Canadian Agency for Drugs and Technologies in Health

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April 2007

Academic Detailing Upskilling Document – Proton Pump Inhibitors

Supporting Informed Decisions

À l'appui des décisions éclairées

COMPUS Academic Detailing Upskilling Document – Proton Pump Inhibitors

April 2007

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Canadian Optimal Medication Prescribing and Utilization Service

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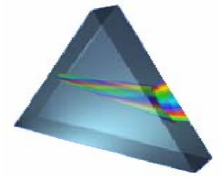
Proton Pump Inhibitors



PrISM

Prescription Information Services of Manitoba

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April 2007

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INTRODUCTION

The academic detailing upskilling document on proton pump inhibitors is intended as a companion document to the Canadian Agency for Drugs and Technologies in Health's (CADTH's) Scientific Report entitled, *Evidence for PPI Use in Gastroesophageal Reflux Disease, Dyspepsia and Peptic Ulcer Disease*.[1] This document focuses on the evidence for proton pump inhibitor (PPI) use in these conditions. Organizations considering academic detailing (or related) interventions based on the Scientific Report recommendations will require additional clinical background information. The act of preparing academic detailers for intervention interactions has been called "upskilling" as it reflects the elevation of background knowledge and skill that is required. The upskilling document will provide some of this background information and enhance the ability of academic detailers to present information and respond to questions in the field. This companion document supplements rather than replaces the information in the Scientific Report. A thorough review of both documents will be required by academic detailers.

This document is divided into five sections. The first three sections correspond to the dyspepsia, gastroesophageal reflux disease, and peptic ulcer disease divisions contained in the Scientific Report. Broader aspects of the disease (epidemiology, diagnosis) and disease management (non-PPI options, lifestyle) beyond PPI use are considered in the upskilling document. In addition, the document covers adverse events and PPI drug interactions that are not considered in the Scientific Report. A recommended reading list is included in each section with key references intended to supplement the information contained in the upskilling document. The combination of the CADTH's Scientific Report and the academic detailing upskilling document should provide an informational cornerstone for interventions to improve the utilization of PPIs.

1 SECTION 1: DYSPEPSIA

1.1 Epidemiology

The management of patients with dyspepsia represents a substantial cost to the Canadian health care system, including health care practitioner time and costs associated with diagnostic services and treatment. Furthermore, patients suffering from upper gastrointestinal (GI) symptoms report a significant reduction in quality of life indicators.[2] A study investigating the prevalence of upper GI symptoms in a random sample of Canadian adults found that approximately 29% reported some form of upper GI symptoms in the previous three months.[2] Over half of those who experienced symptoms described them as dysmotility-like. While the study was not specifically designed to estimate the incidence of dyspepsia, it is widely quoted to describe the prevalence of the condition in Canada.[3]

1.2 Definition and Diagnosis

Concisely defining the diagnosis of dyspepsia is quite difficult. Because of the symptom-based nature of the condition, the diagnosis is based on subjective rather than objective measures. However, attempts have been made to structure the definition of dyspepsia to support clinicians who diagnose and treat the condition. In Canada, the Canadian Dyspepsia (CanDys) Working Group published an evidence-based clinical management tool that included diagnostic as well as treatment recommendations.[3] The following definition of dyspepsia is advocated by the group:

"Dyspepsia is a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, and it may include any of the following symptoms: heartburn, acid regurgitation, excessive burping/belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion, or early satiety." [3]

The inclusion of reflux-related symptoms is somewhat controversial as internationally recognized criteria exclude such symptoms from the diagnosis. However, the CanDys Working Group believes its definition is more practical from the perspective of a primary care practitioner since it better reflects the reality of clinical practice, in which patients often present with heterogeneous symptoms. The group does, however, refer to the internationally developed Rome criteria for the definition of functional dyspepsia.

The Rome criteria were created by consensus opinion of an international panel of clinical investigators. These criteria cover a broad range of GI disorders, including dyspepsia. The original Rome criteria were developed in 1991 (Rome I),[4] revised in 1999 (Rome II),[4] and again in 2006 (Rome III).[5] We will primarily discuss the Rome II criteria for dyspepsia since they have been applied in most recent clinical trials, and we will also review the major differences between the Rome II and III criteria.

Rome II

The broad definition of dyspepsia has not changed from the Rome I:
"dyspepsia refers to pain or discomfort centered in the upper abdomen." [4]

Symptoms that fit under this broad definition include early satiety, fullness, bloating in the upper abdomen, and nausea. A dominant complaint of heartburn is not considered to fall under the definition of dyspepsia under the Rome II criteria; rather, it is considered to be symptomatic gastroesophageal reflux disease (GERD).

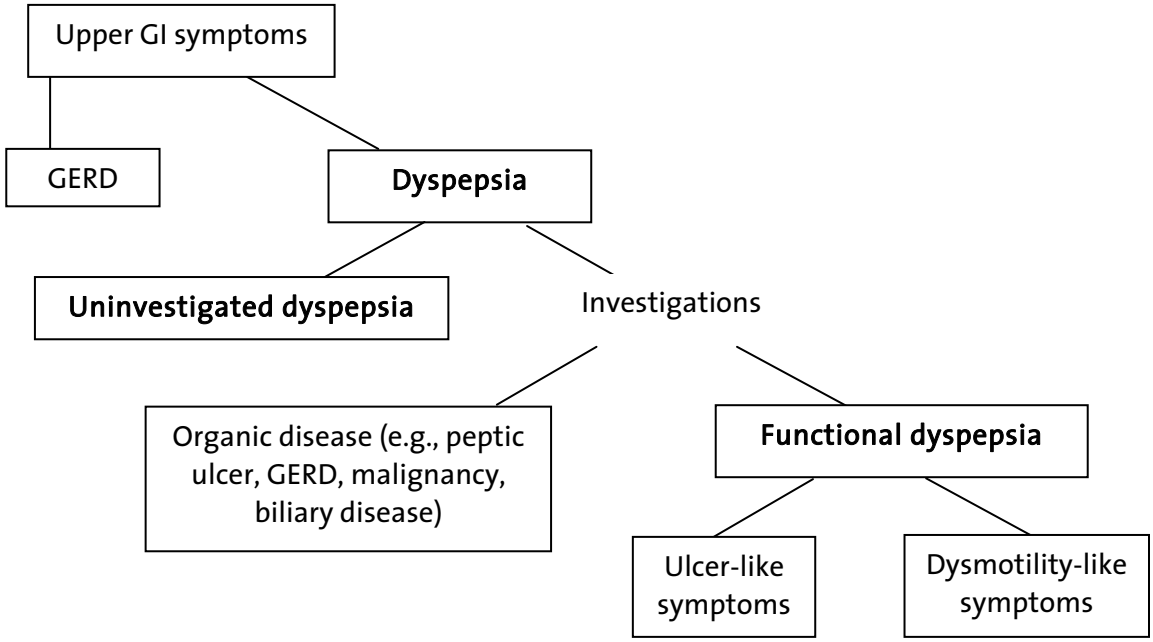
Dyspepsia is further defined by whether diagnostic investigation occurs and by findings upon investigation. Figure 1 provides a representation of the subtypes of dyspepsia and how they relate to each other.

The term "non-ulcer dyspepsia (NUD)" has been used synonymously with the term "functional dyspepsia"; however, NUD is not a recommended term by the authors of Rome II as ulcers are not the only condition excluded in investigations for organic causes.

Functional dyspepsia is essentially a diagnosis of exclusion. The Rome II criteria define it as:
"At least 12 weeks, which need not be consecutive, within the preceding 12 months of:

1. Persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen); and
2. No evidence of organic disease (including upper endoscopy) that is likely to explain the symptoms; and
3. No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel).[4]

Figure 1: Diagram of dyspepsia terms and their relationships



Adapted from Talley *et al.*[4]

Rome II provides a further breakdown of functional dyspepsia by its predominant or most bothersome symptom, as follows:

1. Ulcer-like dyspepsia – "Pain centered in the upper abdomen is the predominant (most bothersome) symptom." [4]
2. Dysmotility-like dyspepsia – "An unpleasant or troublesome non-painful sensation (discomfort) centered in the upper abdomen is the predominant symptom; this sensation may be characterized by or associated with upper abdominal fullness, early satiety, bloating, or nausea." [4]

Rome III

This revised classification system was published in April 2006.[5] Because of its relatively recent publication, the classification has not been used widely in clinical research; therefore, it remains to be validated. The major changes in Rome III centre on the diagnostic criteria for functional dyspepsia and its subclasses.

Functional dyspepsia is defined by:

- One or more of:
  - bothersome postprandial fullness
  - early satiation
  - epigastric pain
  - epigastric burning

and

- No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

The criteria must be fulfilled for the last three months with symptom onset at least six months before diagnosis.

The authors of the Rome III criteria provide extensive rationalization for the changes made. It appears that the key limitation of the Rome II criteria was that it was not uniformly interpreted and accepted by various authorities around the world (including Canada).[3] Consequently, many trials published subsequent to the Rome II criteria included patients with heartburn and acid regurgitation as typical presentations of dyspepsia. The Rome III authors also point to the inadequacy of using predominant symptoms to define the condition, indicating that "this subdivision has ... been criticized because of the difficulty in distinguishing pain from discomfort, the lack of an accepted definition of the term 'predominant,' number of patients who do not fit into one of the subgroups, and especially the lack of stability, even over short time periods."[5]

Instead of using symptom-based sub-classification as in Rome II, the Rome III authors recommend the application of the revised functional dyspepsia criteria to clinical practice. They further defined two new diagnostic entities to be used for pathophysiological and therapeutic research purposes: Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome (EPS). How these new syndromes will be applied in clinical research remains to be seen.

It is recognized in both sets of criteria (Rome II and III) that there may be significant overlap in the symptoms patients present with in primary care. Patients may often complain of occasional symptoms more synonymous with reflux or irritable bowel disease in association with common dyspepsia symptoms. The criteria are provided as a general tool for patients presenting with dyspepsia but must be individualized on a case-by-case basis.

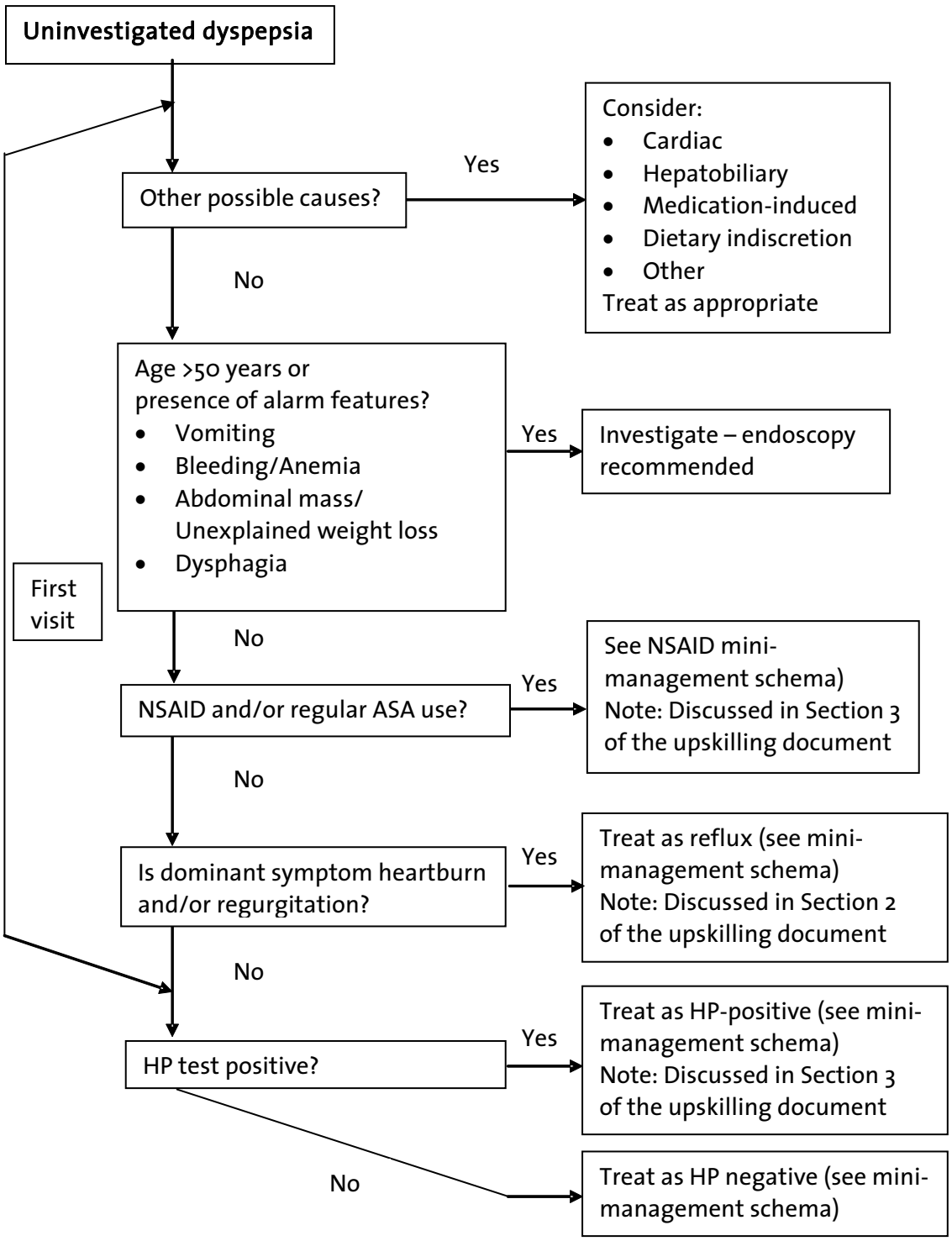
1.3 Treatment: Uninvestigated Dyspepsia

In order to structure the discussion of dyspepsia management, the clinical management tool produced by the CanDys Working Group will be introduced (Figure 2).[3] It is important to be familiar with this tool as it has been promoted to general practitioners and may guide clinical decision making. Discussion of the CanDys approach in this document is not intended to be an endorsement; rather, it is a means to present a logical review of the dyspepsia literature.

Other possible causes[3]

Dyspepsia-like symptoms can be induced or mimicked by other conditions. These other causes may be identified through the patient's history and physical examination and managed accordingly. Non-gastrointestinal pathology causing the symptoms will be managed quite differently from classic dyspepsia. Drugs that may cause or worsen dyspepsia symptoms include NSAIDs (discussed further down in the management tool), bisphosphonates (especially when administered inappropriately), calcium channel blockers, and corticosteroids.

Figure 2: Canadian Dyspepsia Working Group clinical management tool



HP=*H. pylori*

Adapted from: An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. Reprinted from *CMAJ*13-Jun-00; 162(12 Suppl), pages S1-S23 by permission of the publisher. ©2000 Canadian Medical Association.[3]

Age >50 years or presence of alarm symptoms?[3]

This decision point includes two patient groups: those aged >50 years, and those with alarm symptoms. Endoscopy is recommended for symptoms of **v**omiting, **b**leeding, **a**bdominal mass, or **d**ysphagia (VBAD), since these may be due to severe gastrointestinal pathology such as cancer. In those aged >50 years without alarm symptoms, the choice between endoscopic investigation and pharmacological management has been an area of considerable research. The initial management of uninvestigated dyspepsia was considered in the CADTH Scientific Report as per the following Evidence Statement:[1]

> **D1.1.2A:** Management strategy based on initial (prompt) endoscopy does not produce better outcomes (e.g., improvement of symptoms, failure of treatment strategy, quality of life) than empirical PPI therapy in patients with uninvestigated dyspepsia.

The evidence behind this statement consists entirely of one small randomizes control trial (RCT) (n=84) that randomized patients to empiric PPI therapy for two weeks or management based on endoscopy.[6] At the end of one year, there was no significant difference in symptom-free days or quality-of-life (QOL) scores. The mean age of patients in the trial was 43 to 44 years. The results of this study generally support the CanDys strategy to treat empirically in patients under age 50 without alarm symptoms, since prompt endoscopy did not appear to confer benefit over empiric PPI therapy in a younger population.

A recent Cochrane systematic review by Delaney *et al.* investigated initial management strategies for dyspepsia.[7] One section of the review looked at initial endoscopy versus any form of empiric acid suppression therapy (H2RA, antacids, PPIs) for symptom improvement. Five RCTs were identified. Although the RCT described in the previous paragraph as evidence for Statement D1.1.2A in the CADTH Scientific Report was among the five studies, it was removed from the pooled analysis because it did not report symptom scores, only number of symptom-free days.[7] When the other four trials were pooled, they found no statistically significant difference in symptom scores between the two strategies (RR 0.89, 95% CI: 0.77 to 1.02).[7]

None of the studies stratified the benefit of endoscopy based on patient age. Therefore, the available data do not support the empiric decision to scope those patients over age 50, as specified in the Management Tool. The CanDys Working Group defended this recommendation based on a number of factors.[3] The probability of developing gastric cancer in Canadian men and women is exceedingly small until the age of 50. The probability of having been diagnosed with gastric cancer is 0.1% for both men and women at age 50, and rises with increasing age.[3] Furthermore, early detection of gastric cancer increases the cure rate. CanDys also noted that prompt investigation with a normal finding provides reassurance to the patient and physician. Finally, another consideration was that a similar recommendation was made by the Canadian *Helicobacter pylori* Consensus Conference.[8] CanDys assigned a grade of B to the evidence for the recommendation to investigate patients over the age of 50 without alarm symptoms.[3]

A series of Canadian studies known as the Canadian Adult Dyspepsia Empirical Treatment (CADET) looked at different management strategies for uninvestigated dyspepsia. In one of these trials (CADET-PE), all patients presenting with the CanDys Working Group definition of dyspepsia were subjected to endoscopy.[9] This study was not a comparison of endoscopy to another initial management strategy; rather, it was conducted to determine the proportion of patients presenting with dyspepsia that had clinically significant upper gastrointestinal findings (CSF). A total of 1,040

patients 8 to 84 years of age (almost 2/3 were <50 years) were enrolled in the study. In total, 58% of the patients receiving endoscopy had a CSF, of which esophagitis comprised about three quarters of the findings. The proportion of patients with a CSF was 6.6% higher in the age >50 group compared with the age <50 group. This was mostly attributed to greater number of findings in the stomach (e.g., gastric ulcers and erosions). As well, gastric cancer was identified in only two patients, both of whom were over 50 years of age. The authors of the study concluded that:

- clinically significant endoscopic findings were observed in 58% of patients with uninvestigated dyspepsia. Reflux oesophagitis was by far the most common finding. Most patients presented with a complex of three or more dyspeptic symptoms, and the symptom profile was not predictive of the endoscopic findings. Our study did not specifically address management strategies. However, the high prevalence of oesophagitis, the 30% prevalence of *H. pylori* infection, and the observation that 62% (34/55) of patients with a peptic ulcer were infected with *H. pylori*, suggests that most patients presenting with uninvestigated dyspepsia in primary care can be safely managed initially with acid suppressive therapy or treatment of *H. pylori*, if the patient is infected.[9]

Data from both comparative trials and the CADET-PE study do not provide clear evidence to support the cut-off of age 50 for empiric endoscopy. However, they also do not clearly delineate when investigation should be undertaken. This leaves clinicians without direction on which patients should be investigated. Perhaps the take-home message is that clinicians who choose to refer or investigate patients older than 50 years of age without alarm symptoms are justified based on expert recommendations. On the other hand, those who choose a more conservative management approach can do so with the confidence that the majority of patients presenting with dyspepsia suffer from conditions that are amenable to empiric treatment.

