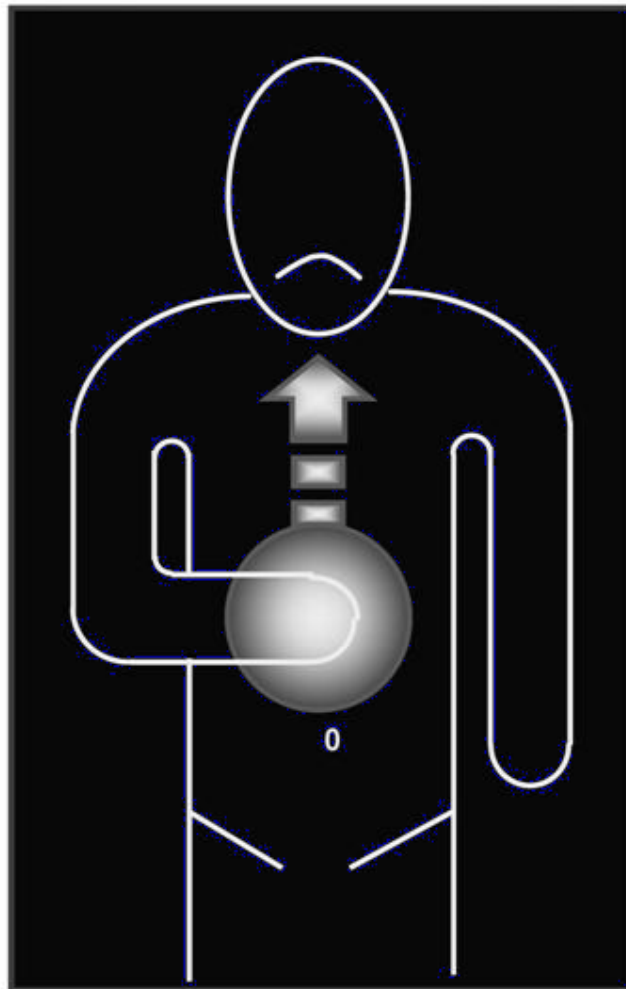


PPIs:

Burning Questions



Academic
Detailing
Service



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February 2008

"Seek simplicity, and mistrust it."
Alfred North Whitehead



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Abbreviations

Proton pump inhibitors

- For ease of reading we will use abbreviations e.g., eso, lanso, ome, panto, rabe to refer to the different PPIs:
 - Eso esomeprazole Nexium®
 - Lanso lansoprazole Prevacid®
 - Ome omeprazole Losec®
 - Panto pantoprazole Pantoloc®
 - Rabe rabeprazole Pariet®
- Abbreviations and trade names are at the foot of each page.

Other abbreviations

- CADTH Canadian Agency for Drugs and Technology in Health
- COMPUS Canadian Optimal Medication Prescribing and Utilization Service
- NICE UK-based National Institute of Clinical Excellence
- NNT Number need to treat
- PAC PPI + Amoxicillin + Clarithromycin therapy for *H pylori* eradication
- PMC PPI + Metronidazole + Clarithromycin therapy for *H pylori* eradication



Definitions

- **Gastroesophageal reflux disease (GERD):** the reflux of gastric contents into the esophagus, causing symptoms severe enough to affect the quality of life and/or cause esophageal injury.
 - **Uninvestigated GERD:** dominant symptoms of heartburn and/or regurgitation which may be associated with other symptoms such as epigastric pain or discomfort and **not** investigated by endoscopy or upper GI series. Note: heartburn-dominant uninvestigated dyspepsia is included in the definition of uninvestigated GERD.
 - **Endoscopy-negative reflux disease:** GERD with normal endoscopy performed while not receiving treatment. Also referred to as non-erosive GERD or non-erosive reflux disease.
 - **Erosive esophagitis (reflux esophagitis):** Presence of reflux symptoms and any length of mucosal break in the esophagus as a result of gastroesophageal reflux.
 - **Mild GERD:** Symptoms are infrequent (fewer than 3 times per week), of low intensity, short duration, and have minimal long-term effect on activities of daily living or health related quality of life.
 - **Moderate or severe GERD:** Symptoms are frequent, associated with intense or prolonged symptoms, and have a significant effect on daily activities or health-related quality of life.
- **Dyspepsia:** a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, in which **heartburn and/or acid regurgitation** are **not** the predominant symptoms. It may include any of the following symptoms: excessive burping or belching, bloating, nausea, a feeling of abnormal or slow digestion, early satiety, or heartburn.
 - **Uninvestigated dyspepsia:** Dyspepsia in a patient who has not undergone radiologic imaging or endoscopy but who may have undergone non-invasive testing for H. pylori infection. Note: If heartburn is the main symptom, uninvestigated dyspepsia is included in the definition of uninvestigated GERD.
 - **Functional dyspepsia:** Persistent or recurrent dyspepsia in the absence of organic cause (i.e., as determined by endoscopy or upper GI x-ray) that is likely to explain the symptoms.
- **Helicobacter pylori (H. pylori):** a spiral-shaped bacterium found in the stomach that causes gastritis and is implicated in peptic ulcer disease, gastric cancer, and MALT lymphoma.
- **Maintenance or long-term therapy:** Treatment given over an indefinite period to reduce or prevent symptoms or disease progression.
 - **Continuous therapy:** Daily intake of medication for an indefinite period to prevent or minimize symptoms.



- **Intermittent therapy:** Daily intake of medication for a predetermined, finite period (usually 2 to 8 weeks) to resolve reflux-related symptoms or heal esophageal lesions following relapse of a patient's previous symptoms or condition.
 - Also refers to the intake of medication for 3 days per week for an indefinite period to prevent or minimize symptoms or risk of disease.
- **On-demand therapy:** Daily intake of medication for a period sufficient to resolve dyspepsia or GERD symptoms. Following symptom resolution, medication is discontinued until symptoms recur, at which point medication intake is resumed until symptoms resolve once again.
- **Step-down therapy:** Initial use of potent acid suppression, followed by decreased dose or the use of less potent agents to tailor therapy according to individual response.
- **Step-up therapy:** Initial use of less potent agents or lower doses of acid suppressive therapy, followed by increased doses or more potent agents if there is an inadequate response to treatment.



Summary statements

Question 1: Are there clinically important differences among standard-doses of PPIs?

- The COMPUS Expert Review Panel on PPIs concluded there are **no clinically important differences** among standard doses of PPIs for treatment of:
 - Symptomatic GERD
 - Endoscopically negative reflux disease
 - Erosive esophagitis
 - NSAID-induced ulcers (treatment and prophylaxis)
 - *H pylori*-related ulcers in triple-therapy regimens
- COMPUS considered **standard doses** to be eso 20 mg, lanso 30 mg, ome 20 mg, panto 40 mg, and rabe 20 mg.
- There is inconsistency in whether the standard dose of eso in initial therapy of erosive esophagitis is 20 mg or 40 mg. Eso 20 mg and eso 40 mg appear to have similar efficacy in healing at 8 weeks (87% vs 90%).
- COMPUS reported **no head-to-head studies** comparing various PPIs in treatment of **dyspepsia**.
- **Erosive esophagitis** is the only condition in which a statistically significant difference in efficacy among the PPIs has been reported.
- Canadian GERD guidelines state:
 - Eso 40 mg may provide better healing at 4 and 8 weeks than standard doses of other PPIs, particularly in more severe erosive esophagitis.
 - However, the overall differences are small (3% to 6%).
 - Their **clinical relevance is debated** and the results have not been replicated consistently in other studies.



Question 2: Is starting with a double-dose PPI better than starting with a standard daily dose?

- The COMPUS Expert Review Panel on PPIs concluded that
 - Doubling the standard daily doses of PPIs, as **initial** therapy, is **no better** than standard daily dose PPI therapy for
 - Healing of erosive esophagitis
 - Healing of NSAID-induced ulcers
 - In *H pylori* eradication:
 - Standard-dose PPI administered twice daily is **more efficacious** than standard-dose PPI administered once daily when used in PAC therapy but not in PMC therapy.
- **No evidence** was reported for double-dose vs standard dose PPI in
 - Uninvestigated GERD
 - Endoscopically negative reflux disease
 - Dyspepsia
- **Canadian GERD** guidelines state:
 - Twice-daily PPI therapy is **not generally required** as initial therapy for typical GERD symptoms. Level of evidence 1,A (see Page 31)
 - Twice-daily, standard dose PPI therapy **may be used** for patients who have
 - **Severe** symptoms **despite standard once-daily** PPI therapy. Level of evidence II-3B. COMPUS identified this area as needing more research.
 - **Severe** esophagitis (LA Grade C or D, or stricture) Level of evidence I,B
- Local expert opinion states that patients may be started on double-dose PPIs when admitted to hospital for emergencies. They may then be discharged on double-dose PPIs. In such situations, family physicians should reassess patients and the continuing need for double-dose PPIs.
- Analysis of Pharmacare data indicates that approximately **30%** of Pharmacare patients **started** on a PPI are started on **double-dose**.



Question 3: When is it reasonable to treat with H₂RAs?

- It is reasonable to consider treatment with H₂RAs in:
 - Uninvestigated GERD
 - ~**60%** of patients will have complete symptom relief at 8 weeks and 52 weeks with H₂RAs vs ~**75%** for PPIs.
 - Endoscopically negative reflux disease
 - ~**40%** of patients will have symptom relief at 4 weeks with H₂RAs vs ~**50%** with PPIs.
 - Uninvestigated dyspepsia
 - At 6 months there was no statistically significant difference in symptom relief in patients treated with H₂RAs vs PPIs (both ~**40%**). There was no difference compared to placebo (~**35%**).
 - Functional dyspepsia
 - Short term trials indicate no statistically significant difference between H₂RAs and PPIs.
- There is no consensus on what constitutes optimal **maintenance** therapy of **uninvestigated GERD** for patients who attain symptomatic relief with PPIs. **Reasonable approaches are:**
 - Continue daily PPI therapy: Approximately **80%** may achieve symptom relief.
 - Switch to on-demand PPI use: Insufficient good-quality evidence to estimate responses.
 - Step-down to H₂RAs: Approximately **65%** may achieve symptom relief.
 - A trial of medication discontinuation: Approximately **20%** of patients with uninvestigated GERD will remain asymptomatic off therapy for up to 6 months after a successful course of initial therapy (4 to 8 weeks) with a PPI or H₂RA.
- Local expert opinion and Canadian guidelines state it is reasonable to use H₂RAs in patients with mild symptoms.
- H₂RAs are **not** considered usual care for patients with:
 - Erosive esophagitis
 - *H pylori* related ulcers
 - NSAID-induced ulcers – treatment and prophylaxis



Question 4: What are the possible adverse effects of acid suppression?

