tried and failed therapy with acid suppression as well as prokinetic agents. Antireflux surgery includes reduction of hiatal hernia, repair of diaphragmatic hiatus, strengthening of gastroesophageal junction at the diaphragm or placement of gastric wrap at the gastroesophageal junction.[19] Candidates for antireflux surgery have to be carefully selected after undergoing many diagnostic tests. A new endoscopic treatment involving the use of radiofrequency ablation to generate a scar tissue at the LES is showing promising results.[18] This procedure is aimed at reducing transient LES relaxation to reduce reflux. Unfortunately, antireflux surgery does not eliminate use of acid suppressive therapy in all patients.

The pharmacist's role

GERD is a chronic, relapsing disease in many patients. A significant number of patients with heartburn have erosive disease, which can cause significant morbidity if not diagnosed and treated appropriately. Pharmacists play an important role in counselling patients about GERD and identifying patients who have unusual symptoms that require medical assessment.

Pharmacists need to emphasize that lifestyle changes are vital in the management of GERD. Based on the type and severity of the symptoms, the pharmacist can guide patients on the appropriate use of OTC products. Careful attention needs to be paid when counselling patients with chronic diseases such as congestive heart failure, hypertension, renal insufficiency and diabetes. Such patients are on multiple drug therapies that may have potential drug interactions with both OTC and prescription medications for GERD. Finally, patients with severe or unrelenting symptoms should be referred immediately to their physician for further investigation and appropriate treatment. Pharmacists can offer a valuable service as they are readily available to counsel patients on the proper use of GERD medications as well as their response to those medications, and to reinforce the need for adherence to the regimen. Pharmacists can also advise patients when to seek medical attention for their symptoms and/or the possibility of the need for prescription therapy.

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Questions

1 Regular use of an antacid with a magnesium/aluminum combination in a patient with renal failure will likely cause:
a) diarrhea
b) sodium excretion
c) high blood sugar
d) magnesium and aluminum retention
e) none of the above

2 Which of the following is true about famotidine?
a) It can be taken concomitantly with an antacid.
b) It should be avoided with a beta-blocker.
c) It works within seconds.

3 Antireflux surgery may be recommended in a patient who has:
a) failed maximum acid suppressive and prokinetic therapy
b) has LES dysfunction
c) either of the above

4 The OTC H_2RAs may be recommended as initial therapy for patients:
a) suffering from heartburn symptoms for a short period of time
b) with meal-related heartburn
c) both of the above
d) none of the above

5 Patients with non-erosive esophagitis:
a) never develop severe symptoms
b) have positive findings in the endoscopic exam
c) should never use pharmacologic interventions
d) none of the above

6 A proton pump inhibitor may be preferred over an H_2RA when a patient has:
a) endoscopically documented severe erosive disease
b) any symptoms
c) neither of the above

7 True or false: Metoclopramide should *not* be used in combination with ranitidine in patients with GERD.
a) True b) False

8 *Helicobacter pylori* testing and eradication is *not* useful in a patient diagnosed with GERD because:
a) *H. pylori* can never be isolated in these patients
b) *H. pylori* eradication in GERD is not associated with symptom relief
c) the regimen used for eradication is too complex for these patients

Case A

BG is a 59-year-old dentist who asks you for advice about his heartburn, cough related to acid indigestion, and laryngitis. He has tried a magnesium/aluminum combination intermittently, up to one tablespoonful three times a day for weeks but still has heartburn, cough and regurgitation, even at night. His profile reveals that he is a smoker, and that he takes a beta-blocker for hypertension plus glyburide 5 mg once a day.

9 How would BG's GERD symptoms be classified?
a) atypical
b) typical
c) both of the above

10 Which of the following is the most important question to ask BG?
a) Do you wear tight-fitting clothes and eat large meals?
b) Do your parents have severe GERD?
c) Have you lost weight, experienced dysphagia or choking, or had any gastrointestinal bleeding?

11 BG asks you if nicotine causes reflux. You answer that:
a) smoking lowers LES pressure and contributes to reflux
b) smoking is associated with poor eating habits that cause heartburn
c) smoking has not been shown to cause or worsen symptoms of GERD

12 What is the most reasonable advice you would give to BG about antacids?
a) Triple the dose and take it hourly or more frequently.
b) Stop taking antacids.
c) Stop the current antacid and try alginic acid/antacid combination tablets, 2 tabs PC and HS.

13 Until BG sees a doctor, which of the following is the best advice?
a) Start OTC famotidine 10 mg twice a day.
b) Start lifestyle modifications.
c) Go to a walk-in clinic if "alarm symptoms" develop.
d) all of the above

14 Endoscopy may be indicated for BG because:
a) he is on antacids intermittently
b) he has atypical symptoms which may be due to a more severe form of GERD
c) he is male with hypertension
d) all of the above

Case B

ZM, a 92-year-old female with a history of seizures, is seen by a specialist because of intermittent dysphagia, sore stomach (heartburn) and substernal pain. She had coffee ground emesis seven days ago. Today, she also has a rash all over her body, likely due to high-dose naproxen. The specialist suspects GERD as well as a drug reaction.

15 True or false: Rather than having smaller and more frequent meals, ZM should have three standard large meals a day to get symptom relief from GERD.
a) True b) False

16 The best treatment for ZM is to:
a) stop naproxen and use another NSAID
b) stop naproxen, start a high-dose H_2RA and rule out any cardiac causes or an actively bleeding ulcer
c) start antacids for control of acid reflux for two to four weeks, then reassess
d) none of the above

17 True or false: If an electrocardiogram cannot be done immediately, a PPI trial may be recommended for ZM to see if she can get symptom relief. If relieved with a PPI, then cardiac-related causes of her substernal chest pain may be ruled out.
a) True b) False

18 ZM, who has GERD symptoms plus difficulty swallowing, will benefit from a barium swallow test because it will reveal if she has:
a) thickening of esophageal folds, strictures or hiatus hernia
b) Barrett's esophagus
c) both of the above

19 Long-term use of the prokinetic agent metoclopramide for ZM is *not* the best choice because of:
a) the need for frequent administration
b) her age and history of seizure disorder
c) metoclopramide's side effect profile
d) all of the above

20 True or false: Cimetidine will have the highest risk of side effects for ZM of all the available drugs in the same class of agents.
a) True b) False

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