NSAID and/or regular acetylsalicylic acid (ASA) use?[3]

The evidence behind treatment recommendations for NSAID and ASA users who experience gastrointestinal side effects will be discussed in Section 3 of this upskilling document.

Is dominant symptom heartburn and/or regurgitation?[3]

The evidence behind treatment recommendations for heartburn will be discussed in Section 2 of this upskilling document.

H. pylori test positive?[3]

The CanDys Working Group recommends taking a "test and treat" approach to the management of patients presenting with dyspepsia. The CADTH Scientific Report has identified the following research gap related to the "test and treat" approach:[1]

Research Gap: Test and treat for *H. pylori* infection as an initial therapeutic strategy for the treatment of uninvestigated dyspepsia (*H. pylori* status unknown) is not more efficacious than empirical PPI therapy.

When this Statement came to a vote, the CADTH Expert Review Panel (ERP) was equally divided between acceptance and rejection of this Statement. The available evidence is from a single, good-quality RCT by Manes *et al.*,[10] in which patients aged 18 to 45 were randomized to either *H. pylori*

test with eradication therapy if positive, or empiric omeprazole 20 mg daily for four weeks. At the end of four weeks, 83% of the empiric PPI group and 71% of the "test and treat" group had improvement in dyspepsia symptoms (p=0.05). The calculated number needed to treat (NNT) for empiric PPI therapy was eight (95% CI: 4 to 104) patients for one additional patient with improved symptoms at four weeks.[1] The dyspepsia scores in the empiric PPI group were also significantly better at four weeks; however, measures at six and 12 months showed significantly better scores in the "test and treat" group. Endoscopy rates also favoured the "test and treat" strategy with 55% of patients receiving endoscopy for relapse of symptoms versus 88% of the empiric PPI group. The generally high rates of endoscopy in this trial resulted from the practice of offering the procedure to all patients returning with relapse symptoms. This degree of diagnostic vigilance is unlikely to reflect routine clinical practice in Canada. The authors concluded "if we choose to offer an empirical treatment the test and treat strategy should be the preferred option."[10] However, as reflected in the ERP vote, factors such as small sample size, marginal differences in efficacy, and the high rate of *H. pylori* infection in the "test and treat" arm (61%), make it difficult to recommend one strategy over another. Further research is therefore required.

H. pylori test positive? Yes[3]

The evidence behind treatment recommendations for *H. pylori* eradication will be discussed in Section 3 of this upskilling document.

H. pylori test positive? No[3]

H. pylori-negative dyspepsia: Initial therapy

The Canadian Dyspepsia working group describes a mini-management scheme for those patients with dyspepsia who are *H. pylori*-negative (Figure 3).[3] For initial therapy, none of the three recommended agents is preferred. It should be noted that the "prokinetic" option in the first treatment box refers to cisapride, which is not routinely available on the Canadian market. Cisapride can be acquired under certain circumstances through the Health Canada Special Access program. The therapeutic value of other prokinetic agents has not been well established.

The CADTH Scientific Report provides more definitive statements regarding the evidence for initial treatment of *H. pylori*-negative dyspepsia patients.[1]

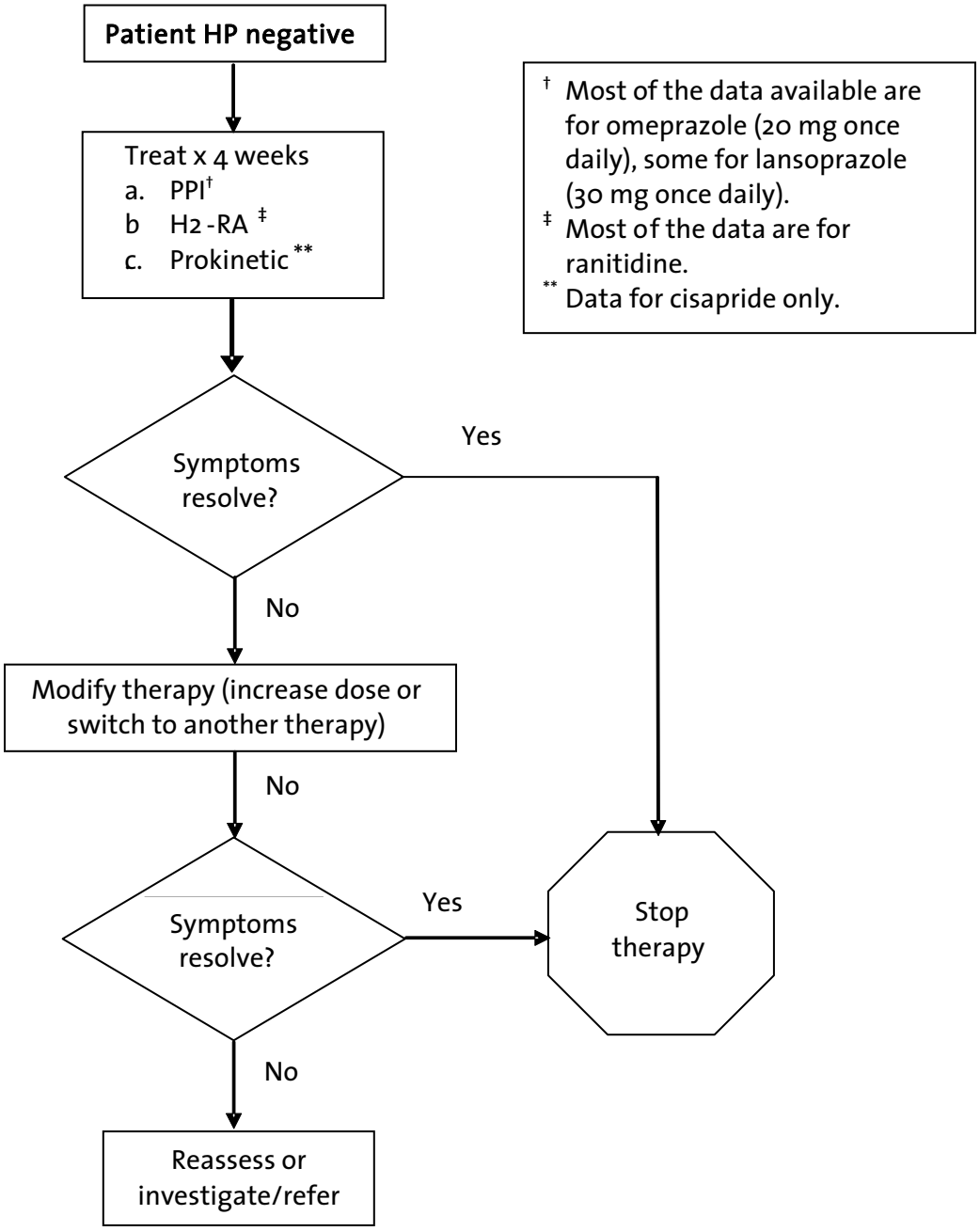
D1.1.1A: Initial (up to four weeks) standard-dose PPI therapy is more efficacious than standard-dose H2RAs at reducing symptoms in patients with *H. pylori*-negative, otherwise uninvestigated dyspepsia.

The evidence supporting this statement is from the CADET-HN trial, a Canadian study that randomized 512 *H. pylori*-negative dyspepsia patients to one of four treatment arms: omeprazole 20 mg/day, ranitidine 150 mg BID, cisapride 20 mg b.i.d., or placebo. Treatment was given daily for four weeks, after which patients used their assigned therapies on demand (i.e., as needed based on symptoms) for an additional five months.[11]

Because cisapride is not routinely available on the Canadian market, the evidence for that treatment arm will not be discussed. The primary endpoints of the study were based on a Global Overall Severity (GOS) score for dyspepsia symptoms.[11] The scores ranged from one (no problem) to seven (very severe problem that markedly limits daily activities). The primary outcome measure was the percentage of treated patients with a GOS ≤2 at four weeks and six months. The secondary

outcome measure was the percentage with a GOS of one at the same times. Figures 4A and 4B show the efficacy of each treatment at four weeks.[11]

Figure 3: Canadian Dyspepsia Working Group *H. pylori*-negative mini-management schema



HP=*H. pylori*

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Figure 4A: Proportion of patients with treatment success (GOS≤2) at four weeks

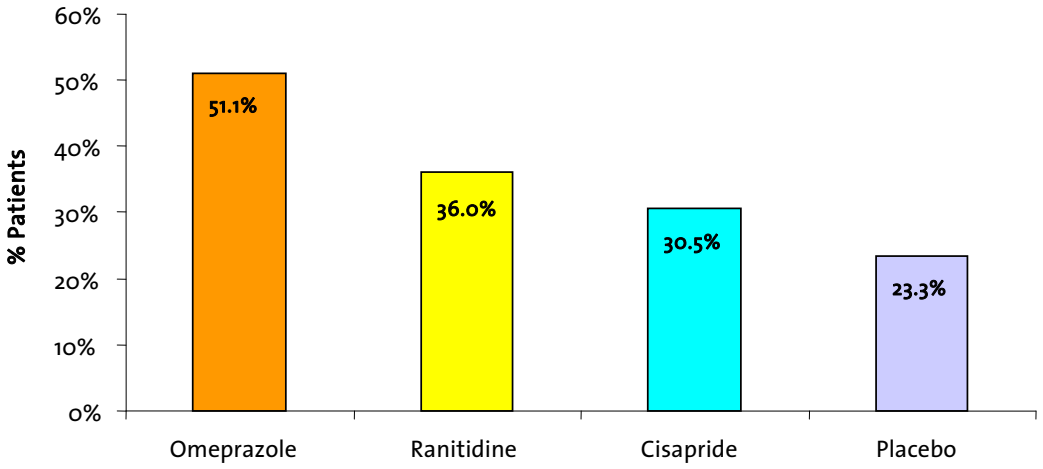

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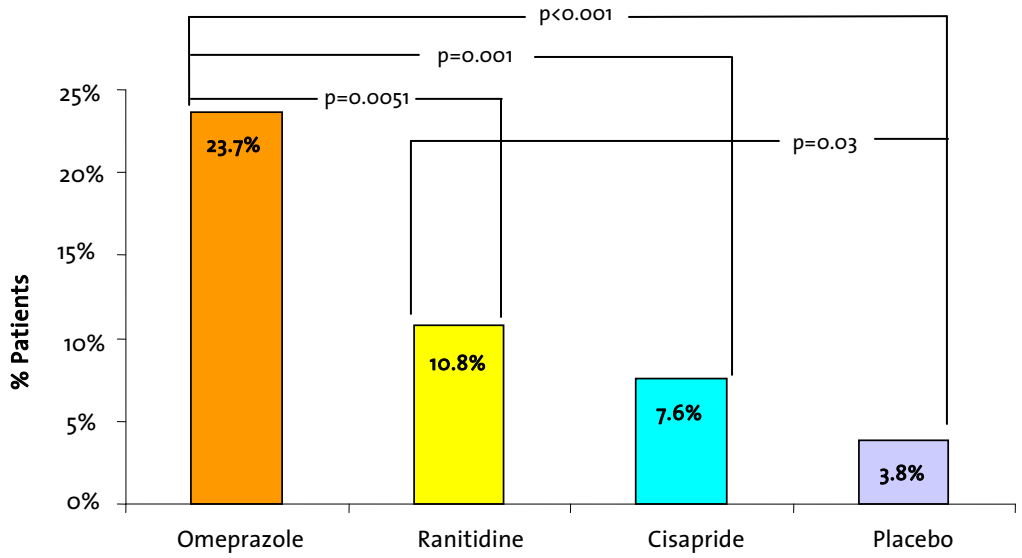
Figure 4B: Proportion of patients with treatment success (GOS=1) at four weeks



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It is evident from Figure 4A and 4B that omeprazole was the most effective therapy. The number needed to treat (NNT) with omeprazole compared to ranitidine was seven to have one additional person achieve GOS ≤2 at four weeks. The outcome was also analyzed based on baseline heartburn severity (i.e., no/minimal versus more than mild heartburn or regurgitation). In the no/minimal symptom group, the proportion of patients with GOS ≤2 at four weeks was significantly greater than placebo in both the omeprazole (48.7%) and ranitidine (39.5%) arms, however the difference between the two treatments was not statistically significant. In the "more than mild" symptom group, omeprazole was significantly superior to ranitidine (54.4% had GOS ≤2 at four weeks in the omeprazole arm versus 31% in the ranitidine arm, p=0.01). After the initial four weeks of daily therapy, patients were switched to maintenance treatment with on-demand therapy for the

remainder of the study (five months). This strategy will be further discussed under "*H. pylori*-negative dyspepsia: Maintenance therapy."

The Cochrane systematic review discussed previously also reviewed various pharmacological options for management of *H. pylori*-negative patients.[7] The results of this review reinforce the findings by van Zanten *et al.* that omeprazole is superior to comparator agents for initial management. The measures of efficacy differed across the studies included in the systematic review, therefore the authors compared treatments by assessing the outcome of global improvement of dyspepsia symptoms. The duration of the studies abstracted in the systematic review varied from as short as two weeks to as long as 24 weeks. Both H2RAs and antacids led to improvement in dyspepsia symptoms in about 40% of patients on average, with PPI therapy adding another 20% of improvement. The systematic review also reported that the relative benefit of PPIs over H2RAs and antacids was greater for heartburn than for epigastric pain. Some other notable points from the review include:[7]

- similar global improvement and relief of epigastric pain and heartburn were achieved at four weeks with lansoprazole 15 mg and omeprazole 10 mg in one study
- no difference in global symptom relief between two doses of omeprazole (20 mg and 40 mg daily) in one study
- no significant differences in global symptom relief and heartburn relief rates between H2RAs and antacids/alginates were reported in one small trial (n=80).

It is noteworthy that many of the studies in the Delaney *et al.* systematic review included subjects with predominant heartburn or reflux symptoms (i.e., GERD).[7] However, CADTH's review of the evidence for dyspepsia was restricted to studies that clearly excluded patients with heartburn predominant symptoms, hence the Delaney *et al.* systematic review was not considered.

One take-home message that can be derived from the available evidence is that the symptoms of a substantial percentage of dyspeptic patients will not be relieved by acid-suppressing or neutralizing therapy. The most optimistic expectation is that about 60% of patients treated with a standard-dose proton pump inhibitor will improve within a few weeks. If a patient presents with predominant epigastric symptoms rather than heartburn, the treatments are likely to be even less effective. The duration of an initial course of therapy of four weeks recommended by the CanDys Working Group is supported by the van Zanten *et al.* trial and a number of studies included in the Delaney *et al.* systematic review: [7,11]

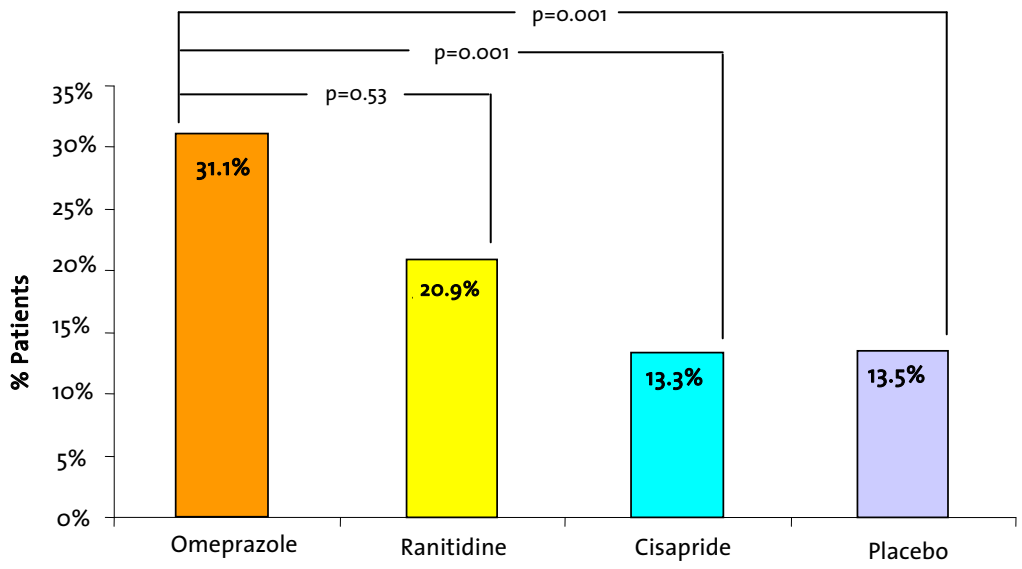
H. pylori-negative dyspepsia: Maintenance therapy

No specific recommendations regarding maintenance therapy are suggested in the CanDys Working Group treatment algorithm.[3] The CADTH Scientific Report contains the following Evidence Statements to guide treatment:[1]

D1.2.1A: On-demand PPI therapy is more efficacious than on-demand placebo for the maintenance treatment of dyspepsia symptoms in *H. pylori*-negative patients with uninvestigated dyspepsia.
D1.2.1B: On-demand PPI therapy is not more efficacious than on-demand H2RAs for the maintenance treatment of dyspepsia symptoms in *H. pylori*-negative patients with uninvestigated dyspepsia.