- Information for adverse effects of acid suppression comes from observational studies, mostly case-control studies. These provide a lower level of evidence than RCTs. Therefore, findings should be regarded with caution.
- These studies show that PPI use is **associated with** adverse effects i.e., patients who take PPIs have been found to be more likely to have these adverse effects. However, this association does not prove that the PPIs **caused** the adverse effects.
- Studies indicate there is a weak to moderate association between acid suppression therapy and:
 - Pneumonia
 - C difficile diarrhea
 - Fractures
 - Fundic gland polyps
- Generally, the association is stronger for PPIs than H₂RAs and in some cases, with increasing dose and duration of therapy.
- Guidelines and expert opinion consider it prudent to use the **least amount** of acid suppression necessary to obtain adequate symptom relief. This requires regular re-assessment of patients.



Clinical tips

GERD/Dyspepsia

- The conditions most commonly encountered by family physicians will be:
 - Uninvestigated GERD
 - Endoscopically negative reflux disease.
 - Uninvestigated and functional dyspepsia
- Although there is little evidence for the effectiveness of lifestyle modification, local expert opinion and consensus recommend strategies such as: smoking cessation, weight loss when appropriate, low fat diet, limitation of caffeine and alcohol, avoiding eating before lying down, and elevating the head of the bed.
- For patients with mild to moderate symptoms it may be reasonable to start therapy with an H₂RA.
- For patients with moderate to severe symptoms a **standard dose** PPI is appropriate. **Double-dose** PPI is generally **no more efficacious** than standard dose as initial therapy for most conditions.
 - If patients are discharged from hospital on double-dose PPI, **re-assess** need for continued double-dose therapy.
- Patients should be assessed after 4 to 8 weeks and if responding to therapy, options are:
 - **Continue** daily PPI therapy (approximately **80%** maintain symptom relief).
 - **Switch to** on-demand PPI use (insufficient evidence to estimate response).
 - **Step-down to** H₂RAs (approximately **65%** maintain symptom relief)
 - A **trial** of medication discontinuation
 - Approximately 20% of patients with uninvestigated GERD will remain asymptomatic off therapy for up to 6 months after a successful course of initial therapy (for 4 to 8 weeks) with a PPI or H₂RA.
 - The majority of patients relapse within 6 months with a median time to relapse of only 8 to 9 days.
- The treatment decision should be individualized, based on discussions with the patient and consider severity of symptoms, cost, and safety.
- Use the **lowest** dose of therapy that will provide adequate relief of symptoms.
- **Erosive esophagitis** is best diagnosed with endoscopy and most patients will require life-long PPI therapy.
- Patients who have **dyspepsia** that does not have heartburn as the predominant symptom are **less likely** to respond to antisecretory therapy than patients with heartburn symptoms.



NSAID-induced ulcers

- For **prevention**, local expert opinion considers NSAIDs to be an important cause of GI bleeds and recommends using the **lowest** dose and frequency possible if they must be used. **Acetaminophen** is a first-line therapy.

H pylori-related ulcers

- Confirm presence of *H pylori* with serum antibody or urea breath test.
- There are no clear recommendations as to which regimen to use:
 - **PAC**: PPI + Amoxicillin + Clarithromycin or
 - **PMC**: PPI + Metronidazole + Clarithromycin
- Because of possible bacterial resistance, consider PAC in patients who have taken metronidazole previously.
- Consider PMC in patients allergic to penicillin.
- Quadruple therapy (PPI + Bismuth Subsalicylate + Metronidazole + Tetracycline) may be used for:
 - Patients who cannot tolerate macrolides (e.g., clarithromycin)
 - Triple-therapy failures
- Duration of therapy is generally 7 days for both regimens.
- *H pylori* related gastric ulcers are much **less** common than duodenal ulcers.
 - For **gastric ulcers**, PPI therapy should be continued for 4 to 8 weeks after a 7-day course of eradication therapy and follow-up gastroscopy should be done to rule out malignancy.
 - For **uncomplicated duodenal** ulcers, (no bleeding, obstruction, or perforation) it is **not necessary** to continue PPIs after a 7-day course of eradication therapy. If symptoms are well-controlled after eradication, there is **no need** for follow-up gastroscopy.
 - **Complicated** duodenal ulcers should be treated like **gastric** ulcers – 4 to 8 weeks of PPI therapy followed by repeat endoscopy.
- If patient remains symptomatic, re-test using urea breath test after patient has been off PPI at least 2 weeks and off antibiotics for 1 month. Serum antibody will stay positive so is not appropriate for confirming eradication.
 - Canadian dyspepsia guidelines¹ state that antisecretory therapy can lead to falsely negative urea breath tests and recommend that PPIs and H₂RAs be stopped for 2 weeks before testing. Patients can use antacids for relief during those 2 weeks.
- If re-testing confirms presence of *H pylori*, treat with alternate regimen. If *H pylori* persists, reconsider diagnosis or refer for consultation.



Introduction

- This topic has been developed based on an extensive review conducted by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS). COMPUS is a branch of the Canadian Agency for Drugs and Technology in Health, (CADTH) Canada's national health technology assessment agency.
 - **CADTH** is an independent, not for profit agency funded by the Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers.
 - **COMPUS** identifies and promotes optimal drug therapy and provides strategies, tools, and services to encourage the use of evidence-based clinical and cost-effectiveness information in decision making among health care providers and consumers.
- COMPUS reviewed current guidelines for use of proton pump inhibitors (PPIs) and the evidence behind those guidelines. A 12-member group of gastroenterologists, family physicians, pharmacists, epidemiologists, and others helped interpret the evidence. Panel members are in **Appendix 1**. Nova Scotian physicians may recognize 2 panel members:
 - Dr Sander van Zanten, Gastroenterologist, now at University of Alberta, formerly at Dalhousie
 - Ms Pam McLean-Veysey, Team Leader, Drug Evaluation Unit, Capital Health, content expert for several previous academic detailing topics and for this topic
- The messages in this topic are also being disseminated by academic detailing programs in British Columbia, Alberta, Saskatchewan, and Manitoba.



- **More information can be found at the following web sites:**
 - CADTH – www.cadth.ca/
 - COMPUS – www.Cadth.Ca/Index.Php/En/Compus
 - COMPUS PPI material
www.cadth.ca/index.php/en/compus/current-topics/ppis
 - Academic detailing programs
 - BC – www.cdup.org
 - AB – www.calgaryhealthregion.ca
 - SK – www.rxfiles.ca
 - MB – www.prisminfo.org
 - NS – <http://cme.medicine.dal.ca/ADS.htm>

Questions addressed

- **The 4 questions addressed for this topic are:**
 1. Are there clinically important differences among standard-doses of PPIs?
 2. Is starting with a double-dose PPI better than starting with a standard daily dose?
 3. When is it reasonable to treat with H₂RAs?
 4. What are the possible adverse effects of acid suppression?

- We will also provide information on costs and some clinical tips for various conditions for which anti-secretory therapy is indicated.



Background information

Mechanism of action of PPIs and H₂RAs (see Figure 1)²

- Parietal cells, located in the body and fundus of the stomach, secrete hydrogen ions into the lumen of the gastric glands.
- Hydrogen ion secretion from the parietal cells is regulated by 3 types of receptors: acetylcholine, histamine and gastrin.
- **H₂RAs** reversibly block the action of **histamine** which is released from other mucosal cells, enterochromaffin-like (ECL) cells, in anticipation of a meal or when food enters the stomach.
 - H₂RAs reduce gastric acid secretion by approximately **70%**.
- **PPIs** irreversibly inactivate acid secretion at the final step - the transport of hydrogen ions (H⁺, K⁺-ATPase /proton -pump) from the parietal cell to the lumen of the gastric glands.
 - PPIs are more potent suppressors of acid secretion, diminishing daily production by **80-95%** with standard doses. Acid secretion resumes when new pump molecules are synthesized.
 - Because not all pumps are active simultaneously, maximal acid suppression may not occur for **2-5 days**. This makes "PRN" use of PPIs less suited for symptom relief. H₂RAs, on the other hand, while less effective in suppressing acid secretion, have a more rapid onset of action and are more useful in this setting.
- Hypergastrinemia can occur with chronic PPI use. This may result in rebound hypersecretion if the PPI is stopped abruptly. Hypergastrinemia may also promote hyperplasia of the enterochromaffin-like cells. **Fundic gland polyps** have also been associated with long term PPI use. (See page 45).