These Evidence Statements were based on results from the RCT by van Zanten *et al.* discussed under the preceding section on initial therapy.[11] As previously mentioned, initial therapy consisting of four weeks of daily dosing was followed by a five-month course of on-demand omeprazole, ranitidine, cisapride, or placebo. At six months, there were no significant differences between omeprazole and ranitidine in terms of the proportion of patients with GOS ≤2, and neither was superior to placebo (44% for omeprazole, 41% for ranitidine, and 35% for placebo). However, significant differences were detected in the subgroup of patients that demonstrated a response to initial treatment (i.e., GOS ≤ two at four weeks), as shown in Figure 5.

Figure 5: Proportion of patients who were responders at both four weeks and six months



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It is evident from Figure 5 that, in the subgroup of responders to initial treatment, omeprazole was significantly better than placebo, but not ranitidine. Therefore, the CADTH Evidence Statement D1.2.1A should be applied only to those patients who respond to initial acid-suppression therapy.

The take-home message for clinicians is that there is not a great deal of information about what should be used for maintenance therapy of dyspepsia. On-demand PPI or ranitidine therapy may help, but the success rate at six months is well below 50% regardless of the regimen employed.

1.4 Treatment: Functional Dyspepsia

Functional dyspepsia is essentially a diagnosis of exclusion that encompasses patients with persistent or recurring dyspepsia who have been investigated and found to have no organic cause for symptoms.[4] Of note, patients may be *H. pylori*-positive and still have the diagnosis of functional dyspepsia if endoscopy results are negative. Management of such patients is not addressed in the CanDys Working Group approach.[3] However, there has been research into the management of these patients. The CADTH Scientific Report makes the following Evidence Statements:

D2.1.1A: Standard-dose PPIs for four to eight weeks are more efficacious than placebo for the improvement of symptoms in functional dyspepsia.
D2.1.1B: Standard-dose PPIs for four to eight weeks are no more efficacious than standard-dose H2RAs for the improvement of symptoms in functional dyspepsia.

Two systematic reviews and three RCTs comprised the evidence for these Statements. The most recent of the systematic reviews was a Cochrane review by Moayyedi *et al.*[12] This analysis looked at a variety of treatment options including prokinetics (cisapride), H2RAs, PPIs, bismuth salts, misoprostol, sucralfate, and antacids. Misoprostol, sucralfate, and antacids were found to have no significant value over placebo. Bismuth salts were found to be slightly better than placebo, although the statistical significance of the effect was marginal. The prokinetic trials were positive, but cisapride is no longer routinely available on the Canadian market so it will not be discussed further. The data on H2RAs and PPIs in both placebo-controlled and head-to-head trials are of greatest interest.

The twelve H2RA studies abstracted by Moayyedi *et al.* measured treatment success by reduction in dyspepsia symptoms.[12] Compared to the placebo response rate of 40% (i.e., the percentage of patients with symptomatic improvement), H2RAs had a statistically significant higher response rate of 54%. The ten PPI studies used a more stringent outcome measure, dyspepsia cure (i.e., no or minimal symptoms) after two to eight weeks. Because of the more restrictive endpoint, the placebo response rate in these trials was only 25%. PPIs were significantly more effective than placebo with a response rate of 34%. This translates to a NNT of 10 patients who must be treated with a PPI to get one additional dyspepsia "cure" over placebo. Six of the PPI studies in the Cochrane review compared half-dose versus standard-dose PPIs in the management of functional dyspepsia and found no significant advantage with the higher dose.

The Cochrane systematic review also identified two studies that directly compared an H2RA with PPIs.[12] One trial lasted two weeks, the other eight weeks. Overall, there was no significant difference in the rate of dyspepsia cure between the two treatments. In the larger of the two studies, Blum *et al.* compared ranitidine 150 mg daily to omeprazole 10 mg and 20 mg and found that the results differed by *H. pylori* status.[13] In those patients who were *H. pylori*-positive, omeprazole 20 mg was more effective than ranitidine at achieving complete symptom relief, although there was no significant difference in terms of the proportion needing further management, the primary outcome of the study. However, the treatment success rate was very low, with the best treatment (omeprazole 20 mg) having only a 19.6% response rate. No significant differences among comparators (including placebo) were found in terms of the primary outcome in *H. pylori*-negative patients, although omeprazole 20 mg was statistically superior to placebo in terms of complete symptom relief.

The take-home message for clinicians is that functional dyspepsia may be refractory to antisecretory therapy. Response rates with PPIs at standard and half doses are better than placebo in short-term comparative trials, but response rates are still quite low. H2RAs have also been shown to be efficacious in placebo-controlled trials. The differential results in the Blum study suggest that ascertainment of *H. pylori* status may be useful in patients with functional dyspepsia to guide treatment. However, it would be reasonable to assume that any patient in whom functional dyspepsia was diagnosed, *H. pylori* status would have been tested for and treated.

1.5 Recommended Reading

van Zanten VSJ, Flook N, Chiba N, Armstrong D, Barkun A, Bradette M, et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. Canadian Dyspepsia Working Group. *CMAJ* 2000;162(12 Suppl):S3-23.

Delaney B, Ford AC, Forman D, Moayyedi P, Qume M. Initial management strategies for dyspepsia. *Cochrane Database Syst Rev* 2005;(4):CD001961.

van Zanten SJOV, Chiba N, Armstrong D, Barkun A, Thomson A, Smyth S, et al. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in *Helicobacter pylori* negative, primary care patients with dyspepsia: the CADET-HN study. *Am J Gastroenterol* 2005;100(7):1477-88.

2 SECTION 2: GASTROESOPHAGEAL REFLUX DISEASE (GERD)

2.1 Epidemiology

GERD refers to the reflux of gastric contents into the esophagus, causing symptoms severe enough to affect the quality of life and/or cause esophageal injury.[1,14] The prevalence of GERD is higher in adults over the age of 40 but occurs in relatively equal numbers of men and women.[15] This equality is disrupted in younger women where pregnancy may result in approximately 50% of women experiencing GERD symptoms.[16] Because many patients do not seek treatment, it is difficult to determine the true rates of GERD in the Canadian population. Survey data suggest that 17% of Canadians have experienced heartburn in the past three months and 13% have moderate to severe symptoms that occur at least weekly.[2] Estimates of the prevalence of erosive esophagitis vary from 2% to 12%.[14] The overall high prevalence of GERD makes it one of the most common medical disorders seen by health care practitioners. While GERD is not usually associated with mortality, it can produce significant impact on health related quality of life (HRQL). One study reported that the effect of GERD on HRQL was greater than that of chronic diseases such as diabetes, arthritis, and mild heart failure.[17]

2.2 Pathophysiology

GERD results from the movement of acidic stomach contents through the lower esophageal sphincter (LES) into the esophagus. It is the increased contact of these acidic contents with the esophageal mucosa that causes the signs and symptoms of GERD, rather than excessive production of gastric acid. Reflux may be due to spontaneous, transient relaxations of the LES, an atonic LES, or to an increase in intra-abdominal pressure. In addition to gastric acid, pepsin, bile acids, and pancreatic enzymes may contribute to esophageal damage.[15]

GERD is associated with a variety of potential complications including esophagitis, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma. The duration, frequency, and severity of GERD appear to be associated with the risk of esophageal adenocarcinoma.[18]

2.3 Risk Factors

Certain medications have been implicated in the loss of LES tone (Table 1).[15] Other medications may exacerbate GERD symptoms due to direct irritant effects on the esophagus. Obesity appears to be a significant and independent risk factor for GERD, since higher body mass index (BMI) is associated

with a greater risk for GERD.[19] Weight gain has also been shown to exacerbate the symptoms of reflux.[20] Smoking is another risk factor for GERD. Some foods (chocolate, alcohol > seven drinks per week, peppermint, excess coffee, orange juice, colas, onions, garlic), eating patterns (large fatty meals) and recumbency after meals have been implicated in GERD.[21] Finally, numerous conditions including chronic obstructive pulmonary disease (COPD), cystic fibrosis, hiatus hernia, scleroderma, motility disorders, acid hypersecretory states (Zollinger-Ellison syndrome), and pregnancy may increase the risk of GERD.[15] The Canadian Consensus Conference has concluded that there is no established relationship between *H. pylori* infection and GERD.[22]

Table 1: Medications that may worsen GERD symptoms	
Medications That May Decrease Lower Esphageal Sphincter Pressure	
Anticholinergics	Ethanol
Barbiturates	Isoproterenol
Benzodiazepines	Narcotics
Caffeine	Nicotine
Dihydropyridine Calcium Channel Blockers	Phentolamine
Dopamine	Progesterone
Estrogen	Theophylline
Medications That May Act as Direct Irritants to the Esophageal Mucosa	
Alendronate	NSAIDs
ASA	Quinidine
Iron	Potassium Chloride

Adapted from Williams.[15]

2.4 Definition and Diagnosis

Signs and symptoms – The classification of GERD

Typical GERD: Symptoms include heartburn (pyrosis – retrosternal pain) which is described as a substernal sensation of warmth or burning that may radiate to the neck.[15] It may wax and wane and may become worse in the supine position or when bending over. Hypersalivation (water brash), belching, and regurgitation (sour or bitter taste in the mouth) may also be present.

The symptoms of GERD do not correlate well with the degree of esophagitis. Patients with severe symptoms may not have esophagitis on endoscopy, while others with limited or no symptoms may have significant erosive disease.[23] Patients without esophagitis may have symptoms that are as, or more, difficult to control as patients with esophagitis.[21]

Atypical GERD: Symptoms that have been attributed to GERD include asthma, chronic cough, hoarseness, pharyngitis, dysphagia, and chest pain. These atypical symptoms are much less common than typical GERD symptoms and it is unclear if they are truly related to GERD.[14]

Complicated GERD: Most often occurs after long-term exposure to acid reflux in untreated or under-treated GERD. Symptoms of complicated GERD include continual pain, dysphagia, odynophagia, bleeding/anemia, unexplained weight loss, and choking.[14,21]

Uninvestigated GERD: Dominant symptoms of heartburn that may be associated with other symptoms such as epigastric pain/discomfort, not investigated by endoscopy (or upper GI series). Note: Heartburn-dominant uninvestigated dyspepsia is included in the definition of uninvestigated

GERD.[1] Most patients encountered in primary care settings will have uninvestigated GERD since endoscopic investigation is relatively infrequent.

If the patient is investigated endoscopically, their disease will likely be defined as either endoscopy-negative reflux disease (ENRD) or erosive/reflux esophagitis.

Endoscopy-negative reflux disease (ENRD): Also referred to as non-erosive GERD or non-erosive reflux disease (NERD), applies to individuals with GERD who have normal endoscopy results while off treatment.[1]

Erosive esophagitis: the presence of reflux symptoms and any length of mucosal break in the esophagus as a result of gastroesophageal reflux. (Also called "reflux esophagitis.")[1]

Diagnostic process

In clinical practice, it is appropriate to diagnose GERD through a careful history in patients presenting with typical symptoms (i.e., heartburn with or without regurgitation).[14,21] Empiric treatment is appropriate in these patients, and successful treatment with antisecretory therapy (i.e., H2RAs or PPIs) confirms the diagnosis.[21] Objective tests (i.e., 24-hour pH monitoring) are invasive, costly, not readily available, and insufficiently reliable.[14] Previously, a symptomatic response to a two-week trial of high-dose PPI was suggested for diagnosis. However, this approach has not been shown to be superior to a trial of standard-dose PPI therapy.[14]

The role of endoscopy in the diagnosis of GERD is complicated and controversial. Most GERD patients have ENRD, with about 70% showing no signs of esophagitis or Barrett's esophagus.[14] Patients presenting with alarm symptoms (Table 2) should undergo further investigations including endoscopy.[14] Dysphagia that does not completely resolve with two to four weeks of PPI therapy should be investigated. Although the prevalence of esophageal cancer is higher in people over the age of 50, it is still a rare condition and does not justify routine endoscopy for all adults over the age of 50 presenting with GERD for the first time.[14] Further investigation including endoscopy may be prudent in some patients over the age of 50 with severe symptoms not responding to four to eight weeks of PPI therapy who have not been previously investigated.[14,21,24] Endoscopy with mucosal biopsies is used to identify Barrett's epithelium.

Table 2: Alarm Symtoms
Gastrointestinal Bleeding / Anemia
Dysphagia / Odynophagia
Vomiting
Unexplained Weight Loss
Chest Pain

Disease severity

Determinations of disease severity may be helpful in selecting an appropriate treatment regimen. GERD severity is determined by the severity of symptoms and/or the presence and extent of esophageal damage (i.e., erosions, ulcers, strictures, Barrett's epithelium). The effect of the frequency, intensity, and duration of GERD symptoms on activities of daily living and health-related quality-of-life determine GERD symptom severity.

Mild GERD: Characterized by GERD symptoms that are infrequent (fewer than three times per week), of low intensity, of short duration, and have minimal long-term effect on the patient's activities of daily living or health-related quality of life.[1,14]

Moderate or severe GERD: Characterized by GERD symptoms that are frequent, associated with intense or prolonged symptoms, and have a significant effect on the patient's daily activities or health-related quality of life.[1,14]

In patients who have erosive esophagitis, the degree of severity can be classified. The Canadian Consensus Conference on GERD selected the Los Angeles Classification for the endoscopic grading of esophagitis (Table 3).[14,25]

Table 3: The Los Angeles Classification System for endoscopic assessment of esophagitis

Grade	Definition
A	One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
B	One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds
C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference
D	Mucosal breaks that involve at least 75% of the esophageal circumference

Reproduced with permission from BMJ Publishing Group Ltd. and the British Society of Gastroenterology.[25]

2.5 Treatment: Initial Therapy

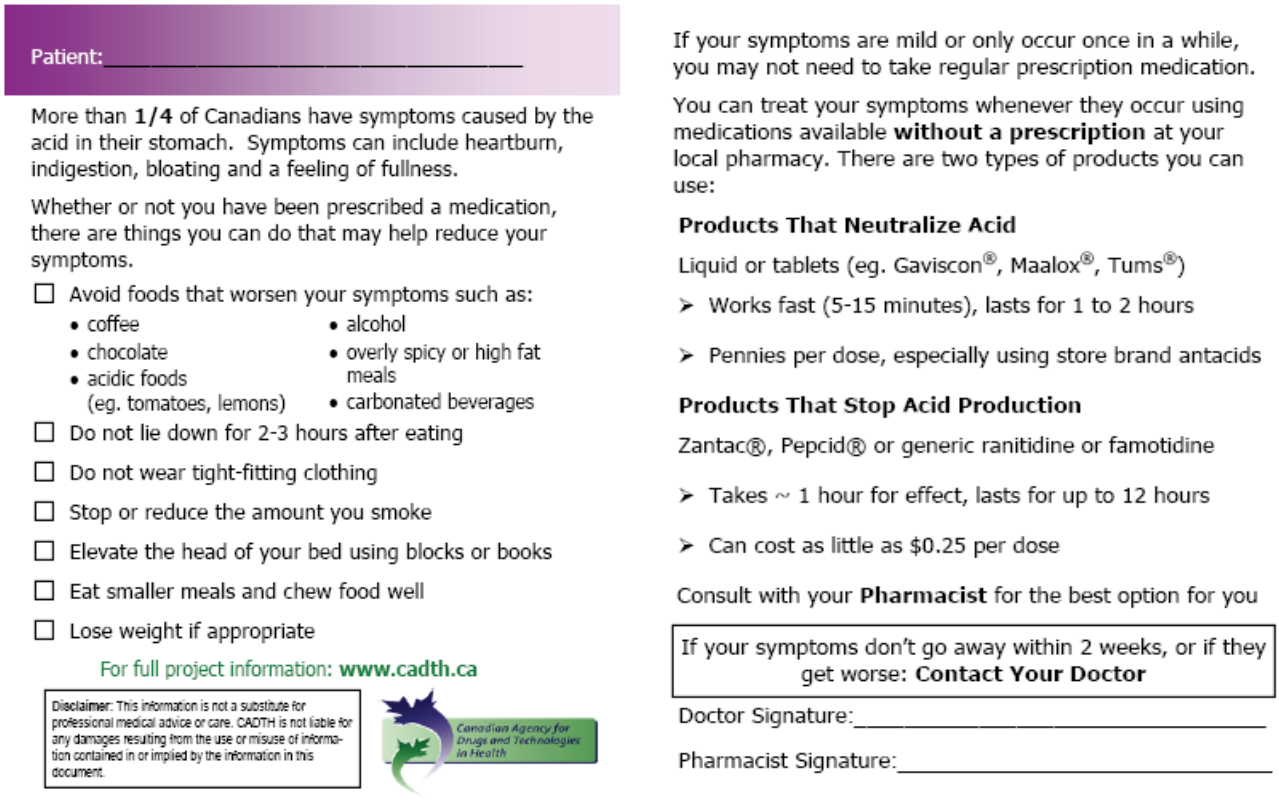
Uninvestigated GERD

For mild disease, treatment with antacids, alginates, or low-dose H2RAs is a safe and effective method of symptom management. While lifestyle modifications are not well-studied, most guidelines recommend that all patients, regardless of disease severity, be counselled on factors that may worsen GERD.[14,21] This approach to mild GERD is covered in the alternate prescription pad found in the toolkit (Figure 6). Antacids may provide rapid relief but have a short duration and may require frequent dosing. Regular dosing seven times per day has been shown to be more effective than as required or four times daily dosing.[24] Alginic acid preparations have also demonstrated efficacy and may be particularly helpful for meal-induced symptoms.[24] Some long-term trials have suggested these measures are sufficient to treat approximately 20% of patients.[26] Over-the-counter (OTC) H2RAs offer another alternative in mild GERD, with guidelines suggesting that the available H2RAs may be used interchangeably.[21,24]

For patients with more significant symptoms (moderate to severe disease), and for those with documented esophagitis, more aggressive treatment is warranted. PPIs have been shown to be superior to H2RAs for initial treatment of moderate to severe GERD. The Canadian Consensus Guidelines recommend once daily standard-dose PPIs for the initial treatment of moderate to severe uninvestigated GERD. This recommendation is also consistent with the following Evidence Statement in the CADTH Scientific Report:[1]

G1.1.1A: Standard-dose PPIs, as initial therapy for up to four weeks, are more efficacious than H2RAs for improvement of reflux symptoms in **uninvestigated GERD.**

Figure 6: Alternate prescription pad



Patient:_____

More than **1/4** of Canadians have symptoms caused by the acid in their stomach. Symptoms can include heartburn, indigestion, bloating and a feeling of fullness.

Whether or not you have been prescribed a medication, there are things you can do that may help reduce your symptoms.

- ☐ Avoid foods that worsen your symptoms such as:
  - coffee
  - chocolate
  - acidic foods (eg. tomatoes, lemons)
  - alcohol
  - overly spicy or high fat meals
  - carbonated beverages
- ☐ Do not lie down for 2-3 hours after eating
- ☐ Do not wear tight-fitting clothing
- ☐ Stop or reduce the amount you smoke
- ☐ Elevate the head of your bed using blocks or books
- ☐ Eat smaller meals and chew food well
- ☐ Lose weight if appropriate

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Canadian Agency for Drugs and Technologies in Health

If your symptoms are mild or only occur once in a while, you may not need to take regular prescription medication.

You can treat your symptoms whenever they occur using medications available **without a prescription** at your local pharmacy. There are two types of products you can use:

Products That Neutralize Acid

Liquid or tablets (eg. Gaviscon®, Maalox®, Tums®)

- ➢ Works fast (5-15 minutes), lasts for 1 to 2 hours
- ➢ Pennies per dose, especially using store brand antacids

Products That Stop Acid Production

Zantac®, Pepcid® or generic ranitidine or famotidine

- ➢ Takes ~ 1 hour for effect, lasts for up to 12 hours
- ➢ Can cost as little as $0.25 per dose

Consult with your **Pharmacist** for the best option for you

If your symptoms don't go away within 2 weeks, or if they get worse: **Contact Your Doctor**

Doctor Signature:_____

Pharmacist Signature:_____

Furthermore, standard-dose PPIs appear to be equivalent to one another for the initial treatment of GERD:[1,27]

G5.1: There are no clinically important differences among standard doses of PPIs (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 20 mg) in treatment of symptomatic GERD, ENRD, and esophagitis.

The standard doses of PPIs available in Canada are displayed in Table 4. It should be noted that the evidence regarding the equivalence of PPIs is restricted to studies of initial therapy. There are no data regarding the safety and efficacy of switching to a different PPI if a patient has been successfully treated with a given agent.

Table 4: Doses of PPIs available in Canada[1]

	Standard-Dose	Low/Half-Dose	High/Double-Dose
Omeprazole	20 mg once daily	10 mg once daily	40 mg once daily
Lansoprazole	30 mg once daily	15 mg once daily	30 mg twice daily
Pantoprazole	40 mg once daily	20 mg once daily	40 mg twice daily
Rabeprazole	20 mg once daily	10 mg once daily	20 mg twice daily
Esomeprazole	20 mg once daily	N/A	40 mg once daily

Having concluded that standard-dose PPIs are the most efficacious choice for initial therapy for GERD, it is worth looking a little further into the supporting data. The CADTH Scientific Report

found that after four to eight weeks of treatment, symptom relief was attained in 55% to 75% of patients using PPIs and 27% to 58% of those using H2RAs.[1] A meta-analysis of five H2RA studies, four standard-dose PPI studies, and two double-dose PPI studies in uninvestigated GERD, conducted by CADTH as part of an economic analysis of GERD treatments, estimated a heartburn relief rate at four weeks of 35% (95% CI: 27% to 44%) for H2RAs, 58% (95% CI: 53% to 64%) for standard-dose PPIs, and 55% (95% CI: 48% to 62%) for double-dose PPIs.[28] While the number of double-dose studies was limited, these findings support initial therapy with standard-dose PPIs. According to another meta-analysis of short-term (two to eight weeks) empirical treatment for GERD, 54% of patients treated with PPIs were heartburn-free, compared with 32% of those given H2RAs [RR=0.66 (95% CI: 0.60 to 0.73)].[29] In reviewing these data, the superiority of PPIs is clear. It is also evident that approximately one-third to one-half of patients were adequately treated with H2RAs. It is therefore possible that H2RAs could be used effectively in patients with less severe GERD.[21] The challenge is to determine which patients will do well on H2RAs.

Switching therapy to a standard-dose PPI is also beneficial when a trial of H2RAs is unsuccessful in uninvestigated GERD. While limited to information from one RCT, CADTH's Evidence Statement G.1.1.1B notes the increased rates of heartburn relief observed at four and eight weeks after a switch to PPI therapy as compared with continued H2RA therapy in patients refractory to H2RAs (at eight weeks, 70% on PPIs experienced total heartburn relief versus 49% with H2RAs, p=0.0004):[1]

G1.1.1B: Standard-dose PPIs are more efficacious than continued H2RAs in patients with uninvestigated GERD who have incomplete response to a previous trial of H2RAs.

It is also important to note that, in a trial of patients poorly responsive to a six-week course of standard-dose ranitidine, double-dose ranitidine was not more effective than continued standard-dose therapy for the relief of heartburn symptoms.[30] Given its lower efficacy and higher cost compared with the most inexpensive PPIs, double-dose H2RA treatment should not be considered in H2RA-refractory patients.

ENRD

Approximately 70% of patients who undergo endoscopy will have endoscopy-negative reflux disease. Clinically, many uninvestigated GERD patients would fall into this category if endoscopy were performed. The difference in efficacy between the PPIs and H2RAs in ENRD studies is less pronounced than in uninvestigated GERD and esophagitis. A meta-analysis of eight H2RA studies and 14 PPI studies in ENRD, conducted by CADTH as part of an economic analysis of GERD treatments, estimated a heartburn relief rate of 43% (95% CI: 26% to 59%) for H2RAs and 53% (95% CI: 42% to 63%) for standard-dose PPIs at four weeks.[28] In another meta-analysis of short-term (two to four weeks) treatments for ENRD, patients were heartburn-free 53% of the time when treated with PPIs compared with 43% with H2RAs [RR=0.78 (95% CI: 0.62 to 0.97)].[29] We can conclude that the relative efficacy of PPIs in ENRD is lower than in erosive esophagitis. Furthermore, there is evidence that high doses do not elicit much greater response than standard doses of PPIs.[31-33]

The CADTH Scientific Report acknowledges the superiority of PPIs in Statement G2.1.1A. However, it is important to recognize that the differences were relatively small, with 53% heartburn relief with PPIs and 42% with H2RA. It is perhaps not surprising that this small difference did not translate into significant differences in quality-of-life measures:

G2.1.1A: PPIs are more efficacious than H2RAs, as initial therapy for improvement of heartburn symptoms at four weeks, in patients with ENRD.
G2.1.1B: PPIs are no more efficacious than H2RAs for improving quality of life in patients with ENRD.

Both standard and half-dose PPIs have been used as initial therapy in ENRD. The CADTH Scientific Report points to the greater efficacy of standard-dose therapy in Statement G2.1.2A, but it is important to recognize the limits of this Statement. Most trials showed either no differences or small differences of limited clinical significance.[34,35] Only one study reported a substantial difference (approximately 20%) between standard- and half-dose therapy.[1]

G2.1.2A: For patients with **ENRD**, half-dose PPI as initial therapy is less efficacious than standard-dose PPI therapy for heartburn resolution.

Erosive esophagitis

There have been a number of comparisons of the efficacy of H2RAs and PPIs in erosive esophagitis. According to one meta-analysis, 83.6% (95% CI: 79.1% to 88.1%) of patients treated with PPIs experienced healing versus 51.9% (95% CI: 46.9% to 56.9%) of patients given H2RAs.[36] A meta-analysis of 21 H2RA studies and 26 PPI studies in erosive esophagitis, conducted by CADTH as part of an economic analysis of GERD treatments, estimated a heartburn relief rate of 48% (95% CI: 38% to 58%) for H2RAs and 75% (95% CI: 69 to 82%) for PPIs at four weeks.[28] The superior efficacy of PPIs over H2RAs is reflected in the following CADTH Evidence Statement:[1]

G3.1.1A: PPIs are more efficacious than H2RAs for improving symptoms and for the healing of **erosive esophagitis**.

The time with gastric pH above four is similar for H2RA and PPIs on the first day of therapy, therefore it is unlikely that the two classes differ in the onset of effect. The superior efficacy of PPIs over H2RAs in esophagitis healing may be due to the observation that with repeat dosing, the percentage of time that gastric pH remains above four increases to a greater extent with PPIs than with H2RAs.[37] In general, PPIs also heal esophagitis more quickly than H2RAs, as reflected in the following CADTH Evidence Statement:[1]

G3.1.1B: The speed of improvement of heartburn and healing is faster with PPIs than H2RAs in patients with **erosive esophagitis**.

Standard-dose therapy is recommended for the initial treatment of erosive esophagitis. Half-dose therapy is considered less efficacious than standard doses and is not recommended for initial therapy.[14] The Canadian Consensus document does not recommend the use of twice-daily therapy as initial therapy.[14] Six RCTs showed no differences in healing rates of erosive esophagitis upon completion of initial treatment (four to eight weeks) with standard- and high-dose regimens.[1] The following CADTH Evidence Statement reflects this evidence and suggests that double doses are no better than standard doses for initial therapy:[1]

G3.1.2A: Doubling the standard daily doses of PPIs, as initial therapy, is no better than standard daily-dose PPI therapy for healing of **erosive esophagitis**.

There is some evidence that esomeprazole 40 mg may produce slightly higher short-term healing rates (by 3% to 6%) in severe esophagitis compared with standard-dose PPIs.[14] This has not been true in all studies,[38] and the clinical significance of these small short-term differences is a matter of debate.

The recommended duration of initial therapy is four to eight weeks.[14] Patients not responding to PPI therapy or whose symptoms worsen could be considered for endoscopy. Alternatively, there is evidence of increased healing and greater resolution of heartburn symptoms with increasing duration of therapy. In general, the best time to administer a PPI is before breakfast, but if a patient experiences night-time symptoms, better symptom control may be achieved by administration before the evening meal.[39] Double-dose therapy may also be considered in these patients.[14] If double doses are required, the dose should be split and given twice daily before breakfast and supper.[14,40]

Other therapies: Prokinetic/Promotility agents

Cisapride is no longer routinely available on the Canadian market and therefore will not be considered. Domperidone has not shown efficacy over placebo[14] and is associated with hyperprolactinemia in 10% to 15% of patients.[21] Metoclopramide is somewhat efficacious but appears to be less so than H2RAs.[41] The lower efficacy of metoclopramide should be considered in the context of a side effect profile that includes drowsiness, irritability, and extrapyramidal effects. Baclofen and bethanechol have also been tried, but once again there is limited efficacy data and considerable potential for adverse effects.[21] The combination of acid-suppression therapy (PPI or H2RA) and prokinetic agents does not seem to offer greater efficacy over acid-suppression therapy alone.[14] Current published data does not support the routine use of these agents in the initial or long-term management of GERD.

2.6 Treatment: Maintenance Therapy

Uninvestigated GERD

The Canadian Consensus Statement on GERD recommends that long-term therapy should be given at the lowest dose and frequency that is sufficient to maintain control of symptoms.[14] Patients who have responded well to initial treatment (for four to eight weeks) may discontinue therapy to assess the need for ongoing therapy. While many patients will relapse, a significant minority (approximately 20%) remains symptom-free for more than six months, as noted in the following CADTH Evidence Statement:[1]

> **G1.1.2A:** Approximately 20% of patients with **uninvestigated GERD** will remain asymptomatic off therapy for up to six months after a successful course of initial therapy (for four to eight weeks) with a PPI or H2RA.

In a US Veterans' Administration Hospital, it was found that 42% of patients needed to remain on a PPI, but 42% were successfully managed with H2RA and 15% were able to remain off medication.[42] Despite the success of step-down therapy and PPI discontinuation in this example, the greater overall efficacy of PPI maintenance therapy is acknowledged in the following CADTH Evidence Statements:[1]

G1.2.1A: PPI therapy in **uninvestigated GERD** is more efficacious than H2RAs for control of symptoms for up to six months.
G1.2.1B: In patients with **uninvestigated GERD** who have completed their initial course of PPIs, continued PPI therapy is more efficacious than step-down to H2RAs for providing symptom relief.

The severity of GERD at baseline may play an important role in the success of step-down therapy.[1] In general, if it is determined that PPIs need to be maintained, there are three main approaches to continued therapy:[1]

Continuous: Daily intake of medication for an indefinite period to prevent or minimize recurrent reflux symptoms and esophageal damage.

Intermittent: Daily intake of medication for a predetermined finite period (two to eight weeks) to produce healing and resolution of symptoms following relapse.

On-demand: Daily intake of a medication for a period sufficient to achieve resolution of 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.

On-demand therapy is a reasonable long-term strategy for uninvestigated GERD. This approach is superior to placebo and maintenance H2RA therapy, as noted in the CADTH Scientific Report (Evidence Statements G1.2.2.A and G1.2.2.2B). The higher efficacy of continuous PPI therapy over on-demand is also noted in the CADTH Scientific Report (Statement G.1.2.2.C), although the CADTH Expert Review Panel noted that the evidence supporting this Statement was limited (i.e., one poor-quality RCT). This study reported that 75.4% of the patients were completely or very satisfied with "on-demand" therapy compared with 82.2% of patients on continuous therapy.[43] The clinical relevance of this difference is questionable. Furthermore, the Canadian Consensus Conference suggests it is reasonable to use on-demand therapy for the maintenance of uninvestigated GERD.

G1.2.2A: For patients with **uninvestigated GERD** who respond to initial PPI therapy, subsequent "on-demand" PPI therapy is more efficacious than placebo.
G1.2.2B: For patients with **uninvestigated GERD** who respond to initial PPI therapy, subsequent "on-demand" PPI therapy is more efficacious than continuous standard-dose H2RAs.
G1.2.2C: For patients with **uninvestigated GERD** who respond to initial PPI therapy, subsequent "on-demand" PPI therapy is less efficacious than continuous standard regular-dose PPI therapy for heartburn resolution.

ENRD

The CADTH Scientific Report contains the following Evidence Statements regarding maintenance therapy in ENRD:[1]

G2.2.1A: Half-dose, continuous PPI therapy in ENRD is more efficacious than placebo for control of symptoms for up to six months.
G2.2.2A**:** For patients with ENRD who respond to initial PPI therapy, subsequent "on-demand" PPI therapy is more efficacious than placebo.

Although half-dose PPI and on-demand PPI (half-dose and standard-dose) therapy performed better than placebo in clinical trials, the differences were sometimes small.[1] In one RCT, half-dose PPI

therapy was superior to placebo at eight and 16 weeks, but not at 24 weeks in terms of heartburn relief (proportion with heartburn symptoms at eight weeks: 47% in PPI arm versus 60% in placebo arm; at 16 weeks: 37% versus 56%; at 24 weeks: 32% versus 34%).[1,28]

In on-demand PPI studies of ENRD, patients average only 0.3 PPI doses per day. A systematic review reported that "willingness to continue" with on-demand PPI therapy was significantly higher than for on-demand placebo (e.g., 83% were willing to continue with on-demand omeprazole 20 mg versus 56% with on-demand placebo). Three other RCTs also reported better symptom control and patient satisfaction with on-demand PPI versus on-demand placebo.[1] H2RAs have shown efficacy in ENRD, providing heartburn relief in 42.7% (95% CI: 26.3 to 59.1) of patients.[28] Evidence supporting the role of H2RAs in step-down from PPIs is lacking.[1]

Erosive esophagitis

In patients with erosive esophagitis who have been treated successfully with initial therapy, 38% will not relapse during the first six months off therapy.[24] However, most patients do relapse, and therefore continuous therapy may be necessary for many patients. CADTH Evidence Statements G3.2.1A, G3.2.1B, while supported by limited evidence, establish the efficacy of maintenance standard-dose PPIs over H2RAs in erosive esophagitis.[1] This is particularly true for patients with more severe esophagitis.

G3.2.1A: Long-term maintenance PPI therapy (i.e., up to 12 months) in **erosive esophagitis** is more efficacious than placebo for prevention of symptomatic and endoscopic relapse.
G3.2.1B: Long-term maintenance PPI therapy (i.e., up to 12 months) in **erosive esophagitis** is more efficacious than H2RAs for prevention of symptomatic and endoscopic relapse.