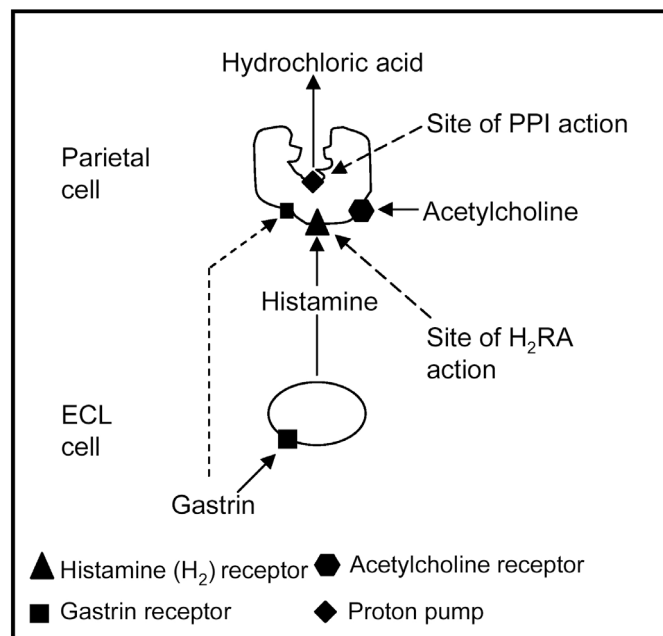


Figure 1 Gastric hydrochloric acid production



Conditions addressed

- The **4 main conditions** for which PPIs may be considered as therapy are:
 1. Treatment of **gastroesophageal reflux disease** (GERD) which may be:
 - Uninvestigated – not investigated with endoscopy or upper GI X-ray.
 - Endoscopically negative reflux disease – endoscopy shows **no pathology**. Up to **70%** of patients with GERD have endoscopically negative reflux disease.³
 - Erosive esophagitis – endoscopy shows **breaks in the mucosa**.
 - GERD may be classified according to:
 - Breaks in the mucosa (Los Angeles Classification) or
 - Symptoms

Los Angeles Classification of Esophagitis³

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in length

Grade B: One or more mucosal breaks > 5 mm in maximum length but not continuous between the tops of 2 mucosal folds

Grade C: Mucosal breaks that are continuous between the tops of 2 or more mucosal folds, but which involve < 75% of the esophageal circumference

Grade D: Mucosal breaks that involve at least 75% of the esophageal circumference

GERD Graded According to Symptoms³

Mild: symptoms are infrequent (fewer than 3 times per week), of low intensity, short duration, and have minimal long-term effect on activities of daily living or health related quality of life.

Moderate or severe: symptoms are frequent, associated with intense or prolonged symptoms, and have a significant effect on daily activities or health-related quality of life.

2. Treatment of **dyspepsia** which may be
 - Uninvestigated – not investigated with endoscopy or upper GI x-ray
 - Functional – no evidence of organic disease that is likely to explain symptoms
3. Treatment of ***H pylori*-related gastric or duodenal ulcers**
4. Prevention and treatment of **NSAID-induced ulcers**

See **page 5** for more complete explanations.



Outcomes

- There are **2** main outcomes in studies of the 4 conditions:
 1. Relief of symptoms determined by patient diary and physician-administered questionnaire
 2. Presence of mucosal erosions determined by endoscopic examination to determine either
 - Acute healing or
 - Prevention of relapse

Conditions where symptom control is the only outcome reported are those in which endoscopy is not done or lesions are not found on initial endoscopy:

- Uninvestigated GERD
- Endoscopically negative reflux disease
- Uninvestigated dyspepsia
- Functional dyspepsia

- Generally, outcomes are reported for initial response or maintenance therapy.
 - Initial response (symptom relief and healing) are reported after **4 weeks** and **8 weeks** of therapy.
 - Generally, we will not report results of studies shorter than 4 weeks.
 - Local expert opinion considers the **most important** outcomes for initial response are:
 - Symptom relief at 4 weeks: indicates how soon patients will feel better. (Symptom relief at 8 weeks gives more complete information on the effect that can be expected with either PPIs or H₂RAs. However, trials do not always report this information.)
 - Healing at 8 weeks: lesions may have been present for months or years so healing at 4 weeks is less relevant.
 - Maintenance therapy (recurrence of symptoms or endoscopic findings) are reported after up to **52 weeks** of therapy.

Definitions of GERD and dyspepsia

- Definitions of dyspepsia are different throughout the world and have been subject to change over time.
- The most relevant point is whether or not symptoms of heartburn are predominant.
- The **COMPUS** definition of dyspepsia is
 - A symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, in which **heartburn and/or acid regurgitation are NOT the predominant symptoms**.



- It may include any of the following symptoms: excessive burping or belching, bloating, nausea, a feeling of abnormal or slow digestion, early satiety, or heartburn.
- **The 2005 Canadian Dyspepsia Guidelines** used a definition of dyspepsia that **includes** heartburn and regurgitation symptoms. This is in contrast to the Rome II Consensus Working Party which considers heartburn and regurgitation to be diagnostic of **GERD** and **distinct** from dyspepsia.
- The relevance to this academic detailing lies with the efficacy of antisecretory therapy in GERD vs dyspepsia. In general, anti-secretory therapy is **less** effective in conditions in which gastric acid is not the cause of the symptoms.

Role of endoscopy in making diagnosis in GERD and dyspepsia

- Most patients will be **uninvestigated** GERD or dyspepsia.
- Erosive esophagitis is best identified by endoscopy, although in clinical practice it is generally unnecessary to differentiate between erosive esophagitis and endoscopically negative reflux disease.³
- The Canadian **GERD** Guidelines state that patients with dominant symptoms of heartburn or regurgitation can be assigned a clinical diagnosis of GERD and treated **without** the need for investigation.³
- The Canadian **Dyspepsia** Guidelines state that patients with heartburn/regurgitation-dominant symptoms can be treated for reflux without endoscopy if:
 - There are no ALARM symptoms (see below).
 - There is no NSAID or ASA use.
 - A test for H pylori, if done, is negative.
- Indications for referral or endoscopy are ALARM symptoms^{1,3}
 - Vomiting
 - Bleeding, anemia
 - Abdominal mass / weight loss
 - Dysphagia
- The Canadian **GERD** guidelines and local expert opinion consider that **age over 50** by itself is not an indication for referral.³ However, the Canadian **dyspepsia** guidelines recommend endoscopy for patients over age 50 who present with **new-onset** dyspepsia.¹



Dosages

- Table 1 lists standard and double doses of PPIs.

Table 1 Definition of standard and double-dose PPIs

Generic Name	Trade Name	Standard Dose	Double Dose
Esomeprazole	Nexium	20 mg once daily	40 mg once daily ¹
Lansoprazole	Prevacid	30 mg once daily	30 mg twice daily
Omeprazole	Losec	20 mg once daily	40 mg once daily
Pantoprazole	Pantoloc	40 mg once daily	40 mg twice daily
Rabeprazole	Pariet	20 mg once daily	20 mg twice daily

¹ Eso 40 mg once daily is the recommended standard dose therapy for healing erosive esophagitis for 4 to 8 weeks in Canada. In the United States, eso **20 mg to 40 mg** once daily is considered the standard dose for healing erosive esophagitis.

- The dosage of eso requires an explanation of the relationship between ome and eso.
- Stereoisomers** are molecules with 1 or more "chiral" centres that allow the possibility of forms with the same chemical formula but differing spatial arrangements.⁴
- Enantiomers** are a type of stereoisomer in which the molecules have 2 mirror image forms. As a hand fits a glove, only the "right" or "left" handed enantiomer may fit a molecular receptor at a drug's desired site of action.⁴ Enantiomers are referred to as R- (right) or S- (left).
- Enantiomers may have differing pharmacokinetic or pharmacodynamic properties, so isolating 1 may theoretically improve on the efficacy or safety of the racemate. For example, S-thalidomide causes birth defects while R-thalidomide helps control morning sickness.
http://www.usm.maine.edu/~newton/Chy251_253/Lectures/Chirality/OpticalActivity.html
- A compound containing an equal proportion of R- and S- enantiomers is called a **racemic** mixture. Most drugs are **racemates**, mixtures of both enantiomers in equal amounts.⁵
 - Ome is a racemate consisting of **equal proportions** of the R- and S- enantiomers i.e., ome 20 mg contains 10 mg of each of the R and S enantiomers
 - Esomeprazole consists of **only the S-** enantiomer, hence its name **eso**
 - Theoretically**, at recommended doses of 20 or 40 mg, eso is potentially 2-4 times as potent as the standard dose of ome 20 mg.
 - Most studies have compared eso 40 mg to standard doses of other PPIs, therefore equipotent doses have not been used. Even so, the clinical relevance of differences in symptom control and healing rates between eso 20 mg or 40 mg and other PPIs at standard doses is questionable. (See Page 22 to 27.)



- It is our understanding that eso is frequently prescribed at a dose of 40 mg daily, although the **only official** indications for this dose are **initial healing of erosive esophagitis** and ***H pylori* eradication**.

Appendix 2 lists the indications, dosages, and duration of therapy recommended in the Canadian product monographs of the various PPIs.

Presentation of information

- For each question, we will give a summary answer followed by details of evidence to support the answer.
- Generally, we will report:
 - Evidence from the COMPUS Scientific Document⁶ for each of the 4 conditions listed on **page 16** and the outcomes on **page 17**.
 - Findings of a Drug Class Review of PPIs done by the Oregon Evidence-based Practice Center,⁷ 1 of the systematic reviews considered by COMPUS. In some cases we have extracted data from this review.
 - Findings of some Cochrane reviews
 - Statements from Canadian Guidelines
 - Comments from Dr Leddin, content expert
- We have not provided references for all studies if they were reported by COMPUS.
- **Table 2, Page 21** summarizes many of the findings and it may help to refer to this when reading the document.



Table 2 Comparison of efficacy of PPIs and H₂RAs. Results are from head-to-head trials of PPIs and H₂RAs unless otherwise specified.

Condition	Approximate percent of patients likely to achieve					
	Symptom relief at 4 wks	Healing at 8 wks	Main ¹ tenance	Symptom relief at 4 wks	Healing at 8 wks	Main tenance
Uninvestigated GERD	<u>62</u> ⁴	NA ²	86 ³	38 ⁴	NA	79 ³
Endoscopically negative reflux disease	<u>52</u>	NA	NR ⁵	43	NA	NR
Erosive esophagitis	70	85	80-90	H ₂ RAs not considered usual care		
Uninvestigated Dyspepsia	<u>51</u>	NA	44 ^{6,7}	36	NA	41 ^{6,7}
Functional dyspepsia	NS ⁸	NA	NS	NS	NA	NS
NSAID-induced ulcer ⁹	NR	<u>75</u>	<u>72</u>	NR	58	59
H pylori-related ulcers	NR	80	NA ¹⁰	H ₂ RAs not recommended		
	PPIs			H ₂ RAs		

Underlined values = statistically significant difference compared to same outcome with H₂RAs

¹ Maintenance refers to symptom control or healing at 1 year unless otherwise specified

² NA: not applicable because mucosal lesions have not been investigated or do not exist

³ Results are from 1 study reporting percentage of patients with sufficient control of symptoms at 1 year, panto 20 mg vs ranitidine 150 mg bid. Those achieving complete control of symptoms were 77% and 59%.

⁴ At 8 weeks symptom relief was 75% with PPIs vs 58% with H₂RAs, P < 0.05

⁵ NR: not reported

⁶ Maintenance at 6 months

⁷ 35% of patients on placebo maintained symptom relief at 6 months, no statistically significant difference from PPI or H₂RA

⁸ NS: Meta-analysis of 2 RCTs showed no significant difference between PPIs and H₂RAs. Percentages not reported.

⁹ Patients remained on NSAIDs in studies evaluating PPIs and H₂RAs for healing and prophylaxis (maintenance)

¹⁰ Continued PPI therapy not required after eradication of H pylori in uncomplicated duodenal ulcer



Question 1: Are there clinically important differences among standard-doses of PPIs?

- This section will report only results of studies which made **head-to-head** comparisons of various PPIs.

Summary response to question 1

- The COMPUS Expert Review Panel on PPIs concluded there are **no clinically important differences** among standard doses of PPIs for treatment of:
 - Symptomatic GERD
 - Endoscopically negative reflux disease
 - Erosive esophagitis
 - NSAID-induced ulcers (treatment and prophylaxis)
 - *H pylori*-related ulcers in triple-therapy regimens
- COMPUS considered **standard doses** to be eso 20 mg, lanso 30 mg, ome 20 mg, panto 40 mg, and rabe 20 mg.
- There is inconsistency in whether the standard dose of eso in initial therapy of erosive esophagitis is 20 mg or 40 mg. Eso 20 mg and eso 40 mg appear to have similar efficacy in healing at 8 weeks (87% vs 90%).
- COMPUS reported **no head-to-head studies** comparing various PPIs in treatment of **dyspepsia**.
- **Erosive esophagitis** is the only condition in which a statistically significant difference in efficacy among the PPIs has been reported.
- Canadian GERD guidelines state:
 - Eso 40 mg may provide better healing at 4 and 8 weeks than standard doses of other PPIs, particularly in more severe erosive esophagitis.
 - However, the overall differences are small (3% to 6%).
 - Their **clinical relevance is debated** and the results have not been replicated consistently in other studies.



Question 1: Are there clinically important differences among standard-doses of PPIs?

Gastroesophageal reflux disease

- Most studies have been done in erosive esophagitis, the most severe of the 3 types of GERD we are reporting. Local expert opinion suggests that PPIs will have a higher response rate in studies of erosive esophagitis (compared to other therapies) than in studies of uninvestigated GERD or endoscopically negative reflux disease.
 - This is because uninvestigated GERD includes some patients with and without erosions. Patients who don't have erosions will dilute the response.
- **Uninvestigated GERD**
 - Symptom relief: COMPUS reported no head-to-head studies presenting outcomes at 4 and 8 weeks. However a **2-week** study of patients (N=3034) with moderate to severe symptoms found no significant difference in GERD **symptoms** between eso 40 mg and lanso 30 mg.⁸
 - Before treatment, patients experienced **88%** of days with heartburn compared to **38%** after treatment. Heartburn severity also decreased.
 - Maintenance therapy: COMPUS reported no head-to-head studies that compared different PPIs for maintenance therapy in uninvestigated GERD.
- **Endoscopically negative reflux disease**
 - Symptom relief at 4 weeks:
 - 3 RCTs⁹⁻¹¹ made comparisons between eso 20 mg or 40 mg and other PPIs.
 - Approximately **65%** (95% CI: 60% to 70%) of patients had symptom relief at 4 weeks.
 - The similarity of results can be seen in **Table 3**. There were **no statistically significant** differences between groups within each study.



Question 1: Are there clinically important differences among standard-doses of PPIs?

Table 3 Percent of patients with symptom relief at 4 weeks in endoscopically negative reflux disease

PPI and doses (results from individual studies)	Percent with symptom relief	95% CI
Eso 20 mg ⁹ Panto 20 mg	79% 80%	74 to 84 75 to 85
Eso 20 mg ¹⁰ Rabe 10 mg	41% 44%	27 to 57 31 to 59
Eso 20 mg ¹¹ Ome 20 mg	62% 60%	57 to 67 54 to 65
Eso 20 mg ¹¹ Eso 40 mg Ome 20 mg	61% 57% 58%	56 to 65 52 to 61 53 to 63
Eso 40 mg ¹¹ Ome 20 mg	70% 68%	65 to 75 63 to 73

- Maintenance therapy of endoscopically negative reflux disease:
COMPUS reported no studies comparing different PPIs using similar regimens (e.g., continuous, intermittent, or on-demand therapy.)
COMPUS identified this as a research gap.
- **Erosive esophagitis**
 - Symptom relief at 4 weeks: The Oregon review performed a meta-analysis of results from trials to determine resolution of symptoms at 4 weeks for various PPIs.⁷
 - Table 4 shows results for standard dose PPIs.

Table 4 Percent of patients with symptom relief at 4 weeks in erosive esophagitis

PPI and doses (results from Oregon meta-analysis)	Percentage with symptom relief	95% CI
Eso 40 mg	73%	65 to 82
Lanso 30 mg	70%	61 to 80
Ome 20 mg	65%	54 to 76
Panto 40 mg	72%	62 to 83
Rabe 20	69%	52 to 86

- Approximately **70%** of patients had symptom relief at **4 weeks.**
 - The 95% CIs all overlap indicating the drugs are similarly efficacious for symptom relief at 4 weeks.



Question 1: Are there clinically important differences among standard-doses of PPIs?

- Meta-analysis of head-to-head trials showed a statistically significant benefit of **eso 40 mg vs ome 20 mg**: NNT = 10 (95% CI:6 to 14).
 - Not all comparisons of various PPIs were reported. However, no statistically significant differences were found between eso 40 mg and lanso 30 mg or panto 40 mg.
- Healing of erosive esophagitis at 8 weeks:
- The Oregon review reported results of 19 RCTs comparing various PPIs.⁷
- **Table 5** shows results of a meta-analysis of results from head-to-head trials of standard dose PPIs on healing rates at 8 weeks.

Table 5 Percent of patients with healing at 8 weeks in erosive esophagitis

PPI and doses (results from Oregon meta-analysis)	Percentage with healing	95% CI:
Eso 20 mg	87%	84 to 91
Eso 40 mg	90%	88 to 92
Lanso 30 mg	86%	83 to 90
Ome 20 mg	85%	81 to 88
Panto 40 mg	89%	86 to 92
Rabe 20	82%	76 to 89

- Approximately **85%** of patients showed healing at **8 weeks**.
 - The 95% CIs all overlap indicating the drugs are similarly efficacious for healing at 8 weeks.
- Meta-analysis of head-to-head trials showed a statistically significant benefit of eso 40 mg vs ome 20 mg: NNT = 17 (95% CI: 10 to 100)
 - Not all comparisons were analyzed. However meta-analysis of ome 20 mg compared to eso 20 mg, lanso 30 mg, panto 40 mg, and rabe 20 mg showed no statistically significant differences.
- **Figure 2** and **Figure 3** on page 27 summarize results of studies showing symptom relief and healing.
- Maintenance therapy of erosive esophagitis
 - A Cochrane review of 3 RCTs compared lanso 30 mg or rabe 20 mg to ome 20 mg for 48 to 52 weeks.¹²

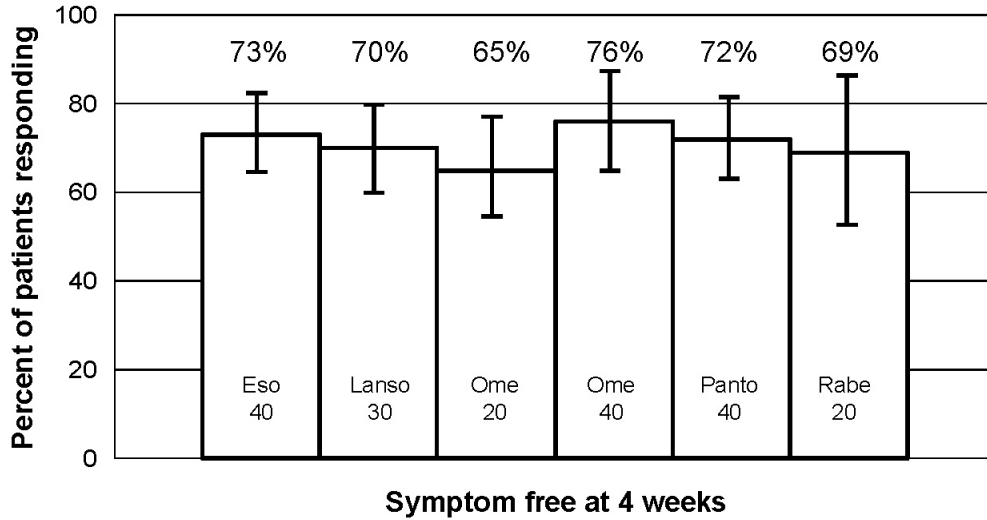


Question 1: Are there clinically important differences among standard-doses of PPIs?