Although other approaches are generally less efficacious, they may be suitable for patients with milder disease.[27] With respect to a strategy of on-demand dosing, the CADTH Scientific Report notes that this approach is less efficacious than continuous PPI therapy:[1]

G3.2.3A: For patients with **erosive esophagitis** who respond to initial PPI therapy, subsequent "on-demand" PPI therapy is less efficacious than continuous standard-dose PPI therapy.

One study of on-demand PPI versus placebo in patients with mild to moderate esophagitis reported that the mean consumption of PPIs was about 0.7 doses per day.[44,45] Although on-demand dosing in patients with milder disease (i.e., ENRD) is a reasonable option since it results in much less PPI consumption than continuous dosing, consumption in patients with erosive esophagitis offered on-demand therapy is nearly as high as with continuous dosing. Therefore, a strategy of on-demand may not be preferred in most patients with esophagitis.[44]

Other step-down regimens intended to limit PPI consumption have also been tested in clinical trials. These include intermittent (three days per week or weekend) therapy and half-dose PPI therapy. The CADTH Scientific Report contains the following Evidence Statements regarding these approaches:[1]

G3.2.1D: In patients with **erosive esophagitis** who have completed an initial course of PPIs, half-dose PPI maintenance therapy is more efficacious than step-down to H2RAs for preventing relapse and providing improvement of symptoms.

G3.2.2A: Half-dose PPIs are less efficacious than standard-dose PPIs as maintenance treatment for the prevention of symptomatic and endoscopic relapse in patients with **erosive esophagitis**.
G3.2.4A: In patients with **erosive esophagitis**, intermittent PPI therapy (e.g., three days per week) is less efficacious than continuous PPI therapy.

Intermittent PPI therapy was shown to be inferior to continuous therapy in terms of maintenance of esophagitis healing and symptom remission in one systematic review (moderate to severe symptoms recurred in 15% of continuously dosed patients versus 67% of intermittently dosed subjects, p<0.001). However, there is a paucity of data in patients with mild esophagitis.[1,21] Half-dose PPI therapy outperformed H2RA therapy in terms of proportion with relapse of esophagitis (39% in PPI arm versus 66% in H2RA arm, RR=0.57 [95% CI: 0.47 to 0.69]), although relapse in both arms was quite frequent.[1,46] Standard-dose PPIs administered continuously have been found to be more effective than half-doses in terms of maintenance if esophagitis healing and symptom remission. However, the difference in the latter outcome may not be large. In one systematic review, 31% on standard-dose PPI had significant symptoms at 24 to 52 weeks compared with 36% on half-doses (p<0.009). In the same study, esophagitis relapse occurred in 18% on standard doses versus 29% on half-doses (p<0.00001). The Canadian Consensus document noted that half-dose therapy can maintain esophagitis remission, but the results have been variable (35% to 95%) in patients with erosive esophagitis.[14]

Patients with severe erosive esophagitis may require daily therapy.[14] Daily PPI therapy is recommended for those with Barrett's esophagitis, but it remains unclear if this slows the progression of Barrett's.[47] This same caution applies to patients with complications of erosive esophagitis complicated by strictures, as reflected in the following CADTH Evidence Statement that highlights the superior efficacy of continuous PPI therapy versus H2RAs:[1]

G3.2.3A: For patients with **erosive esophagitis** who respond to initial PPI therapy, subsequent "on-demand" PPI therapy is less efficacious than continuous standard-dose PPI therapy.
G3.2.1C: Long-term PPI therapy is more efficacious than H2RAs for **erosive esophagitis** complicated by strictures.

Combination PPI and H2RA therapy

In general, the combination of H2RAs and PPIs is not warranted in the treatment of GERD. In a patient with breakthrough GERD symptoms at night, the addition of an evening H2RA to daily PPIs has been suggested. Although this strategy appeared to increase nocturnal gastric pH, there was no evidence of a clinical improvement in symptoms. More recent data suggest that an evening dose of PPI is as effective as ranitidine, and that tachyphylaxis to nocturnal acid suppression by H2RA may develop as early as one week after therapy is started.[14]

Helicobacter pylori

It is not necessary to routinely test for *H. pylori* in patients receiving initial or long-term treatment for GERD. Furthermore, eradication of *H. pylori* does not have a clinically relevant impact (positive or negative) on the long-term outcome of GERD. *H. pylori* potentiates the acid suppressive effects of PPIs, an effect that may produce greater symptom relief in infected patients.[48] *H. pylori* is a class I carcinogen and although it is not necessary to test for it prior to treating GERD, if found, standard eradication therapy should be offered.[22] Despite the acid-reducing effects of *H. pylori,* its eradication does not seem to influence the dose of PPI required, reflux symptoms, or relapse rate.[49,50] A few

studies of reflux-dominant uninvestigated dyspepsia have even reported a decrease in heartburn symptoms after *H. pylori* eradication.[51]

Survey data collected for the purpose of an economic analysis of GERD treatments suggest that family practitioners are much more likely to test for *H. pylori* in GERD than gastroenterologists. With initial treatment, family practitioners tested 16.4% of the time with a higher rate of testing after failure of H2RAs (27.3%) or failure of PPIs (34.6%). Upon the recurrence of symptoms, family practitioners tested 32.7% to 43.6% of patients. This compares with just 2.1% to 6.3% of gastroenterologists who tested in similar circumstances.[28]

Therefore, although there is no particular reason to seek out *H. pylori* when treating GERD, eradication treatment should be offered to all patients in whom *H. pylori* is detected.[22]

Barrett's epithelium

Barrett's epithelium can be suspected if there is a change in the epithelium of the esophagus beyond the limit of the gastroesophageal junction on endoscopy. There is a natural division between the squamous epithelium of the esophagus and the reddish gastric columnar epithelium that is visible as the Z-line or squamocolumnar junction. This Z-line usually occurs at the gastroesophageal junction; with the damage induced by GERD, the Z-line may shift proximally along the esophagus. This indicates that the normal squamous epithelium of the esophagus has been replaced by columnar epithelium through a process known as specialized intestinal metaplasia.[47] The diagnosis of Barrett's esophagus is confirmed if histological examination of an endoscopic biopsy reveals specialized intestinal metaplasia. An area of change that extends less than three centimetres is called "short-segment Barrett's esophagus" with longer areas of change referred to as "long-segment Barrett's esophagus." Short-segment (10% to 15%) is more common than long-segment Barrett's esophagus (3% to 5%).[52]

The presence of intestinal metaplasia predisposes GERD patients to esophageal adenocarcinoma.[47] While esophageal adenocarcinoma rates are rising, it is unclear if this is related to the increasing prevalence of GERD in our society.[47] The risk of esophageal adenocarcinoma is higher in white males with long standing (>20 years), frequent, and severe GERD.[14] Using patients with symptoms of GERD for less than one year as a reference, patients with GERD for one to three years are three times more likely and patients with GERD for >10 years are 10 times more likely to have Barrett's esophagus.[53] Older reports suggest a 1% to 2% rate of esophageal cancer with Barrett's epithelium, however recent studies estimate a rate of 0.4% compared to 0.07% in the general population.[47] It has been suggested that longer segment disease is more likely to be associated with greater risk of cancer, but this has not been proven.[54] Having Barrett's esophagus does not affect longevity, likely because of the relatively low rate of conversion to cancer.[47]

While PPI therapy of Barrett's makes theoretical sense, it has not been proven to prevent the development and progression of Barrett's epithelium and has not been demonstrated to reduce the incidence of esophageal adenocarcinoma. The lack of evidence suggests that aggressive anti-reflux therapy is probably not warranted in an effort to reduce cancer and therapy should be prescribed to control signs and symptoms.[47] It is suggested that an endoscopy for Barrett's esophagitis be performed after a course of treatment because it may allow for more accurate diagnosis of Barrett's by reducing inflammation that could be misinterpreted as dysplasia.

Endoscopic testing to detect Barrett's epithelium is controversial. Testing patients with risk factors (e.g., GERD >10 years, over age of 50, white males) or testing "once in a lifetime" have been

suggested. Such strategies are of high cost and unproven benefit. For example, it was estimated that the risk of esophageal adenocarcinoma (0.00065/patient/year) is lower than the risk of complications from endoscopy.[55] Furthermore, there is no evidence that screening of patients with long-standing GERD reduces mortality due to esophageal adenocarcinoma.[14] Finally, 40% of esophageal adenocarinomas are not associated with reflux, hence a surveillance strategy aimed at Barrett's esophagus would not impact a significant proportion of cases.[47]

Once Barrett's esophagus is detected, endoscopic surveillance is controversial but suggested by the Canadian Consensus Guidelines.[14] With low grade dysplasia, endoscopy is suggested annually until no dysplasia is found. In the absence of dysplasia, endoscopy should be performed every two to five years. Unfortunately, endoscopic surveillance is an imperfect predictor of malignancy and it may be difficult to distinguish low-grade dysplasia of a neoplastic nature from the injury response of normal tissue. Even with high-grade dysplasia, only 32% of patients had progressed to esophageal adenocarcinoma after eight years of follow-up.[56] As such, there is only modest evidence that surveillance results in earlier detection of cancer and better survival rates.[14] However, 93% to 96% of esophageal cancers occur in patients who did not have a prior diagnosis of Barrett's epithelium.[57] Economic modeling suggests a cost per QALY of $98,000 for every five years and $590,000 for every two years compared with approximately $20,000 for breast and colon cancer screening.[14,58]

Treatment of atypical GERD

As discussed in the preceding pages, atypical symptoms that have been attributed to GERD include asthma, chronic cough, and laryngeal symptoms (hoarseness, pharyngitis, globus, throat clearing). It is unclear if these atypical symptoms are truly related to GERD.[14] Relatively high doses of PPIs have been tried to address these symptoms.[15] A good-quality systematic review reported that PPIs did not improve FEV_1, morning peak expiratory flow in patients with asthma and concomitant GERD. Another good-quality systematic review reported that PPIs were not significantly better than placebo in reducing laryngeal symptoms, presumed to be related to GERD. A third systematic review reported no significant difference between PPIs and placebo for relief of cough with or without GERD.[1]Although sample size limitations, variability in exclusion/inclusion criteria across trials, and the questionable validity of some outcome measures are important limitations of the available data, there is insufficient evidence to recommend the use of PPIs for these atypical symptoms. This was reflected in the following Evidence Statements in the CADTH Scientific Report:[1]

G4.1: PPIs are not efficacious in improving asthma in patients with concomitant GERD.
G4.2: PPIs are not efficacious in improving laryngeal symptoms (i.e., cough, throat clearing, globus, hoarseness, sore throat) associated with reflux.
G4.3: PPIs are not efficacious in improving chronic cough with or without GERD.

2.7 Recommended Reading

Armstrong D, Marshall JK, Chiba N, Enns R, Fallone CA, Fass R, et al. Canadian consensus conference on the management of gastroesophageal reflux disease in adults: update 2004. *Can J Gastroenterol* 2005;19(1):15-35.

DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005;100(1):190-200.

Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. On-demand therapy of gastroesophageal reflux disease. *Am J Gastoenterol* 2007;102:642-653.

Spechler SJ. Clinical practice: Barrett's esophagus. *N Engl J Med* 2002;346(11):836-42.

3 SECTION 3: PEPTIC ULCER DISEASE

3.1 Epidemiology

Peptic ulcer disease (PUD), unlike dyspepsia and GERD, is relatively simple to define as ulceration(s) of the gastric and/or duodenal mucosa.[24] An ulcer is a "disruption of the mucosal integrity of the stomach and/or duodenum leading to a local defect or excavation due to active inflammation."[59] The lifetime incidence rate is approximately 10% for men and 4% for women; although several key factors substantially impact a given person's risk of developing ulcers.[24] A study published almost a decade ago in the United States estimated that the economic cost of peptic ulcer disease was about $5.7 billion, with $2.7 billion coming from hospitalization costs, $1.6 billion from physician office visits, and $1.4 billion from lost productivity.[60] This study did not estimate the costs of medications used to treat the condition. Regardless of the precise cost impact, management of PUD places a significant burden on the Canadian health care system.

Complications of PUD

A differentiating aspect of PUD versus other gastrointestinal disorders such as dyspepsia or GERD is the greater possibility of developing severe, even life-threatening complications. The most common complication is gastrointestinal bleeding, estimated to occur in approximately 15% of patients with PUD, although the rate increases in those over the age of 60.[59,61] The mortality associated with acute gastrointestinal bleeding is 6% to 10%.[61]

The next most common complication is perforation. This can occur in patients with both gastric and duodenal ulcers, although perforations in the former are generally more severe.[61] The incidence of PUD-related perforation is approximately 7% although the rates of NSAID-associated ulcer perforation is rising due to increased utilization.[59,61]

The least common complication is gastric outlet obstruction which occurs in only 2% of patients with PUD.[59,61] Obstruction can occur from the swelling and edema of an ulcer site located in the pyloric region of the stomach.[59] These obstructions tend to resolve when the ulcer is treated. Obstruction can also occur from scarring of active ulcers, a condition that may require surgical intervention.[59,61]

3.2 Pathophysiology and Risk Factors

A majority of peptic ulcers can be attributed to one of three contributing factors: infection with *H. pylori*, non-steroidal anti-inflammatory (NSAID) associated injury, and stress-related mucosal damage.[59,62] The latter leads to acute ulcer formation in critically ill, hospitalized patients.[62] The diagnosis, prevention, and management of this acute condition will not be discussed in this upskilling document. The former two contributing factors will be reviewed individually, followed by a brief discussion of acid hypersecretory conditions.

H. pylori

The infection rate for *H. pylori* in the general Canadian population varies between 20% to 40% with rates increasing with age.[22] However, many patients have asymptomatic infection, and only 10% to 15% of patients infected with *H. pylori* actually develop ulceration.[59] Overall, rates of infection have been decreasing in industrialized countries over the past decades presumably due to improved sanitation.[59] Besides increased age, other risk factors for *H. pylori* infection include:[59]

- birth or residence in a developing country
- domestic crowding
- unsanitary living conditions
- food or water contamination
- exposure to gastric content of an infected individual.

The *H. pylori* infection rate in patients with non-NSAID associated duodenal ulcers is between 80% and 90%, and for non-NSAID associated gastric ulcers the rate is 70%.[22] The relationship between *H. pylori* infection and the development of ulcers is complex. The bacterium compromises the integrity of the mucosal membrane through enzymes such as urease, virulence factors, and adherence to the mucosa.[61] The presence of the bacteria also activates the host inflammatory response, causing an increase in the migration of neutrophils and macrophages to the area. This further weakens the mucosal lining, making it susceptible to erosion. Finally, the bacteria may induce mucosal damage by causing acid hyper-secretion.[61]

NSAID-associated ulcer

The prevalence of gastric ulcers in patients taking chronic NSAIDs for rheumatoid arthritis is 12% to 30%, much higher than ulcer rates in the general population.[1] NSAID use has a predominant role in ulcer development, especially gastric ulcer. Two different mechanisms by which NSAIDs cause peptic ulcers are postulated.[59,61] The first mechanism is direct mucosal irritation from contact of acidic drugs with the GI epithelium. ASA is the most acidic and thus most damaging of the NSAIDs.[61] Even low-dose daily ASA therapy has the potential to induce ulceration. After NSAID ingestion, minor hemorrhaging of the sub-epithelium begins within 15 to 30 minutes due to the irritant effects of the drug.[61] These effects are quickly compensated for by natural defence mechanisms. However, prolonged utilization and a variety of other factors may compromise the ability to recover from NSAID-induced damage. Strategies to avoid or minimize direct GI toxicities such as use of enteric-coated preparations and alternative delivery routes (topical, rectal) may impact this mechanism of injury, but have no effect on prostaglandin synthesis (the second mechanism) and, as such, are not a fail-safe way of preventing ulcers.

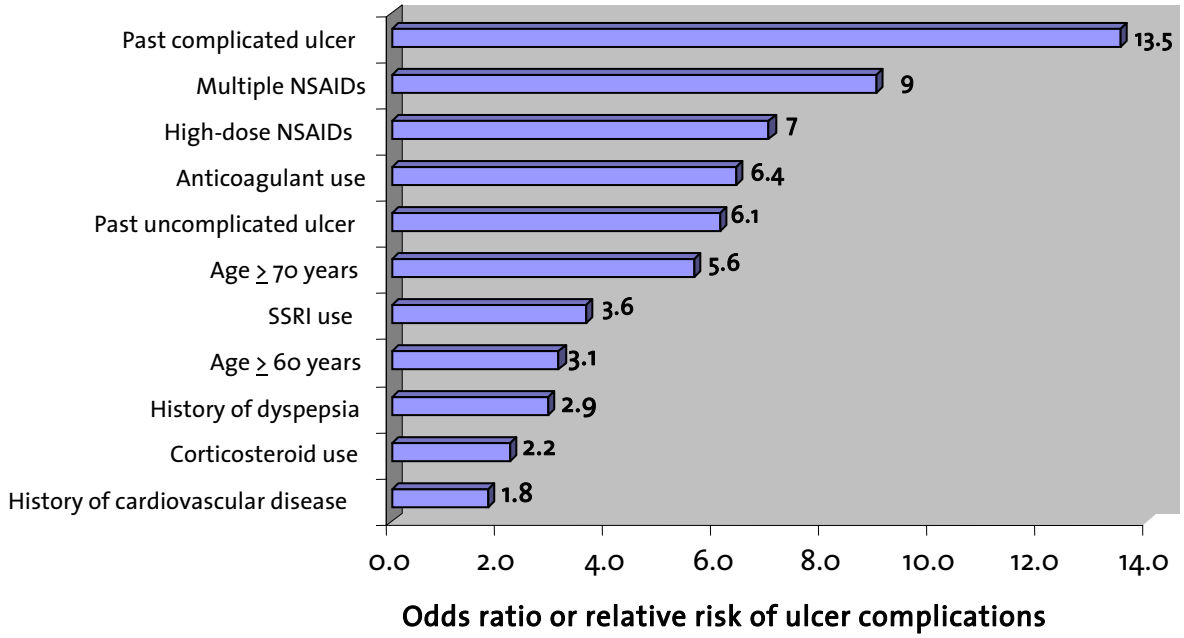
The second mechanism of NSAID-associated GI injury involves prostaglandins, endogenous hormone-like substances that contribute to the production of the GI mucosa. Through inhibition of the cyclooxygenase (COX) enzyme, specifically COX-1, NSAIDs inhibit the production of

prostaglandins, consequently disrupting processes that maintain GI mucosal integrity.[61] Most NSAIDs inhibit both COX-1 and COX-2, albeit to varying degrees. The COX-2 specific anti-inflammatory agents (lumiracoxib and celecoxib) avoid the inhibition of COX-1 and thus may have a more favourable GI toxicity profile.[24]

There are also other factors that influence an individual's risk of NSAID-induced ulcer complications. The relative risks associated with these factors are shown in Figure 7.