- *Symptom relief*: ome 20 mg was statistically significantly **less likely** to maintain relief of symptoms than lanso 30 mg or rabe 20 mg.
 - 63% vs 69% of patients had symptoms $P < 0.03$
 - $NNT = 17$ (95% CI: 9 to 100) Note the wide confidence intervals.
- *Healing*: There was **no difference** in maintenance of healing between ome and lanso or rabe (90% vs 89%, $P > 0.05$).
- **COMPUS** states that there are no **clinically** important differences among standard-doses of PPIs (eso 20 mg, lanso 30 mg, ome 20 mg, panto 40 mg and rabe 20 mg,) in treatment of symptomatic GERD, endoscopically negative reflux disease, and esophagitis.
 - The Panel recognized that the Canadian Association of Gastroenterology in their GERD guideline defines the standard dose of eso as 40 mg/day. In the Product Monograph, the recommended **initial** dose of eso is 20 mg/day for all indications except **erosive esophagitis and H. pylori eradication**.
 - For erosive esophagitis the recommended dose is 40 mg/day **for 4 to 8 weeks** of treatment. In the United States, eso **20 mg to 40 mg** once daily is considered the standard dose for healing erosive esophagitis.
 - The recommended **maintenance** dose following the initial 4-8 weeks is 20 mg daily.¹³
 - There is some evidence that eso 40 mg produces higher healing rates in erosive esophagitis than standard doses of eso or other PPIs although the observed differences **may not be clinically important** and the NNTs are potentially high.
 - The **2004 Canadian GERD Guidelines** are similar to the COMPUS statement. They state that there is evidence from a meta-analysis and some RCTs that eso 40 mg may provide better healing at 4 and 8 weeks than standard doses of other PPIs, particularly in **more severe erosive** esophagitis. However, the overall differences are small (3% to 6%) "their **clinical relevance is debated** and the results have not been replicated consistently in other studies."
 - A **2007 Cochrane** review found no significant differences in healing at **8 weeks** between standard doses of ome and standard doses of lanso and rabe. At **4 weeks** statistically significantly more patients taking eso 40 mg had healing compared to patients taking ome 20 mg (35% vs 29%).
 - The authors concluded that standard doses of individual PPIs do not show statistically significant different effects on healing of oesophagitis.¹⁴ We do not know why this review did not report comparisons for 8 weeks when they were reported in original studies.

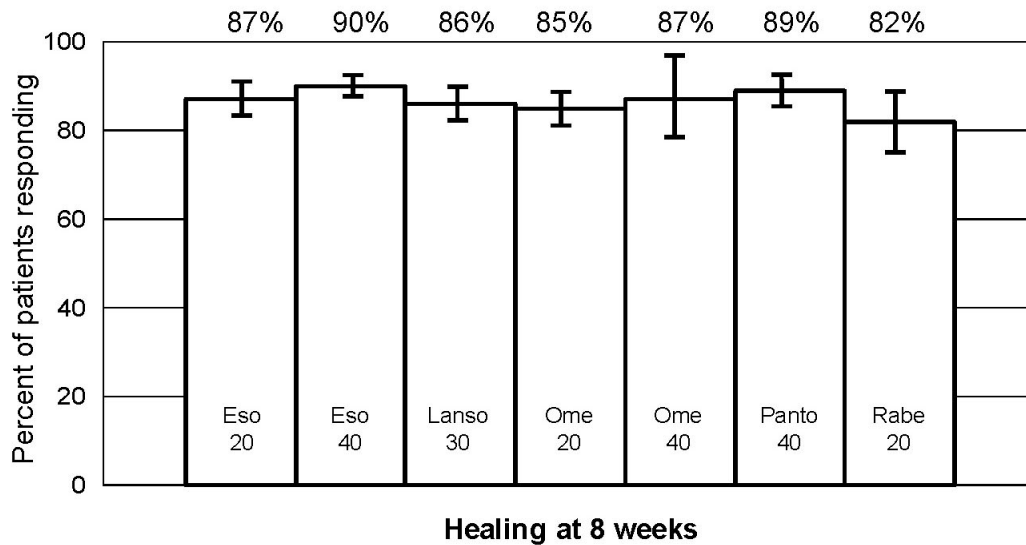
Question 1: Are there clinically important differences among standard-doses of PPIs?

- **Local expert opinion** considers that eso 40 mg does not show any extra clinical benefit compared to other PPIs.



Direct comparisons showed a statistically significant benefit of eso 40 mg over ome 20 mg but not all comparisons were reported. *McDonagh M 2006 Oregon Evidence-based Practice Center*

Figure 2 Head-to-head trials of PPIs in erosive esophagitis: percent of patients with symptom resolution at 4 weeks



Direct comparisons showed a statistically significant benefit of eso 40 mg over ome 20 mg but not all comparisons were reported. *McDonagh M 2006 Oregon Evidence-based Practice Center*

Figure 3 Head-to-head trials of PPIs in erosive esophagitis: percent of patients with healing at 8 weeks



Question 1: Are there clinically important differences among standard-doses of PPIs?

Treatment of dyspepsia

- COMPUS reported no head-to-head studies comparing various PPIs in treatment of dyspepsia.

Prevention and treatment of NSAID-induced ulcers

There is less research comparing various PPIs in the prevention and treatment of NSAID-induced ulcers than in GERD.

• For prevention of NSAID-induced ulcers

- One RCT found that after 6 months, ome 20 mg, panto 20 mg, and panto 40 mg all led to **over 90%** of patients being free of severe symptoms or in endoscopic remission (no peptic ulcer disease or esophagitis, <10 mucosal erosions/petechiae).¹⁵
 - There was no control group in this study. No P values were given but the authors state there was **no significant difference** among PPIs.
- The Oregon review which was conducted before this RCT was published did not find any head-to-head studies comparing various PPIs with respect to NSAID-ulcer prevention.⁷ However, there did not appear to be differences among the various PPIs from studies that compared PPIs with **other** ulcer prophylaxis medications, such as H₂RAs or misoprostol.
- **COMPUS** states that different PPIs reduce ulcer risk to a similar degree when given to NSAID users for ulcer prophylaxis.⁶
- A **2006 Canadian Consensus Conference** on prescribing NSAIDs recommends prescribing a PPI if an NSAID must be used in a patient at high risk of developing ulcers but does not specify 1 PPI over another.¹⁶
- A **2002 Cochrane** review found no direct comparisons between PPIs. It stated that standard doses of PPIs are effective at preventing **endoscopic** duodenal and gastric ulcers, reducing NSAID related dyspepsia, and are better tolerated than misoprostol. However, the effectiveness of these agents at preventing **ulcer complications** has not been directly assessed.¹⁷
 - Ulcer complications include bleeding, obstruction, or perforation. Endoscopic ulcers are an intermediary outcome and are less clinically important than complications. PPIs have **not** been shown to reduce ulcer complications.



Question 1: Are there clinically important differences among standard-doses of PPIs?

- **For treatment of NSAID-induced ulcers**

- The Oregon review found no head-to-head comparison of various PPIs and again found no differences among the various PPIs from studies that compared PPIs with other ulcer prophylaxis medications, such as H₂RAs or misoprostol.⁷
- **COMPUS** states that different PPIs produce similar healing rates of NSAID-associated ulcer.
- We found no Canadian guidelines or Cochrane reviews that recommended 1 PPI over another in treatment of NSAID-related ulcers.

Treatment of *H pylori*-related gastric or duodenal ulcers

- The discussion below refers to eradication of *H pylori* when it is associated with gastric or duodenal ulcers.
 - Gastric ulcers are much **less** common than duodenal ulcers.
 - For **gastric ulcers**, PPI therapy should be continued for 4 to 8 weeks after a 7-day course of eradication therapy and follow-up gastroscopy should be done to rule out malignancy.
 - For **uncomplicated duodenal** ulcers, (no bleeding, obstruction, or perforation) it is not necessary to continue PPIs after a 7-day course of eradication therapy. If symptoms are well-controlled after eradication, there is no need for follow-up gastroscopy.
 - **Complicated** duodenal ulcers should be treated like **gastric** ulcers – 4 to 8 weeks of PPI therapy followed by repeat endoscopy.
 - The Oregon review concluded that while there were some differences between PPIs in individual studies, generally there was not a difference in eradication rate between the PPIs.⁷ There were also no differences among PPIs in symptom improvement and healing rates in duodenal or gastric ulcers.
 - COMPUS cited 7 systematic reviews that included comparisons of all the PPIs including eso 20 mg BID.
 - There were no significant differences among the PPIs.
 - Eradication rate was approximately **80%**.
 - 100% of the COMPUS Expert Review Panel agreed completely that all PPIs have similar efficacy in triple therapy regimens for *H pylori* eradication.
 - The 2005 Canadian Dyspepsia Guidelines state that all PPIs available in Canada have similar efficacy in curing *H pylori* with combinations of clarithromycin-metronidazole or clarithromycin-amoxicillin.¹



Question 2: Is starting with a double-dose PPI better than starting with a standard daily dose?

- This section deals mainly with **initial** therapy and generally, will not report data for maintenance therapy.

Summary response to question 2

- The COMPUS Expert Review Panel on PPIs concluded that
 - Doubling the standard daily doses of PPIs, as **initial** therapy, is **no better** than standard daily dose PPI therapy for
 - Healing of erosive esophagitis
 - Healing of NSAID-induced ulcers
 - In *H pylori* eradication:
 - Standard-dose PPI administered twice daily is **more efficacious** than standard-dose PPI administered once daily when used in PAC therapy but not in PMC therapy.

(See Table 1, page 19 for definitions of standard doses.)

- **No evidence** was reported for double-dose vs standard dose PPI in:
 - Uninvestigated GERD
 - Endoscopically negative reflux disease
 - Dyspepsia
- **Canadian GERD** guidelines state:
 - Twice-daily PPI therapy is **not generally required** as initial therapy for typical GERD symptoms. Level of evidence 1,A (see Page 30)
 - Twice-daily, standard dose PPI therapy **may be used** for patients who have
 - **Severe** symptoms **despite standard once-daily** PPI therapy. Level of evidence II-3B. COMPUS identified this area as needing more research.
 - **Severe** esophagitis (LA Grade C or D, or stricture) Level of evidence I,B
- Local expert opinion states that patients may be started on double-dose PPIs when admitted to hospital for emergencies. They may then be discharged on double-dose PPIs. In such situations, family physicians should reassess patients and the continuing need for double-dose PPIs.
- Analysis of Pharmacare data indicates that approximately **30%** of Pharmacare patients **started** on a PPI are started on **double-dose**.



Question 2: Is starting with a double-dose PPI better than starting with a standard daily dose?

Gastroesophageal reflux disease

- Again, most studies have addressed erosive esophagitis. COMPUS reported no studies about **uninvestigated GERD** or **endoscopically negative reflux disease**.
- **Erosive esophagitis**
 - COMPUS reported 5 RCTs comparing double-dose vs standard-dose therapies for panto, lanso, and ome.
 - Symptom relief at 4 weeks was reported in only 1 trial.¹⁸ Percent of patients obtaining heartburn relief at 4 weeks:
 - Ome 40 mg: 82%
 - Ome 20 mg: 81%
 - Healing at 8 weeks: Table 6 shows percentage of patients with healing in the 4 studies that reported this outcome at 8 weeks. There were **no** significant differences between double-dose and standard-dose.

Table 6 Percent of patients with healing of erosive esophagitis at 8 weeks with standard and double-dose PPIs

PPI and doses (results from individual studies)	Percent patients with healing at 8 weeks 95% CI	
Lanso 30 mg ¹⁹	92%	84 to 96
Lanso 60 mg	90%	81 to 96
Lanso 30 mg ²⁰	87%	77 to 93
Lanso 60 mg	89%	80 to 94
Ome 20 mg ¹⁸	73%	Not available
Ome 40 mg	73%	
Panto 40 mg ²¹	85%	76 to 91
Panto 80 mg	86%	78 to 92

- **COMPUS** states that doubling the standard daily doses of PPIs, as initial therapy, is **no better** than standard daily dose PPI therapy for healing of erosive esophagitis.
- The **2004 Canadian GERD Guidelines**³ state:
 - Twice-daily PPI therapy is **not generally required** as initial therapy for typical GERD symptoms
 - Level of evidence I, A
 - Twice-daily, standard dose PPI therapy may be used for patients who
 - Have **severe** symptoms **despite standard once-daily** PPI therapy
 - Level of evidence II-3, B
 - Have severe esophagitis (LA Grade C or D, or stricture)
 - Level of evidence I, B
 - Note – endoscopy is required for diagnosis of severe esophagitis



Question 2: Is starting with a double-dose PPI better than starting with a standard daily dose?

2004 Canadian GERD Guidelines Levels of Evidence

I	Evidence from at least 1 properly randomized controlled trial
II -1	Evidence from well-designed controlled trials without randomization
II-2	Evidence from well-designed cohort or case-control analytic studies
II-3	Evidence from comparisons between times or places with or without the intervention, or dramatic results in uncontrolled experiments
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
A	Good evidence to support the treatment
B	Fair evidence to support the treatment

• **Comment from Academic Detailing Service**

- Uncertainty in the Canadian guidelines is reflected in:
 - The low level of evidence for twice daily PPIs for patients with severe symptoms despite standard dose once-daily PPI. COMPUS identified this as an area needing further research.
 - The Canadian guideline gave no reference or explanation in the text for the recommendation for use of twice-daily PPIs in severe esophagitis.
- A 2004 Guideline from the UK-based National Institute of Clinical Excellence (**NICE**) recommends a **standard dose PPI** for treatment of erosive esophagitis for **1 to 2 months** with double-dose therapy for **1 month** if there is no response.²²
 - The Guideline also states that:
 - It may be appropriate to increase the dose of PPI if Los Angeles grade C and D patients fail to respond to full (standard) doses of PPI.
 - Severe esophagitis represents only approximately 5% of all GERD and it is not appropriate to increase the dose of PPI beyond full doses unless there is endoscopic evidence of Los Angeles grade C or D esophagitis.
- The above comments refer to comparisons of double-dose and standard-dose PPIs in **initial** therapy of erosive esophagitis. A Cochrane review also found **no statistically significant difference** in **maintenance** therapy of erosive esophagitis with double-dose vs standard-dose PPIs.¹²

Treatment of dyspepsia

- We found no reports in COMPUS or Cochrane about double vs standard doses of PPIs in treatment of dyspepsia.



Question 2: Is starting with a double-dose PPI better than starting with a standard daily dose?

- However, the 2005 Canadian Dyspepsia Guidelines¹ state that because there is little data on management of heartburn-dominant uninvestigated dyspepsia, recommendations are extrapolated from studies of erosive esophagitis or endoscopically negative reflux disease. An algorithm for GERD from the dyspepsia guidelines suggests double-dose PPI after 4 weeks if there is inadequate symptom relief from standard-dose PPI (**Figure 4, Page 34**).

Prevention and treatment of NSAID-induced ulcers

- Two RCTs have compared ome 20 mg to ome 40 mg in treatment of NSAID-induced ulcers.^{23,24}
 - With both regimens, 80% to 90% of patients obtained healing at 8 weeks. There was no statistically significant difference between double-dose and standard-dose ome.

Treatment of *H pylori*-related gastric or duodenal ulcers

- The 2 commonly used regimens for treatment of *H pylori*-related ulcers are:
 - **PAC**: PPI + Amoxicillin + Clarithromycin
 - **PMC**: PPI + Metronidazole + Clarithromycin
- A meta-analysis NICE²² showed rates of *H. pylori* eradication in
 - **PAC**:
 - Twice daily standard dose PPI 85%
 - Once daily standard dose PPI 79%
 - Absolute risk increase: 6% (95% CI: 2% to 11%)
 - NNT = 17 (95% CI 9 to 50)
 - **PMC**:
 - Twice daily standard dose PPI 86%
 - Once daiy standard dose PPI 84%

No statistically significant difference. There were fewer patients in this meta-analysis, so there was less power to detect a statistically significant difference. However the absolute difference is small (2%).
- **COMPUS** states that standard-dose PPI administered twice daily is more efficacious than standard-dose PPI administered once daily when used in PAC therapy for *H pylori* eradication but not in PMC therapy.
- COMPUS also states that in **uncomplicated duodenal** ulcer:
 - Continued treatment with PPI after *H pylori* eradication therapy does not produce higher healing rates than eradication therapy alone.

This statement does **not** apply to **gastric** ulcers or **bleeding** ulcers. They require PPI treatment for 4 to 8 weeks.



Question 2: Is starting with a double-dose PPI better than starting with a standard daily dose?

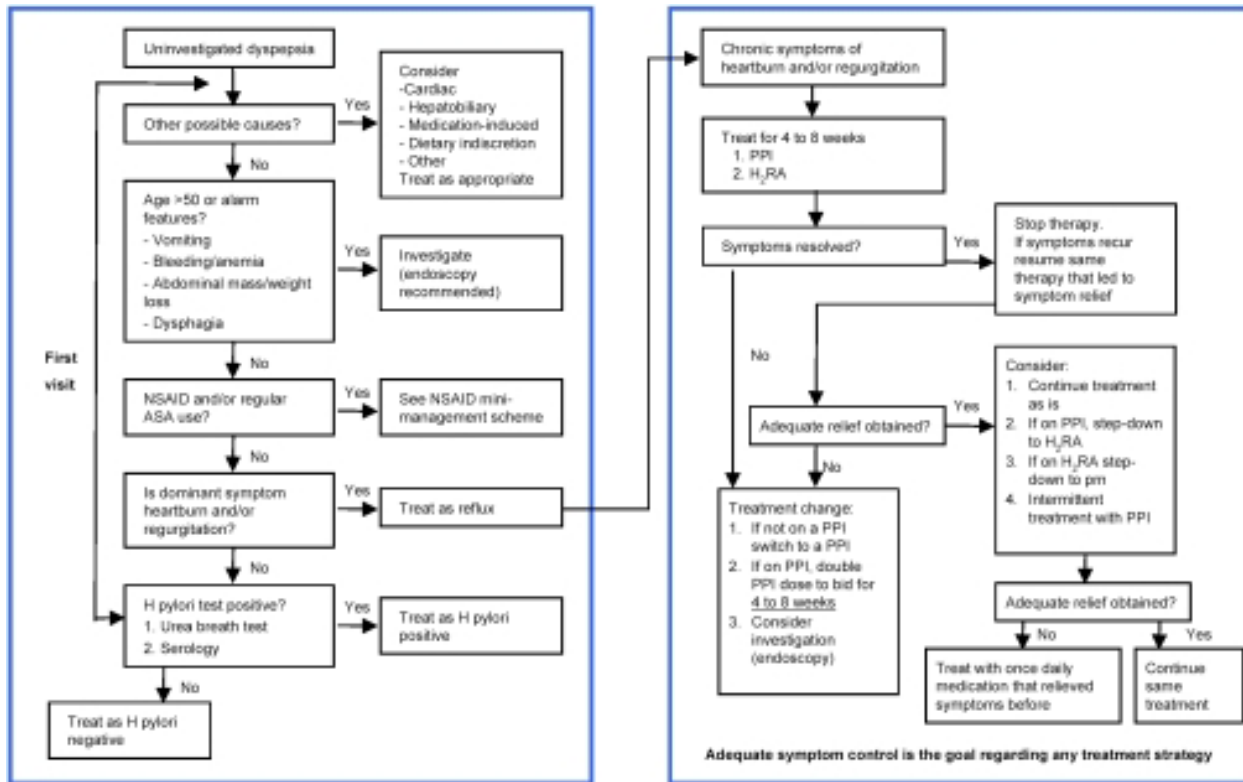


Figure 4 Algorithms for management of dyspepsia and GERD

Adapted from Evidence-based recommendations for short- and long-term management of dyspepsia in primary care: An update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. Can J Gastroenterol Vol 19 No 5 May 2005.



Question 3: When is it reasonable to consider treatment with H₂RAs?

Summary response to question 3

- It is reasonable to consider treatment with H₂RAs in:
 - Uninvestigated GERD
 - ~**60%** of patients will have complete symptom relief at 8 weeks and 52 weeks with H₂RAs vs ~**75%** for PPIs.
 - Endoscopically negative reflux disease
 - ~**40%** of patients will have symptom relief at 4 weeks with H₂RAs vs ~**50%** with PPIs.
 - Uninvestigated dyspepsia
 - At 6 months there was no statistically significant difference in symptom relief in patients treated with H₂RAs vs PPIs (both ~**40%**)
There was no difference compared to placebo (~**35%**).
 - Functional dyspepsia
 - Short term trials indicate no statistically significant difference between H₂RAs and PPIs.
- There is no consensus on what constitutes optimal **maintenance** therapy of **uninvestigated GERD** for patients who attain symptomatic relief with PPIs.
Reasonable approaches are:
 - Continue daily PPI therapy: Approximately **80%** may achieve symptom relief.
 - Switch to on-demand PPI use: Insufficient good-quality evidence to estimate responses.
 - Step-down to H₂RAs: Approximately **65%** may achieve symptom relief.
 - A trial of medication discontinuation: Approximately **20%** of patients with uninvestigated GERD will remain asymptomatic off therapy for up to 6 months after a successful course of initial therapy (4 to 8 weeks) with a PPI or H₂RA.
- Local expert opinion and Canadian guidelines state it is reasonable to use H₂RAs in patients with mild symptoms.
- H₂RAs are **not** considered usual care for patients with
 - Erosive esophagitis
 - *H pylori* related ulcers
 - NSAID-induced ulcers - treatment and prophylaxis



Question 3: When is it reasonable to consider treatment with H₂RAs?