It should be noted that, although the endoscopically identified rate of ulcers in NSAID users may be over 25%, some estimate that 85% of these will never become clinically apparent.[66] This is important to remember when evaluating the studies conducted on ulcer treatment and prevention. Most studies use endoscopic ulcer healing and prevention as a surrogate marker for treatment efficacy rather than reductions in clinically important endpoints such as ulcer complications, since the former are much more frequent and therefore can be studied in smaller trials of shorter duration.

Figure 7: Risk factors for NSAID-associated GI complications [62-65]



Acid hyper-secretion

A certain level of acid and pepsin is required for the formation of ulcers associated with *H. pylori* and NSAIDs.[61] Once the mucosal barrier has been compromised by one of these factors, acid and pepsin are responsible for the actual erosive process that causes an ulcer. Patients with Zollinger-Ellison syndrome have basal hyper-secretion of acid which itself can lead to ulcer formation.[61] The control of acid production in this syndrome is therefore key to the prevention of ulcer development.

3.3 Diagnosis

PUD usually presents with burning epigastric pain that gets worse with fasting and is relieved by eating, although symptoms are highly variable and depend on the location and severity of the ulcer.[59] There is also great inter-patient variability in symptoms, with many patients remaining completely asymptomatic until ulcer complications occur.[61] Symptom-based diagnosis is therefore quite unreliable.

In order to conclusively determine the presence of ulcers, invasive testing in the form of barium radiographic studies or endoscopic investigation must occur.[59] Barium studies have been the traditional initial diagnostic measure, although they are less sensitive at detecting ulcers (especially small ones) than endoscopy.[61] The advantage of barium studies is that they are safer, cheaper, and more accessible, compared with endoscopic procedures.[61] The advantage of endoscopy, beyond increased sensitivity and specificity, is the ability to conduct diagnostic testing such as tissue biopsy (for cancer and *H. pylori* testing).[59]

In the general practice setting, routine endoscopy or barium studies are impractical. Therefore, determining a patient's *H. pylori* infection status is an important step in the preliminary investigation of patients presenting with possible PUD. Determining this status can be done through non-invasive diagnostic tests, which include blood serology, urease breath test (UBT), and stool antigen testing. The usefulness of stool antigen testing was considered in the most recent Canadian Helicobacter Study Group recommendations. They do not recommend stool antigen testing for the diagnosis of *H. pylori*.[67] The main reason for not accepting this test is lack of experience. A majority of the evidence that supports the sensitivity and specificity of the stool antigen test comes from clinical trials in which the laboratories had specialized training.[67] Whether the same level of accuracy is achievable outside these controlled settings is yet to be determined. However, the stool antigen test has been accepted as a method of diagnosing *H. pylori* infection in some countries.[68]

Serological testing, whereby blood is sampled to detect antibodies against *H. pylori*, is a popular diagnostic test because it is inexpensive and easy to conduct. However, concerns have been raised about the accuracy of this diagnostic technique, especially in populations with a low prevalence of *H. pylori* infection.[22] Since antibodies to *H. pylori* may persist for six to 12 months after successful eradication, this test is not specific for active infection, hence it cannot be used to determine the success of eradication therapy.[22,68]

The UBT is considered the preferred non-invasive diagnostic test.[67] Although more expensive than serology, it demonstrates a sensitivity and specificity of >90%.[59] Since the UBT is specific for active infection, it can be used to confirm eradication.[24]

3.4 Treatment: *H. pylori* Eradication

The focus of PUD treatment is management of the factors implicated in ulcer formation. The treatment of ulcer in *H. pylori*-infected patients will be the focus of this section, followed by NSAID-associated ulcer treatment and prophylaxis in the next.

For patients presenting to their family physician with symptoms consistent with peptic ulcer disease (i.e., uninvestigated dyspepsia), the CanDys Working Group advocates a "test and treat" approach to *H. pylori* infection.[3] The Canadian Helicobacter Study Group also recommends a similar

approach.[67] The evidence relating to this strategy was discussed in greater detail in Section 1 of this upskilling document. Once a patient is determined to be *H. pylori*-positive, eradication of the infection is recommended. The main reason for this is that, in patients with established PUD who are *H. pylori*-infected, eradication leads to substantial reductions in recurrence rates of both gastric (from 67% to 6% recurrence) and duodenal (from 59% to 4% recurrence) ulcers.[59] Another reason for eradicating *H. pylori* is its role in the development of gastric mucosal-associated lymphoid tissue (MALT) lymphoma and gastric cancer.[59,67]

Treatment regimens

There are a number of treatment regimens that have been studied in the eradication of *H. pylori*. The regimens include one or more acid suppressants in conjunction with two antibiotics. The Canadian Helicobacter Study Group has maintained a requirement that any therapy it recommends as first-line must have an average eradication rate of at least 80%.[67,69] As such, three regimens are recommended for first-line therapy (Table 5).[22,67]

Table 5: Canadian Helicobacter Study Group recommended eradication therapies

Treatment Regimen	Duration
Standard-dose PPI twice daily OR Rantidine bismuth citrate twice daily† AND Clarithromycin 500 mg twice daily AND Amoxicillin 1,000 mg twice daily	7 days
Standard-dose PPI twice daily OR Rantidine bismuth citrate twice daily† AND Clarithromycin 500 mg twice daily AND Metronidazole 500 mg twice daily	7 days
Standard-dose PPI twice daily AND Metronidazole 375 to 500 mg twice daily AND Tetra cycline 375 or 500 mg four times daily AND Bismuth subsalicylate 262 mg four times daily	10 to 14 days

Adapted from Ontario Program for Optimal Therapeutics 2000.[24]
† Removed from the Canadian market in 2000.[70]

The group further recommends that, in the event of treatment failure with one of the listed regimens, one of the other two regimens should be considered.[69]

The choice of PPI for use in the *H. pylori* eradication regimens was assessed in the CADTH Scientific Report and resulted in the development of the following Evidence Statement.[1]

P1.1.1A: All PPIs have similar efficacy in triple-therapy regimens for *H. pylori* eradication.

This statement was supported by five good-quality systemic reviews, two poor-quality systematic reviews, and two good-quality RCTs. In one good-quality systematic review, Vergara *et al.* identified 14 trials that directly compared different PPIs in eradication regimens.[71] Without exception, the meta-analysis showed no significant difference between the different PPIs. The following comparisons were reported in the analysis (percentages represent pooled eradication rates):

- Omeprazole versus lansoprazole, 74.7% versus 76% (OR 0.91 - 0.69-1.21) NS
- Omeprazole versus rabeprazole, 77.9% versus 81.2% (OR 0.81 - 0.58-1.15) NS
- Omeprazole versus esomeprazole, 87.7% versus 89% (OR 0.89 - 0.58-1.35) NS
- Lansoprazole versus rabeprazole, 81% versus 85.7% (OR 0.77 - 0.48-1.22) NS

It should be noted that the only generic PPI available (omeprazole) does not have the indication for *H. pylori* eradication. Because the product is interchangeable with name-brand Losec® in a number of jurisdictions, practitioners may consider this lack of official indication to be of little concern. However, based on civil action taken by AstraZeneca against the Government of Manitoba over utilization of the generic product for the indication of *H. pylori* eradication,[72] many jurisdictions have modified their coverage criteria to specifically exclude the use of Apo-omeprazole® in these cases.

PPI dosing

All of the comparisons in the Vergara *et al.* systematic review were of standard daily doses of PPIs administered twice daily.[71] This dosing strategy is consistent with most eradication trials as noted in the CADTH Scientific Report.[1] However, once-daily strategies have also been studied in some regimens. The following evidence statements from the Scientific Report discuss these findings.

P1.1.2A: Standard-dose PPI administered twice daily is **more efficacious** than standard-dose PPI administered once daily (when used in a PAC triple-therapy regimen) for *H. pylori* eradication.
P1.1.2B: Standard-dose PPI administered twice daily is **no more efficacious** than standard-dose PPI administered once daily (when used in a PMC triple-therapy regimen) for *H. pylori* eradication.

The evidence for these statements comes from a single good-quality meta-analysis that compared PPI dosing schedules (once daily versus twice daily) in two different eradication regimens: PAC (PPI, amoxicillin, and clarithromycin), and PMC (PPI, metronidazole, and clarithromycin).[73] Overall, eradication rates were significantly greater with the twice-daily dosing schedule compared with once-daily dosing [pooled eradication rates were 83.9% versus 77.7%, respectively, OR=1.51 (95% CI: 1.23 to 1.85); p<0.01, NNT=16].[73] However, when the results were analyzed by treatment regimen, the overall difference appeared to be driven by the PAC regimen in which the eradication rate was significantly higher in the twice-daily arm compared with once daily [pooled eradication rates were 84.5% versus 75.9%, respectively, OR=1.73 (95% CI: 1.38 to 2.18)].[73] In contrast, there was no significant difference between the two arms for the PMC regimen [OR=1.01 (95% CI: 0.60 to 1.69)]. However, it was noted in the Scientific Report that the PMC results was based on only two studies that included a total of 304 patients, whereas the analysis of PAC treatment included nine trials with a total of 1,870 patients.[1]

From a clinician's point of view, the value of differentiating the dose of PPI based on the choice of eradication regimen is debatable. The cost of a second PPI dose over the course of a seven-day

treatment course would amount to, at most, $16. Furthermore, a short course of double-dose PPIs is unlikely to result in a substantial increase in adverse drug events. Finally, the Canadian Helicobacter Study Group has attempted to ingrain a treatment edict regarding *H. pylori* eradication of "triple regimens are as easy as 1, 2, 3 – one week, twice a day, three medications".[22] An attempt to contradict this message for only the PMC regimen may lead to confusion among practitioners.

Therapy duration

The recommended duration of therapy is also a matter of debate. This is recognized in the following Evidence Statements:[1]

P1.1.3A: *H. pylori* eradication therapy with triple therapy (PAC and PMC) for seven days is **less efficacious** than 14 days.
P1.1.3B: *H. pylori* eradication therapy with triple therapy (PAC and PMC) for seven days is **as efficacious** as 10 days.

These statements are supported with evidence of relatively limited quality. A meta-analysis conducted by Calvet *et al.* provided most of the evidence for this Statement.[74] This study found no significant differences in eradication rates between 10-day and 14-day treatment regimens, nor did it find a difference between seven-day and 10-day regimens.[74] Treatment duration of 14 days resulted in a 9% absolute increase in eradication rates over seven-day treatment.[74] This analysis was subsequently updated in 2004 by the North of England Dyspepsia Guideline Group.[68] The updated analysis confirmed that the seven-day regimen had a significantly lower eradication rate (67.8%) versus 14 days (77.2%). The NNT for seven extra treatment days to get one extra eradication was 11 patients. The authors further noted that there was a trend towards greater eradication with the 10-day regimen over the seven-day but the difference was statistically non-significant.[68]

The North of England Dyspepsia Guideline Group further examined the cost-effectiveness of 14-day versus seven-day treatment from the perspective of the UK health care system.[68] They concluded that the additional benefit achieved by the longer duration did not justify the greater cost. Hence, it recommended that the seven-day regimen be used as first-line therapy. This recommendation is in line with the Canadian Helicobacter Study Group recommendations[22] as well as the reimbursement criteria in four Canadian provinces that specify treatment duration.[1] Careful consideration of individual provincial coverage restrictions is required prior to pursuing an educational intervention on this topic.

Eradication follow-up

As indicated throughout this section, eradication rates with standard therapy are quite high (approximately 80%). Also, eradication therapy is highly effective at reducing recurrence of uncomplicated ulcers. As such, routine confirmatory tests (either by endoscopy or non-invasive means) are usually not required.[22] The exception to this is patients who remain symptomatic and those who have had bleeding or perforated ulcers.[22] When re-testing is required, it should occur at least four weeks after the completion of the eradication regimen or administration of other antibiotics or bismuth and at least seven days after stopping a PPI or H2RA.[22] Recent use of these agents can suppress *H. pylori* and lead to false negative results.[22,24,75]

The continuation of a PPI after eradication therapy, although not recommended in the Canadian or Ontario guidelines,[22,24,67,69] does occur in clinical practice. In fact, the practice of continuing PPI monotherapy for three weeks after one-week eradication therapy is considered to be a traditional

treatment strategy in patients with PUD.[76] The evidence for this practice was considered in the CADTH Scientific Report:[1]

> **P1.2.1A:** Continued treatment with PPI after a course of *H. pylori* eradication therapy does not produce higher ulcer healing rates than eradication therapy alone in *H. pylori*-infected patients with uncomplicated duodenal ulcer. **This does not apply to gastric ulcers.**

A meta-analysis by Gisbert *et al.* provides the evidence for this statement.[76] This analysis was restricted to studies of non-NSAID-associated ulcers and assessed ulcer healing rates for patients given seven-day eradication therapy alone versus those that extended PPI treatment for two to four weeks. The six studies identified showed no significant difference in ulcer healing rates upon assessment at weeks four to nine. The healing rate with eradication therapy alone was 91%, whereas that of eradication plus PPI monotherapy for two to four weeks was 92% (OR 1.11, 95% CI: 0.71 to 1.74).[76] It was noted in the Evidence Statement that these results do not apply to gastric ulcers.[1] This is because, of the six studies in the meta-analysis, only one included patients with gastric ulcers as a subset of the population.[76] Therefore, there is insufficient data to extend this statement to gastric ulcers. In addition, the authors noted that gastric ulcers are generally more refractory to treatment, requiring greater time to heal compared with duodenal ulcers.[76] In the end, there is no clear message regarding the extension of PPI mono-therapy after completion of a *H. pylori* eradication regimen in patents with gastric ulcers. At most, PPI treatment for a total of four weeks[76] could be considered a conservative management strategy until further research is conducted.

3.5 Treatment: NSAID-Associated Ulcers

Agent of choice

Patients using NSAIDs who present to their primary care physician with dyspeptic symptoms represent a management challenge. The CanDys Working Group recommends that, if possible, the NSAID should be discontinued and the patient monitored for improvement in symptoms.[3] Should it be impossible to discontinue the NSAID or the patient's symptoms do not improve with discontinuation, the physician has a choice to either investigate or treat empirically with a PPI, cytoprotective, high-dose H2RA, or switch anti-inflammatory therapy to a COX-2 selective NSAID.[3] CanDys rated the evidence for these recommendations as grade C (i.e., based on consensus) as there is little research to dictate the most appropriate course of action.

In patients diagnosed with NSAID-associated ulcer(s), the therapeutic goal is to cure the ulcer and prevent recurrence. As such, discontinuation of the offending agent (if possible) is recommended. Barring this, pharmacological intervention is also required. The CADTH Scientific Report contains the following Evidence Statement relating to NSAID-associated ulcer treatment.[1]

> **P2.1.1A:** Standard-dose PPI therapy for four to eight weeks produces **higher healing rates** of NSAID-associated ulcers than H2RAs, when NSAIDs are continued.
> **P2.1.1B**: Standard-dose PPI therapy for four to eight weeks produces **higher healing rates** of NSAID-associated ulcers than 800 µg/day misoprostol, when NSAIDs are continued.

The first statement is based on evidence from two RCTs, one comparing lansoprazole 15mg and 30 mg to ranitidine 300 mg/day and the other omeprazole 20 mg and 40 mg to the same dose of ranitidine.[77,78] The ulcer healing rates at eight weeks are shown in Table 6. It should be noted that

the endpoint measures of the two trials were different. In Agrawal *et al.*, endoscopically evaluated ulcers healing was the primary measure while in Yeomans *et al.* it was a combined endpoint of ulcer healing, <5 erosions and no more than mild dyspepsia symptoms.[77,78]

All doses of PPIs were superior to ranitidine, with NNT's of between four and seven in the two studies. There were no significant differences between PPI doses.[77,78] A similar study conducted more recently by Goldstein *et al.* compared esomeprazole 20 mg and 40 mg with ranitidine 150 mg given twice daily in the healing of NSAID-associated gastric ulcers.[79] The rates of ulcer healing at eight weeks was 91.5% for esomeprazole 40 mg, 88.4% for esomeprazole 20 mg, and 74.2% for ranitidine (p<0.005 for both doses of esomeprazole versus ranitidine). Although the statistical significance of the difference between the two doses of esomeprazole was not reported, similar healing rates were observed at both four and eight weeks. These results confirm Evidence Statement P2.1.1A as well as the associated contextual information indicating that higher doses are not superior to standard doses of PPIs for healing of NSAID-associated ulcer.[1]

Table 6: RCTs of PPIs versus ranitidine for healing of NSAID-associated ulcers

Study	Agent	Proportion successfully treated at 8 weeks*	Significance vs. Rantidine
Agrawal *et al.* 2000 [77]	Lansoprazole 15 mg/day Lansoprazole 30 mg/day Ranitidine 300 mg/day	69% 73% 53%	p=0.01 p<0.001
Yeomans *et al.* 1998 [78]	Omeprazole 20 mg/day Omeprazole 40 mg/day Ranitidine 300 mg/day	80% 79% 63%	p<0.001 p=0.001

* The endpoint in Agrawal *et al.* was healing of gastric ulcer. In Yeomans *et al.*, a composite endpoint consisting of ulcer healing, <5 erosions, and no more than mild dyspepsia symptoms was measured.