- Of the 4 main conditions we are discussing in this document, there are 2 in which it is particularly reasonable to consider treatment with H₂RAs:

1. Gastroesophageal reflux disease

- Uninvestigated GERD
- Endoscopically negative reflux disease

2. Dyspepsia

- Uninvestigated dyspepsia
- Functional dyspepsia

- We shall discuss the evidence for each of the 2 conditions in turn.

Gastroesophageal reflux disease

Uninvestigated GERD initial therapy

- COMPUS reported 3 RCTs providing estimates of percentage of patients obtaining **symptom relief at 4 weeks**.²⁵⁻²⁷ Ome 20 mg and panto 20 mg were compared to ranitidine 300 mg daily.
 - We carried out a meta-analysis of these 3 trials using a statistical program called Comprehensive Meta-analysis (www.meta-analysis.com). Percent of patients obtaining symptom relief at **4 weeks** was:
 - PPIs 62% (95% CI: 58 to 66)
 - H₂RA 38% (95% CI: 35 to 43) P < 0.001
 - NNT = 4 (95% CI: 3 to 6)
 - COMPUS reported 1 RCT providing estimates of percentage of patients obtaining complete **symptom relief at 8 weeks**.²⁷ These estimates were extrapolated from a figure and no confidence intervals were provided.
 - PPI 75%
 - H₂RA 58%
 - NNT = 6

Table 7 Approximate percentages of patients obtaining symptom relief with initial treatment of uninvestigated GERD with PPIs and H₂RAs

Treatment	Percent with symptom relief 95% CI where reported	
	4 weeks	8 weeks
PPI	62% 58 to 66	75%
H ₂ RA	38% 35 to 43	58%
NNT	4 3 to 6	6



Question 3: When is it reasonable to consider treatment with H₂RAs?

- The COMPUS Expert Review Panel acknowledges that PPIs are superior to H₂RAs for improvement of reflux symptoms in **initial therapy** of uninvestigated GERD.
 - Symptom relief is faster with PPIs with higher percentages of patients experiencing symptom relief at 4 weeks; however by 8 weeks up to 58% of H₂RA users will also experience relief. Up to 75% of PPI users will obtain symptom relief by 8 weeks.
 - However, the Panel also noted that most subjects had **moderate** symptoms. COMPUS found no studies specifically comparing PPIs and H₂RAs in patients with **mild** GERD symptoms.
- Local expert opinion and the Canadian GERD Guidelines considers that H₂RAs can provide adequate symptomatic relief in patients with mild symptoms (< 3 times per week).³
- The Canadian Dyspepsia Guidelines algorithm suggests initial treatment of GERD may be PPI or H₂RA (**Figure 4, Page 34**).

Uninvestigated GERD maintenance therapy

Continuous PPI vs continuous H₂RA

- In continuous therapy, medication is taken daily for an indefinite period of time to prevent or minimize symptoms.
- Continuous therapy: PPI vs H₂RA
 - COMPUS reported 1 RCT comparing panto 20 mg daily to ranitidine 150 mg bid and provided percentage of patients obtaining **complete** relief of symptoms at 6 months and 12 months:

	6 months	12 months
• Panto 20 mg daily:	71%	77%
• Ranitidine 150 mg bid:	56%	59%
NNT (95% CI)	7 (4 to 23)	6 (4 to 13)

- Percentage of patients with **sufficient** symptom control at 12 months:
 - Panto 20 mg daily: 86%
 - Ranitidine 150 mg bid: 79% Non-significant
- Another RCT compared eso 20 mg daily to ranitidine 150 mg bid and provided percentage of patients without heartburn at 6 months
 - Eso 20 mg daily: 72%
 - Ranitidine 150 mg bid: 33% NNT = 3



Question 3: When is it reasonable to consider treatment with H₂RAs?

- The COMPUS Expert Review Panel states that continuous PPI therapy is superior to H₂RAs for maintenance of symptom control in uninvestigated GERD for **up to 6 months**.
 - Referring to the study we summarized on the previous page, COMPUS stated:
 - In the only **12-month** study, nearly 60% of patients on H₂RA had **complete** symptom control at 6 and 12 months and there was no difference between PPI and H₂RA in the proportion with **sufficient** symptom control at 12 months.
- **Comments from Academic Detailing Service**
 - Treatment with H₂RAs, although less efficacious than PPIs **may be adequate treatment** for many patients requiring maintenance therapy.
 - The maintenance of symptom relief at 12 months in patients who obtained relief with PPI or H₂RA at 8 weeks does not support the idea that tolerance develops to PPIs or H₂RAs.

Step down therapy

- In step down therapy initial treatment with PPIs is followed by step-down to an H₂RA.
- COMPUS reported 1 RCT providing evidence for continued PPI therapy vs initial PPI therapy followed by H₂RA.
 - Patients (N~150 per group) with moderate to severe heartburn took either²⁸
 - Lansoprazole 30 mg daily for 20 weeks or
 - Lansoprazole 30 mg daily for 8 weeks and ranitidine 150 BID for 12 weeks
 - At the end of **20 weeks** the percent of patients with **heartburn relief** was:
 - Lansoprazole 30 mg daily: 82%
 - Lansoprazole 30 mg/ranitidine 150 mg: 67%
 - NNT 7 (95% CI 4 to 20)
- The **COMPUS** expert panel noted that the severity of symptoms at baseline may affect the response to step-down therapy.
- The 2005 Canadian dyspepsia guidelines state that:
 - Consideration can be given to trying an H₂RA but data are limited.
 - A **small proportion** of patients can tolerate stepping down to an H₂RA but in the majority of patients, the data show that step-down treatment should not be considered because it leads to worsening of symptoms.¹



Question 3: When is it reasonable to consider treatment with H₂RAs?

• **Comments from Academic Detailing Service**

- To support these statements, the guidelines refer to:
 - The above study²⁸ in which **67%** of patients on step-down therapy to H₂RA obtained heartburn relief.
 - A small cohort study in which **58%** of patients were asymptomatic off PPI therapy after 1 year of follow-up. (Thirty-four percent obtained relief with H₂RAs and 15% required no therapy.)²⁹
- In both studies, a **majority** of patients were able to continue without PPIs, not a small proportion as stated in the guidelines.

Summary

- There is **no consensus** on what constitutes optimal maintenance therapy of uninvestigated GERD for patients who attain symptomatic relief with PPIs. Reasonable approaches are:³⁰
 - Continue daily PPI therapy (approximately **80%** achieve symptom relief).
 - Switch to on-demand PPI use (insufficient good-quality evidence to estimate responses).
 - Step-down to H₂RAs (approximately **65%** may achieve symptom relief)
 - A trial of medication discontinuation
 - Approximately **20%** of patients with uninvestigated GERD will remain asymptomatic off therapy for up to 6 months after a successful course of initial therapy (for 4 to 8 weeks) with a PPI or H₂RA.
 - The majority of patients relapse within 6 months with a median time to relapse of only 8 to 9 days.
- The treatment decision should be individualized, based on discussions between the patient and the physician considering severity of symptoms, cost and safety.

Endoscopically negative reflux disease

Initial therapy

- If investigated, up to 70% of patients with GERD-like symptoms will have endoscopy-negative disease; yet, the severity and chronicity of symptoms in patients with endoscopically negative reflux disease is similar to that of patients with erosive esophagitis.³¹ COMPUS reported 1 Cochrane review³¹ of 4 RCTS comparing PPIs to H₂RAs in initial therapy of endoscopically negative reflux disease.
 - Relief of heartburn symptoms at 4 weeks was approximately **52% for PPIs** and **43% for H₂RAs** (relative risk 0.78; 95% CI: 0.62 to 0.97; p = 0.03)
 - However, the Cochrane review also found no difference between PPIs and H₂RAs in **quality of life**.
- Canadian guidelines do not differentiate between endoscopically negative reflux disease and symptomatic GERD in their recommendations for treatment and state:³



Question 4 What are some possible adverse effects of acid suppression?

Summary response to question 4

- Information for adverse effects of acid suppression comes from observational studies, mostly case-control studies. These provide a lower level of evidence than RCTs. Therefore, findings should be regarded with caution.
- These studies show that PPI use is **associated with** adverse effects i.e., patients who take PPIs have been found to be more likely to have these adverse effects. However, this association does not prove that the PPIs **caused** the adverse effects.
- Studies indicate there is a weak to moderate association between acid suppression therapy and:
 - Pneumonia
 - *C difficile* diarrhea
 - Fractures
 - Fundic gland polyps
- Generally, the association is stronger for PPIs than H₂RAs and in some cases, with increasing dose and duration of therapy.
- Guidelines and local expert opinion consider it prudent to use the **least amount** of acid suppression necessary to obtain adequate symptom relief. This requires regular re-assessment of patients.



Question 4: What are some possible adverse effects of acid suppression?

- Data for adverse effects of acid suppression come from case-control studies that:
 - Are considered a lower level of evidence than RCTs or cohort studies. (However, they are commonly used in assessing safety.)
 - Do not provide estimates of absolute risk. Therefore we can present only relative risks in this section. (Odds ratios are a relative measure of risk.)
- Case-control studies can be either:
 - Population based: subjects are selected from the community
 - Hospital based: subjects are selected among patients admitted to a clinical facility.
- The odds ratios cited in the studies below reflect the odds (or relative risk) of developing the adverse event in patients taking a PPI or H₂RA compared to a patient not taking 1 of those drugs. The higher the odds ratio, the stronger the association between taking the drug and having the adverse event.
- In interpreting the results it may help to keep in mind the strength of association implied by different relative risks (or odds ratios):³³

Relative risk	Strength of association
1.01 to 1.50	Weak
1.51 to 3.0	Moderate
> 3.0	Strong
- The postulated effects of long-term acid suppression and associated adverse effects are:
 - Gastric acid may be necessary to maintain normal bacterial flora. Acid suppression may be associated with **pneumonia** or **enteric infections (C difficile)**.
 - Gastric acid suppression may lead to
 - Decreased calcium absorption and **osteoporotic fractures**
 - Increased gastrin production and **fundic gland polyps**



Question 4: What are some possible adverse effects of acid suppression?