The evidence for the second Evidence Statement comparing PPIs to misoprostol consisted of a single good-quality RCT. In this study, Hawkey *et al.* used a composite endpoint of "success rate," consisting of ulcer healing, number of erosions, and symptoms of dyspepsia, as the primary endpoint.[80] There was no significant difference between omeprazole 20 mg and 40 mg and misoprostol 800 µg in the primary endpoint.[80] However, when only ulcer healing was considered, omeprazole 20 mg produced higher healing rates of both gastric and duodenal ulcers. As expected, the side effect profile was significantly worse for misoprostol compared to omeprazole, with more than twice the number of patients reporting gastrointestinal adverse effects such as diarrhea and abdominal pain.[80] This study also provided further indication that standard-dose PPI is sufficient to heal NSAID-associated ulcers, since healing rates were similar for the two doses of omeprazole. Ulcer healing data from this trial are presented in Table 7.

Table 7: RCT of omeprazole versus misoprostol for healing of NSAID-associated ulcers[80]

Ulcer Type	Agent	8-Week Ulcer Healing	Significance vs. Misoprostol
Duodenal	Omeprazole 20 mg/day Omeprazole 40 mg/day Misoprostol 800 µg/day	93% 89% 77%	p.<0.001 p.<0.001
Gastric	Omeprazole 20 mg/day Omeprazole 40 mg/day Misoprostol 800 µg/day	87% 80% 73%	p.<0.001 NS

The take-home message for clinicians is that an eight-week course of standard-dose PPI appears to be the most effective choice of therapy. The CADTH Scientific Report notes that all comparative studies used endoscopically proven ulcers as a surrogate marker for efficacy.[1] The extrapolation of this data to more clinically important endpoints such as symptomatic or complicated ulcers remains uncertain.

When it comes to the choice of PPI for healing of NSAID-associated ulcers, the CADTH Scientific Report has the following Statement:[1]

P2.1.2A: Different PPIs produce similar healing rates of NSAID-associated ulcers.

Unlike the treatment of dyspepsia, GERD, and *H. pylori*, there are no head-to-head comparisons of PPIs in NSAID-associated ulcer healing. Indirect comparisons in one good-quality systematic review by McDonagh *et al.*[81] included the three trials discussed in the ranitidine and misoprostol comparisons in the preceding pages.[77,78,80] The authors noted that there was overlap in the confidence interval of the difference in ulcer healing rate between omeprazole and ranitidine and that of the difference between lansoprazole and ranitidine. Therefore, no difference in healing rates between these two PPIs could be discerned. However, the possibility of differences in populations across the two studies, as well as the lack of data for other PPIs, makes the findings less convincing.[81] The esomeprazole study by Goldstein *et al.* was not included in the systematic review by McDonagh *et al.* The gastric ulcer healing rates in the PPI arms are higher in this study than reported by Agrawal *et al.* (e.g., the eight-week healing rate in the esomeprazole 20 mg arm was 88.4% as compared to 73% in the lansoprazole 30 mg arm of the RCT by Agrawal *et al.*). However, since the healing rate in the ranitidine arm was also higher (74.2% in Goldstein *et al.* versus 53% in Agrawal *et al.*), study population differences may explain the observed discrepancy in healing rates between the PPIs.[77,79]

3.6 Prevention: NSAID-Associated Ulcers

The value of NSAID therapy, both for cardio-protection with low-dose ASA and management of musculoskeletal symptoms, means that they are an essential part of some patients' treatment regimens even if they are at significant risk for an ulcer complication. This has led to the study of preventative therapies for NSAID-associated ulcers.

Placebo comparisons

Similar to the research on NSAID-associated ulcer healing, prevention studies often lack data on the clinically important endpoint of ulcer complications.[1] A majority of the data for preventative therapies is for the surrogate endpoint of endoscopic ulcers, many of which will not become clinically important.

The CADTH Scientific Report contains the following Evidence Statement regarding the efficacy of PPIs for the prevention of endoscopic NSAID-associated ulcers:[1]

P2.2.1A: Standard-dose PPIs are more efficacious than placebo for the prevention of NSAID-associated endoscopic gastric and duodenal ulcers.

This Statement is based on the results of two good-quality systematic reviews, both of which included prevention of endoscopic ulcer as an outcome.[66,82] The reviews found that PPI therapy

reduced the risk of developing an endoscopic ulcer compared to placebo, with NNTs ranging from six to 13 depending on the ulcer type (gastric or duodenal). The duration of therapy and baseline patient risk (e.g., whether the population studied had a history of ulcer or ulcer complications) varied across the studies.

One of the systematic reviews, by Hooper *et al.*, also included a composite end-point of the following clinically relevant outcomes:[82]

- serious GI complications (hemorrhage, recurrent GI bleeding, perforation, obstruction, melena, death from any of these)
- symptomatic ulcers
- HRQL
- mortality
- serious CV or renal illness.

Due to the insufficient number of events, the data was considered insufficient to draw conclusions regarding the efficacy of PPIs versus placebo for the prevention of serious GI complications due to NSAIDs.[82] In terms of symptomatic ulcers, PPIs were estimated to reduce the relative risk by 91% (RR=0.09, 95% CI: 0.02 to 0.47). Although statistically significant, this estimate was derived from pooling of a relatively small number of events (one in 168 patients receiving gastroprotection versus 17 in 175 patients receiving placebo). The relative risk of endoscopic ulcer was 0.37 (95% CI: 0.3 to 0.5).[82]

What was also notable about this systematic review was the other agents that were studied, including H2RAs, misoprostol, COX-2 selective NSAIDs (etodolac, meloxicam, etc.) and COX-2 specific NSAIDs (celecoxib and rofecoxib).[82] There was insufficient data on the H2RAs in terms of complications or symptomatic ulcers, although a significant risk reduction was evident for the outcome of endoscopic ulcers [RR=0.55 (95% CI: 0.4 to 0.7)]. There was relatively less data on all outcomes, including endoscopic ulcer outcomes, for the COX-2 selective agents; a significant risk reduction was observed for the outcome of symptomatic ulcers but not endoscopic ulcers for this class of agents.[82] Misoprostol showed reductions in both serious GI complications [RR=0.57 (95% CI: 0.36 to 0.91)], and symptomatic ulcers [RR=0.36 (95% CI 0.20 to 0.67)]. COX-2 specific agents also showed reductions in the same endpoints (RR for serious complications was 0.55 [95% CI 0.38 to 0.80] and RR for symptomatic ulcers was 0.49 [95% CI 0.38 to 0.62]).[82]

It should be noted that the pooled sample sizes of the misoprostol and COX-2 specific trials were several-fold larger than that of the PPI trials. The power to detect a significant difference, especially for rarer outcomes such as complications, was therefore lower for PPIs. Regardless, this study effectively narrows the scope of effective agents in NSAID-associated ulcer prophylaxis to PPIs, misoprostol, and COX-2 specific agents, with the latter two groups having data on serious GI complications.

The results reported by Hooper *et al.* corroborated those of an earlier Cochrane review by Rostom *et al.*[66] However, Rostom *et al.* also reported subgroup analyses based on dose, and found that misoprostol 800 µg per day had greater efficacy in terms of endoscopic gastric ulcer prevention than 400 µg per day, although there was no such dose-response relationship for duodenal ulcer. As well, the review analyzed the available H2RA data according to dose and found that double-dose H2RAs (e.g., ranitidine 300 mg twice daily) demonstrated significant reductions in the risk of both endoscopic duodenal and gastric ulcers (RR=0.26 and 0.44 respectively), while standard doses only

reduced the risk of duodenal ulcer (RR=0.24).[66] Only misoprostol was shown to reduce the risk of serious NSAID-associated ulcer complications.

The lack of data on clinically relevant endpoints regarding H2RAs, as well as the higher cost of double-dose H2RAs as compared to some standard-dose PPIs, substantially limits the value of this therapeutic option.

There remain some important caveats to the data supporting the gastrointestinal safety of COX-2 specific agents. The CLASS trial compared high-dose celecoxib (400 mg twice daily) against ibuprofen (800 mg three times daily) and diclofenac (75 mg twice daily) with the main outcome of GI complications.[83] The reported results at six months showed reductions in GI ulcer complications and symptomatic ulcers favouring celecoxib over both traditional NSAIDs.[83] An important exception noted in the study was that patients taking concomitant low-dose ASA for cardiovascular protection did not have any significant reduction in GI toxicity with celecoxib over the other NSAIDs. Of further note, the patient populations in the six-month CLASS trial actually continued on therapy for between 12 and15 months. Subsequent publications on data from the longer studies showed much of the benefit of celecoxib was lost with no significant risk reduction in serious GI complications and symptomatic ulcers compared to both traditional NSAIDs.[84] Practitioners should be made aware of the potential concerns regarding concomitant ASA and long-term use of COX-2 specific agents when considering options for reducing GI complications.

Active agent comparisons

The CADTH Scientific Report provides the following Evidence Statements related to active comparators in the prevention of NSAID-associated ulcers:[1]

P2.2.1B: Standard-dose PPIs are **more efficacious** than standard-dose H2RAs for the secondary prevention of NSAID-associated endoscopic gastric and duodenal ulcers.
P2.2.1C: In patients with a history of ulcers, standard-dose PPIs have **similar efficacy** to misoprostol 400 µg to 800 µg daily for the prevention of NSAID-associated endoscopic gastric and duodenal ulcers.
P2.2.2A: There is **no difference** in ulcer recurrence and bleeding rates between COX-2 selective NSAIDs and the combination of PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding.

Based on evidence from the placebo-controlled trials, the evidence statement P2.2.1B regarding PPI versus H2RAs is somewhat expected. However, only one RCT comparing a PPI and a H2RA comprises the evidence. This trial, by Yeomans *et al.*, is a six-month extension of the NSAID-associated ulcer healing study discussed previously under "Treatment."[78] The six-month relapse rates for gastric and duodenal ulcers were significantly lower with omeprazole versus ranitidine (gastric ulcer: 5.2% versus 16.3%, NNT=10; duodenal ulcer: 0.5% versus 4.2%, NNT=27).[78]

The relative efficacy of PPIs to misoprostol in preventing NSAID-associated ulcers is less clear. Only two trials provide direct comparisons, and their use of different doses of misoprostol (800 µg and 400 µg per day) makes interpretation difficult.[66,80,85] Graham *et al.* found that misoprostol 800 µg per day resulted in significantly more patients being free of gastric ulcers at 12 weeks [93% (95% CI: 87.2 to 97.9%)] than lansoprazole 30 mg [82% (95% CI: 75.0 to 89.6%)].[86] The NNT for misoprostol over lansoprazole was nine. This treatment effect did not, however, hold for total ulcers (i.e., gastric and duodenal ulcers), for which no significant difference was detected. The second trial by Hawkey

et al. was longer in duration (six months), studied misoprostol 400 µg per day, and used a different endpoint (remission rate, a composite of ulcers, erosions, dyspeptic symptoms, and adverse events).[80] This trial found that omeprazole had a higher six-month remission rate (61%) than misoprostol (48%) that was statistically significant (NNT=8).[86] This difference was largely driven by a lower rate of duodenal ulcer relapse in the omeprazole group, since the rate of gastric ulcer recurrence was similar in both treatment arms.[86]

When discussing the difference in efficacy between misoprostol and PPIs, one must consider the risk of adverse events, a commonly cited reason to avoid misoprostol therapy. Graham *et al.* reported the comparative adverse event rates between the two treatment groups. As expected, compared to lansoprazole, misoprostol had significantly higher rates of:[86]

- daytime abdominal pain (% days with pain), 41% versus 31%, p<0.05
- antacid use (% days used), 42% versus 25%, p<0.001
- any treatment-related adverse drug reaction, 31% versus 16%, p=0.006
- diarrhea, 22% versus 7%, p<0.01.

Compliance was also substantially better with lansoprazole (>90%) compared with misoprostol (72%).[86] However, despite these differences in adverse effects, there was no difference in the percentage of patients completing the trial or discontinuing therapy due to adverse events. Therefore, although patient tolerance favours PPIs, more than half of patients on misoprostol 800 µg per day appear to tolerate it, making it a reasonable therapy to consider especially in light of the data that shows it reduces the risk of serious GI complications.

In terms of the comparison of COX-2 specific NSAIDs versus PPI plus traditional NSAIDs, the data for Statement P2.2.2A are limited to one systematic review (that identified only one trial) and two other RCTs. The studies found no significant differences between the two treatment strategies regardless of the endpoint measured: endoscopic ulcer recurrence, recurrence of GI bleeding, recurrence of any ulcer complication. All comparisons found no significant difference.[1]

Choice of PPI

The CADTH Scientific Report contained the following Evidence Statement regarding the efficacy of various PPIs for the prevention of NSAID-associated ulcers:[1]

> **P2.2.4A:** Different PPIs reduce ulcer risk to a similar degree when given to NSAID users for ulcer prophylaxis.

Similar to the evidence for NSAID-ulcer healing, indirect comparisons in the systematic review by McDonagh *et al.* found no significant differences between the PPIs for which comparative data with other agents were available (i.e., omeprazole, lansoprazole, and pantoprazole).[81] However, a single poor-quality RCT published since then studied omeprazole 20 mg and pantoprazole 20 mg and 40 mg in a six-month prospective comparison.[87] This study found no significant difference in the rate of endoscopically evaluated remission, showing very high rates with both pantoprazole 40 mg (95%), pantoprazole 20 mg (91%), and omeprazole 20 mg (93%).[87]

H. pylori eradication

In the 2004 update of the Canadian Helicobacter Study Group consensus statements the following recommendations related to NSAID use and *H. pylori* eradication[67] are:

- Patients initiating long-term non-steroidal anti-inflammatory drug (NSAID) therapy should be tested for *H. pylori* infection and treated if positive.
- Patients initiating long-term acetylsalicylic acid (ASA) prophylaxis for cardiovascular disease should be tested for *H. pylori* infection and treated if positive.

The quality of the evidence behind the first recommendation was rated as level II-1 by the majority of the group (i.e., at least one appropriately designed controlled trial without randomization). However, an examination of the study referenced in the discussion section[88] does not validate the statement or even relate to the statement. The evidence quality for the second statement was unanimously voted as level III (i.e., opinions of experts based on clinical experience or descriptive studies).[67] There is evidence that *H. pylori* infection independently increases the risk of ulcer and ulcer bleeding in NSAID users and that its eradication reduces the risk of these events. In a meta-analysis of observational studies, Huang *et al.* reported that the odds ratio for uncomplicated ulcer associated with NSAID use was 19.1, while that for NSAID use in the presence of *H. pylori* infection was 61.1 (i.e., presence of *H. pylori* infection led to a 3.2-fold increased risk).[89] A similar pattern was seen for ulcer bleeding, although the magnitude of additional risk posed by *H. pylori* infection was smaller. Three RCTs also warrant discussion. Chan *et al.* conducted two of these studies in *H. pylori*-positive NSAID-naïve patients requiring long-term NSAID therapy, the first in patients without a history of ulcer[90] and the second in patients with a history of ulcer or dyspepsia.[91] In both studies, patients were randomized to either one-week eradication therapy or control treatment (no therapy or omeprazole alone). In both studies, *H. pylori* eradication significantly reduced the risk of ulcer.[90,91] In the study of patients with a history of dyspepsia or ulcer, 12.1% of *H. pylori*-eradicated subjects had ulcers at six months versus 34.4% of placebo-treated subjects ($p<0.01$). The incidence of complicated ulcers was also reduced in this study (4.2% in the *H. pylori*-eradicated group versus 27.1% in the control group, $p<0.005$).[91] However, several studies have shown that the risk of NSAID-ulcer is greatest in the first few months of therapy.[91] In a study of *H. pylori*-positive patients already using NSAIDs, Hawkey *et al.* were unable to detect a significant difference in the six-month risk of ulcer between *H. pylori*-eradicated and control subjects.[92] It therefore appears that the risk conferred by *H. pylori* infection may differ between NSAID-naïve patients and current NSAID-users, and that *H. pylori* eradication may be most advantageous in the former group. It should also be noted that evidence is lacking regarding the utility of *H. pylori* eradication in new or existing low-dose ASA-users, as reflected in the level III rating that the Canadian Helicobacter Study Group assigned to their second recommendation.

The CADTH Scientific Report contained the following Evidence Statements regarding the comparative efficacy of *H. pylori* eradication versus PPI prophylaxis in patients with a history of GI complications:[1]

> **P2.2.3A:** Standard-dose PPIs are **more efficacious** than *H. pylori* eradication in preventing recurrent upper GI bleeding in *H. pylori*-positive patients with (non-ASA) NSAID-associated ulcers or bleeding erosions who have been healed with a course of PPIs.
> **P3.1:** Standard-dose PPIs are **not more efficacious** than *H. pylori* eradication in preventing recurrent upper GI bleeding in *H. pylori*-positive patients with low-dose ASA-associated ulcers or bleeding erosions who have been healed with a course of PPIs.

This Statement was supported by another trial by Chan *et al.* that studied patients who were *H. pylori*-positive, had a history of gastrointestinal bleeding, and were on ongoing NSAID therapy (250

took naproxen, 150 took low-dose ASA).[93] Patients were randomized to a one-week eradication regimen or daily omeprazole 20 mg for six months. The primary endpoint was recurrence of GI bleeding. The results for the primary endpoint are shown in Table 8.[93]

The significant difference in the naproxen patient group shows that ongoing PPI prophylaxis is more efficacious than *H. pylori* eradication. It also corroborates the view that, in existing NSAID users, *H. pylori* eradication alone is insufficient to prevent ulcer complications.[91] The results in the ASA group are difficult to interpret as the event rate, hence the power to detect a difference, is very low, although there is no evidence that one strategy is advantageous over the other. Unfortunately, this trial did not provide information on the efficacy of the combination of *H. pylori* eradication and PPI prophylaxis.