Pneumonia

- A Danish population-based case-control study found a **weak to moderate** risk of community acquired pneumonia with current PPI use.³⁴
 - Odds ratio: 1.5 (95% CI 1.3 to 1.7) with no dose-response effect. (No P-value reported.)
 - No association was found with current H₂RA use.
- A population-based case-control study from the Netherlands found a **moderate** risk for current PPI use.³⁵
 - Odds ratio: 1.7 (95% CI 1.3 to 2.3).
 - The odds ratios increased with increasing dose.
 - <1 dose per day: 1.2 (95% CI 0.8 to 1.9)
 - 1 dose per day: 1.9 (95% CI 1.4 to 2.7)
 - >1 dose per day: 2.3 (95% CI 1.3 to 4.1)
 - Current **H₂RA** use was associated with a similar risk.
 - Odds ratio: 1.6 (95% CI 1.1 to 2.2)
 - The authors concluded that, given the average use of PPIs for approximately **5 months**, it would be expected that:
 - **one of 226** patients treated with PPI would develop pneumonia
 - **one of 508** patients treated with H₂RA would develop pneumonia

C. difficile associated diarrhea

- While many observational studies suggest an increased risk of C. difficile infection with the use of PPIs both in the community and hospital settings, the evidence is inconclusive.
- A recent systematic review of 12 studies³⁶ reported a **moderately** increased risk of enteric infections in patients taking antisecretory therapy:

Odds ratio 1.9 (95% CI 1.4 to 2.8)

 - The association was significant for PPI use:

Odds ratio 2.0 (95% CI 1.3 to 3.0)

But **not** for H₂RA use Odds ratio 1.4 (95% CI 0.9 to 2.3)
- Prospective studies are required to establish whether the association between PPIs use and C. difficile associated diarrhea is causal.



Question 4: What are some possible adverse effects of acid suppression?

Fractures

- Data below is given as odds ratios with 95% CIs and P values when provided.
- 2 community-based case-control studies from Denmark and the United Kingdom have demonstrated **increased** risk for fractures in PPI users.

	Odds Ratio	95%CI	

• Denmark: ³⁷ Use of PPI within the last year showed following odds ratios:			
• Risk of fracture	1.2	1.1 to 1.4	P<0.05
• Risk of hip fracture	1.5	1.3 to 1.7	P<0.05
• Risk of spine fracture	1.6	1.3 to 2.0	P<0.05
• H ₂ RAs were associated with a slightly decreased risk of fracture	0.9	0.8 to 1.0	P<0.05
• United Kingdom: ³⁸			
• The overall increased risk of having a hip fracture associated with PPI use of ≥ 1 year was approximately 40%:	1.4	1.3 to 1.6	P<0.001
• The risk of having a fracture increased with the time on PPI therapy:			
• 1-year	1.2	1.1 to 1.3	
• 2-year	1.4	1.3 to 1.6	
• 3-year	1.5	1.4 to 1.7	
• 4-year	1.6	1.4 to 1.8	
• The highest risk was found in those taking > 1.75 doses PPI per day for more than 1 year:	2.7	1.8 to 3.9	P<0.001



Question 4: What are some possible adverse effects of acid suppression?

Fundic gland polyps

- Fundic gland polyps are polyps found in the fundus of the stomach. They are **usually benign** but there have been case reports of them harbouring severe dysplasia or gastric adenocarcinoma, especially in patients with familial adenomatous polyposis.
- A recent case-control study from the Netherlands looked at the association between PPI use and presence of fundic gland polyps in 634 patients undergoing gastroscopy.³⁹
 - PPI use was associated with presence of fundic gland polyps, and the greater duration of use, the stronger the association.

	Odds Ratio	95%CI
• Overall	2.3	1.5 to 3.6
• 1 to 4.9 years on PPI	2.2	1.3 to 3.8
• ≥ 5 years on PPI	3.8	2.2 to 6.7

- The main clinical significance of these polyps is that they may show up on an upper GI x-ray, prompting the need for gastroscopy.

Comments from Academic Detailing Service

- It is important to remember that these findings come from **observational** studies and are not conclusive. Most of the associations would be characterized as weak to moderate. Furthermore, association found in observational studies does not necessarily prove causation. Prospective studies are better able to prove causation.
- Nevertheless, the Canadian GERD guidelines³ and local expert opinion suggest that long term maintenance therapy should be given at the lowest dose and frequency that is sufficient to achieve optimal control of symptoms.
 - This is given level III B evidence:
 - III: Opinions of respected authorities, based on clinical experience, descriptive studies, or expert committees
 - B: Fair evidence to support the procedure or treatment



Costs

- Table 8 shows costs for different doses of antisecretory medications. PPIs are listed in ascending order of cost of standard doses.

Table 8 Costs of antisecretory medications as of January 2008

Drug	Standard daily dose Double daily dose	Unit cost	Cost for 30 days* (rounded)
Proton Pump Inhibitor (PPI)			
Generic rabeprazole ¹	20 mg	\$0.91	\$27
Double dose	40 mg	\$1.82	\$54
Omeprazole (Losec Capsules) ¹ ®	20 mg	\$1.10	\$33
Double dose	40 mg	\$2.20	\$66
Generic omeprazole ¹	20 mg	\$1.25	\$38
Double dose	40 mg	\$2.50	\$75
Rabeprazole ¹ (Pariet)®	20 mg	\$1.41	\$42
Double dose	40 mg	\$2.82	\$84
Pantoprazole (Pantoloc)®	40 mg	\$2.06	\$62
Double dose	80 mg	\$4.12	\$124
Lansoprazole (Prevacid)®	15 or 30 mg	\$2.17	\$65
Double dose	60 mg	\$4.34	\$130
Esomeprazole (Nexium)®	20 mg	\$2.28	\$68
Double dose	40 mg	\$2.28	\$68
H₂RA - Ranitidine chosen as most common comparator in class			
Generic ranitidine	150 mg bid	\$0.18	\$11
	300 mg bid	\$0.36	\$22

¹ As of January 11 2008 omeprazole and rabeprazole at standard daily doses are open benefit on the Nova Scotia Pharmacare formulary. Maximum allowable costs are rabeprazole 20 mg \$0.91 and omeprazole \$1.10.



Appendix 1 COMPUS Expert Review Panel on PPIs

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Director, Division of Clinical Pharmacology and Therapeutics
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Appendix 2 Approved indications for Proton Pump Inhibitors (PPI) from Product Monographs ¹

Indication	Omeprazole	Rabeprazole	Lansoprazole	Pantoprazole	Esomeprazole
Symptomatic GERD (Investigate if symptoms not controlled after 4-8 wks)	20 mg once daily x 4 wks.	10-20 mg once daily x 4 weeks.	15 mg once daily x 8 wks	40 mg once daily x 4 wks.	ENRD- 20 mg once daily x 2-4 wks.
Symptomatic GERD Maintenance	10 mg once daily	NS	NS	NS	ENRD - 20 mg once daily on-demand
Reflux esophagitis acute healing	20 mg once daily x 4-8 weeks Refractory patients 40 mg daily X 8 weeks	20 mg once daily x 4-8 wks	30 mg once daily x 4-8 wks	40 mg once daily x 4-8 wks	40 mg once daily x 4-8 wks
Maintenance reflux esophagitis	10 mg once daily, increased to 20-40 mg once daily with recurrence	10-20 mg once daily	15 mg once daily x 12 months	20-40 mg once daily	20 mg once daily studies up to 6 months
Gastric ulcer healing (e.g., NSAID or <i>H. pylori</i> -related)	20 mg once daily x 4-8 wks Refractory patients 40 mg daily X 8 wks. 20mg-40 mg once daily x up to 12 weeks after <i>H.pylori</i> eradication for active ulcer.	20 mg daily x up to 6 wks	Gastric ulcer: 15 mg once daily x 4-8 wks NSAID related: 15-30 mg once daily x 8 wks	40 mg once daily x 4-8 wks	20 mg once daily x 4-8 wks No additional benefit with 40 mg daily.
NSAID ulcer maintenance or prophylaxis	20 mg once daily x 6 months	Not indicated	15 mg once daily x 12 wks.	20 mg once daily	20 mg once daily. Studies up to 6 months. No additional benefit with 40 mg daily.
Duodenal ulcer acute healing	20 mg once daily x 2-4 wks Refractory patients 20-40 mg once daily x 4 wks	20 mg daily x up to 4 wks.	15 mg once daily x 2-4 wks	40 mg once daily x 2-4 wks	Indicated as part of <i>H. pylori</i> eradication regimen – see below
Ulcer Maintenance <i>H.pylori</i> negative	Duodenal Ulcer 10 mg once daily, increased to 20-40 mg once daily	NS	Duodenal ulcer 15 mg once daily	NS	See below
	Gastric Ulcer 20 mg daily, increased to 40 mg daily as necessary		Gastric Ulcer NS		
<i>H.Pylori</i> ulcer As part of triple therapy	20 mg twice daily x 7 days	20 mg twice daily x 7 days	30 mg twice daily for 7,10 or 14 days	40 mg twice daily x 7 days	Duodenal ulcer: 20 mg twice daily x 7 days. No further treatment is required for healing and/or symptom control.
Dyspepsia	10-20 mg once daily x 2-4 wks.	Not indicated	Not indicated	Not indicated	Not indicated
ZE syndrome Initial dose	60 mg once daily.	60 mg once daily.	60 mg once daily	Not indicated	40 mg bid
Pediatric GERD Age 1-11	Not indicated	Not indicated	≤ 30 kg - 15 mg once daily > 30 kg - 30 mg once daily	Not indicated	< 20 kg - 10 mg once daily ≥ 20 kg - 10-20 mg once daily

ZE= Zollinger Ellison Syndrome; NS = not specified; ENRD= endoscopically negative reflux disease

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