Table 8: Recurrence rates of GI bleeding with continuous omeprazole versus eradication therapy.[93]

Patient Group	Number of Recurrent Bleeds		Probability of Recurrent Bleeding (95% CI)		Absolute Difference in Probability (95% CI)	NNT
	Omeprazole Therapy	Eradication Therapy	Omeprazole Therapy	Eradication Therapy		
ASA	1	2	0.9 (-0.8 to 2.6)	1.9 (-0.7 to 4.5)	1.0 (-1.9 to 3.9)	NS
Naproxen	3	13	4.4 (-0.5 to 9.3)	18.8 (9.5 to 28.1)	14.4 (4.4 to 24.4)	7

Although the Chan paper did not show a difference between eradication and ongoing PPI use for recurrent bleeds in ASA users,[93] a similar population was chosen for a study by Lai *et al.* that looked at following eradication therapy with either one year of lansoprazole or placebo.[94] The results of this study formed the basis of the following evidence statement:[1]

P3.2: In patients in whom *H. pylori* has been eradicated, standard-dose PPIs are **more efficacious** than placebo for the secondary prevention of ulcer complications in users of low-dose (≤325 mg/day) ASA.

Although the study population was small (n=123) and the event rate low, there was a significant difference in the recurrence of complications: nine events (14.8%) occurred in the placebo group compared with one event (1.6%) in the treatment group.[94] This translates to an NNT of eight for the prevention of one complication recurrence. About seven times the number of complications were seen in the placebo arm of the Lai *et al.* study compared with the eradication arm of the Chan paper, even though both populations received essentially the same management.[93,94] This difference may be attributable to the longer duration of the study or inherent differences in the populations studied.

Once again, the take-home message for clinicians is somewhat unclear. There is evidence that *H. pylori* eradication reduces the risk of ulcers and ulcer complications in new NSAID users,[90,91] therefore the recommendation by the Canadian Helicobacter Study Group that higher risk patients should have *H. pylori* eradicated before starting NSAID therapy appears justified. However, *H. pylori* eradication may not be sufficient and ongoing prophylaxis may still be required especially in existing users, as shown by Chan *et al.*[93] The optimal strategy for users of low-dose ASA is even more ambiguous. *H. pylori* eradication appears to confer no benefit in ASA users as demonstrated by Chan *et al.*,[93] although the event rate was low in the subset of ASA users. The Lai *et al.* study

indicates that PPI prophylaxis provides additional benefit beyond *H. pylori* eradication alone in existing users. Data on new users of ASA is lacking, as recognized by the level III rating given to the recommendation to eradicate *H. pylori* in new ASA users by the Canadian Helicobacter Study Group.

Clopidogrel

The risk of GI bleeding with clopidogrel has been found to be somewhat lower than low-dose ASA.[1] As such, it may represent an option in managing patients with a history of GI bleeding with ASA. The treatment strategy of combining a PPI and low-dose ASA to reduce ulcer complications has also been compared with clopidogrel. The CADTH Scientific Report provides the following Evidence Statement:[1]

> **P3.3:** In *H. pylori*-negative patients who have a history of ulcer bleeding on low-dose ASA alone, the combination of low-dose ASA and a PPI is associated with a **lower risk of recurrence** of ulcer complications as compared to clopidogrel alone.

Two RCTs of one-year duration reported a lower recurrence of ulcer complications with PPI plus ASA versus clopidogrel alone. Therefore, although there may be a lower risk of bleeding with clopidogrel versus ASA alone, the former is inferior to ASA in combination with gastroprotection with a PPI. It was noted within the comments for this statement in the CADTH Scientific Report that higher rates of GI complications have been seen when ASA is combined with clopidogrel (compared to each agent alone), however, there is no data indicating if PPIs have a role in reducing risk in combination users.

3.7 Recommended Reading

Hunt R, Thomson AB. Canadian Helicobacter pylori consensus conference. Canadian Association of Gastroenterology. *Can J Gastroenterol* 1998;12(1):31-41.

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Hunt RH, Fallone CA, Van Zanten VSJ, Sherman P, Smaill F, Flook N, Thomson ABR. Canadian Helicobacter Study Group Concensus Conference: update on the management of *Helicobacter pylori* – An evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for *H pylori* infection. *Can J Gastroenterol* 2004;18(9): 547-554.

Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, et al. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* 2002;(4):CD002296.

4 SECTION 4: PROTON PUMP INHIBITOR ADVERSE EFFECTS

4.1 Introduction

PPIs are generally well tolerated and most patients experience limited side effects from these medications. Diarrhea, abdominal pain, flatulence, headache, eructation (the oral ejection of gas from the stomach), nausea, and rash have been reported.[14] Prolonged high-dose PPI therapy may reduce serum B_{12} concentrations.[14,21] The CADTH Scientific Report makes the following statement on adverse event rates for PPIs:

G6.1: PPIs have a similar adverse event rate (generally minor) as H2RAs in GERD randomized controlled trials of up to one year duration.

Two case reports suggest that long-term PPI therapy may be associated with hypomagnesemia and hypocalcemia associated with low levels of parathyroid hormone. In both cases, the patients' electrolyte and hormone levels returned to normal when the PPI was stopped and replaced with ranitidine.[95]

PPIs have also been associated with a number of cases of acute interstitial nephritis (AIN).[96] It is estimated that PPI-induced AIN may occur in approximately one in 12,000 patients taking a PPI. AIN was more common in elderly patients and improved when the PPI was withdrawn. Fever, malaise, lethargy in conjunction with elevated erythrocyte sedimentation rate, C-reactive protein, and urinary sediment should raise the suspicion of AIN. Routine screening is likely not justified, but increased awareness of the potential of PPI-induced AIN may facilitate early detection and help to avoid permanent kidney damage.[96]

4.2 Proton Pump Inhibitors and Fracture Risk

Two case-control studies have recently been published suggesting that PPI are associated with increased risk of fracture.[97,98] It is biologically plausible that PPIs may limit the absorption of calcium from the GI tract through induction of hypochlorhydria. Given that hip fractures are associated with significant morbidity and mortality, further investigation and caution is warranted. The risk of fracture may be proportional to the dose and duration of PPI therapy. Increased duration of therapy was associated with an increasing risk of hip fracture in one observational study [adjusted OR: 1-year 1.22 (95% CI: 1.15 to 1.20), 2-year 1.41 (95% CI: 1.28 to 1.56), 3-year 1.54 (95% CI: 1.37 to 1.73), 4-year 1.59 (95% CI: 1.39 to 1.80)].[98] Likewise, higher dosages were associated with greater risk of hip fracture [(adjusted OR: Dose ≤1.75 doses per day 1.40 (95% CI: 1.26 to 1.54), Dose >1.75 doses per day 2.65 (95% CI: 1.80 to 3.90)].[98] The authors suggest that physicians should use the lowest effective dose of PPIs and consider increased calcium intake for long-term/high-dose PPI users.[98]
It is important to remember that observational data such as that from case-control studies should be considered hypothesis-generating and must be interpreted with caution due to the possibility of confounding factors. The overall adjusted odds ratio of 1.44 (95% CI: 1.20-1.59) is relatively modest (OR of >3 are considered by some as the threshold for clinical importance in observational research).[99] In fact, one of the case-control studies on PPIs and fracture risk concludes that the risk estimates are small and the clinical consequences limited.[97] The same studies also suggest an effect of H2RAs on fracture risk; one suggested an increase in risk of hip fracture [adjusted OR 1.23 (95% CI: 1.14 to 1.39)][98] and the other a decreased risk in hip fractures [OR 0.69 (95 CI: 0.57 to 0.84)].[97] Clearly, more study is needed. Fracture risk is primarily a potential issue for long-term users of PPIs. Advising patients to limit PPI use to the lowest effective dose and ensuring adequate calcium/vitamin D intake is prudent regardless of whether the association between PPIs and fractures is corroborated by future research.

4.3 Proton Pump Inhibitors and *Clostridium difficile*

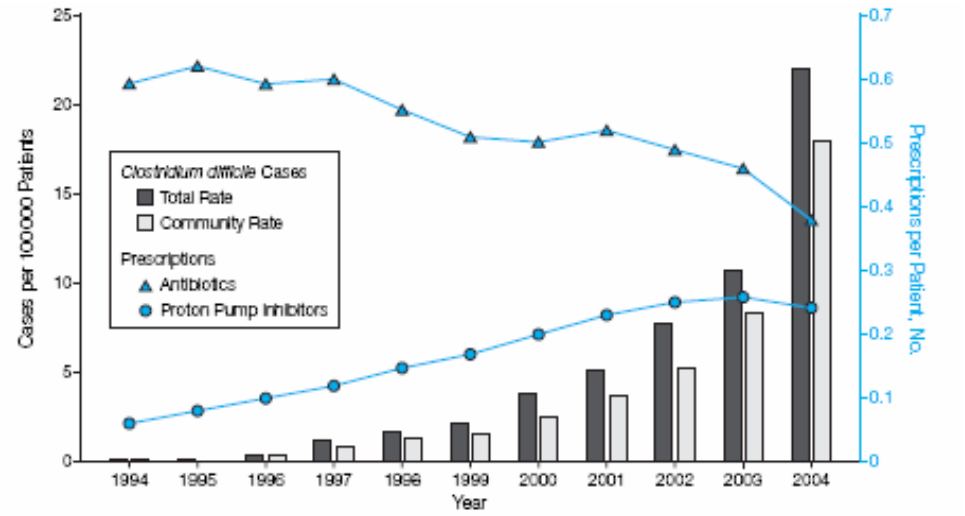
Clostridium difficile is a spore-forming gram-positive bacillus that produces a toxin that may cause symptoms ranging in severity from mild diarrhea to colitis and even death. Antibiotics use is a well-established risk factor in the development of *C. difficile* infection.[100] Recent attention has also focused on PPIs as a potential risk factor.[101] It is suggested that gastric acidity acts as an important

defence mechanism against pathogens, and that PPIs allow greater colonization of pathogenic bacteria by increasing gastric pH. Figure 8 shows increasing rates of *C. difficile* infections (one per 100,000 in 1994 to 22 per 100,000 in 2004) set against a backdrop of decreasing antibiotic use and increasing use of PPIs.[101]

In the case-control study from which this figure is reproduced, PPI use was associated with an adjusted odds ratio of 2.9 (95% CI: 2.4 to 3.4) for *C. difficile* infection in community patients.[101] Other observational studies have produced results with similar odds ratios.[102-104] These results have generated considerable controversy. It has been suggested that the escalating rates of *C. difficile* may be related to increased reporting rather than a rising incidence of infection.[105] Studies have also been criticized for relying on physician reporting of the disease rather than laboratory confirmation.[105,106] Oral vancomycin prescriptions have been used as an alternative marker of disease, since this is the only indication for this medication. Using this marker has also shown a significant increase in the development of *C. difficile* [OR 3.5 (95% CI: 2.3 to 5.2)].[107] However, not all of the observational evidence has shown a positive association.[108] Recent Canadian data failed to find an increased risk of hospitalization for *C. difficile* in patients using PPIs [adjusted OR 0.9 (95% CI: 0.8 to 1.1)].[106] Ultimately, this issue may be solved by studies of randomized design;[109] although, given the low absolute risk of infection, it may be difficult to prove with that PPIs predispose patients to *C. difficile* in the absence of antibiotic treatment.[104]

While many observational studies suggest an increased risk of *C. difficile* infection with the use of PPIs, the evidence is inconclusive at present. Many authors have suggested that the high level of use of PPIs is suggestive of overuse of these agents and that appropriate use may help to mitigate the potential risk.[103,106,110,111]

Figure 8: *Clostridium difficile*, antibiotics, and PPIs in United Kingdom General Practice Research Database



Reproduced with permission from the American Medical Association.[101]

4.4 Proton Pump Inhibitors and Pneumonia

As with *C. difficile* infection, it has been suggested that PPIs and other acid suppression therapy interfere with the protection against bacteria normally conferred by gastric pH of less than four.[112]

A retrospective cohort study found an unadjusted relative risk for pneumonia of 4.63 (3.84 to 5.43) for PPI users compared with non-users of acid suppression therapy.[113] The lack of adjustment fails to take into account confounders and as such has limited meaning. The use of a nested case-control study attempted to deal with these concerns and found a much more modest odds ratio of 1.73 (1.33 to 2.25) for those on active PPI treatment.[113] There was an increased risk with higher doses of PPIs [adjusted OR for <1 dose per day 1.23 (95% CI: 0.78 to 1.93), 1 dose per day 1.94 (95% CI: 1.41 to 2.68), >1 dose per day 2.28 (95% CI: 1.26 to 4.10)]. The authors concluded that, given the average use of PPIs for approximately five months, it would be expected that one of 226 patients treated with PPI would develop pneumonia.[113]

It would be difficult to study pneumonia and PPIs in a randomized, controlled trial.[114] This outcome has only rarely been measured in trials of PPIs. In seven trials (total of 2,271 patients) that included respiratory infection as an outcome, patients using PPIs had an infection rate of 4.3% compared to 4.9% in the placebo group.[115] No firm conclusion can be drawn from these data, but they point to the need to weigh the benefits and risks of PPI treatment on a case-by-case basis. Evidence-based and appropriate use of PPIs, considering both dose and duration of therapy, should be encouraged.[115]

4.5 Recommended Reading

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Lowe DO, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for *Clostridium difficile*-associated disease: a population-based study. *Clin Infect Dis* 2006:43:1272-1276.

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5 SECTION 5: PROTON PUMP INHIBITOR DRUG INTERACTIONS

5.1 Introduction

PPIs are widely used for the treatment of gastric acid-related conditions. While short-term treatment may be all that is required for many patients, long-term therapy will be required for some. The widespread and growing use of PPIs is manifest in the increasing numbers of prescriptions filled for these drugs in Canada. Such high levels of use translates into an increased risk of drug interactions with other medications that patients may be using.[116] The majority of drug interactions of PPIs relate to their effects on drug absorption and drug metabolism.

5.2 Interactions Related to Absorption

PPIs significantly increase the gastric pH by inhibiting the H+/K+ATPase pump. Increased pH has the potential to affect the absorption of other medications. Specifically, the absorption of weak bases is decreased while that of weak acids is increased. Weak bases (e.g., ketoconazole, chlorpromazine, indomethacin, and tetracycline) undergo increased ionization which decreases absorption. For weak

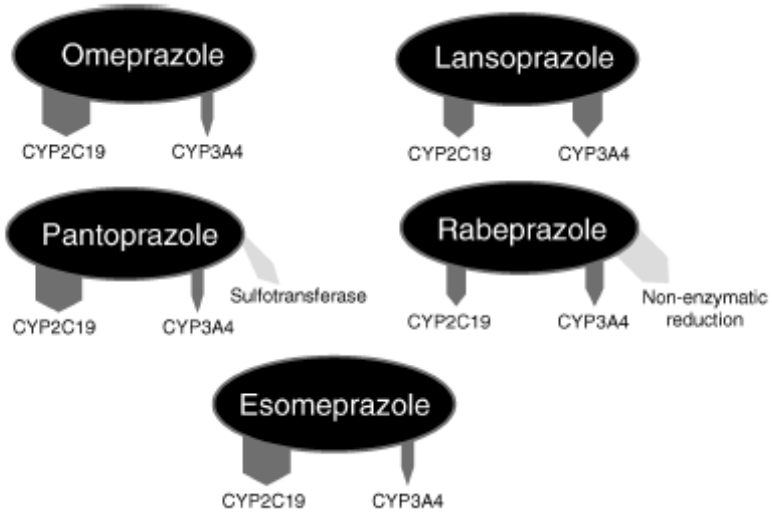
acids (e.g., ASA, diazepam, furosemide), ionization is decreased, thereby allowing for increased absorption.[117]

Given that acid reduction is the basis of these theoretical interactions, a class effect would be expected. All five of the PPIs should be approximately equal in their potential for this type of interaction. While some of these interactions are of limited clinical significance, others merit more careful consideration. The absorption of some anti-infectives (e.g., ampicillin, atazanavir, ketoconazole, itraconazole) may be affected by PPIs, and concurrent administration is not recommended. The absorption of iron and calcium salts may be reduced with higher gastric pH, the latter of which has implications for the association between PPIs and the risk of fractures, as discussed in Section 4 of this upskilling document.

5.3 Interactions Related to Metabolism

All five PPIs are metabolized in the liver via the cytochrome P450 system. The CYP2C19 and CYP3A4 are the most important isoenzymes in PPI metabolism (Figure 9).[118,119] The relative affinity and importance of the CYP2C19 and CYP3A4 pathways varies between the various PPIs. The CYP2C19 pathway is the major pathway for most PPIs (except rabeprazole).

Figure 9: Metabolic pathways of PPIs



From: Martin de Argila, Safety of potent gastric acid inhibition. *Drugs* 2005;65(S1): 97-104 (Figure 1 page 98).[118]

In some situations, genetic variation in the CYP2C19 isoenzyme may be relevant to whether a potential drug interaction with PPIs is clinically relevant. The genetic polymorphism associated with this isoenzyme results in two main phenotypes: poor metabolizers (a minority) and extensive metabolizers (the majority).[118] Although the bioavailability of PPIs will be greater in poor metabolizers, this is unlikely to result in a clinically significant effects.[118,120] Conversely, it is theoretically possible for some individuals who are extensive metabolizers to have reduced effects of PPIs.[119,120] In one small study, the degree of reduction in intragastric pH was related to

polymorphism of CYP2C19 such that homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers given omeprazole 20 mg demonstrated a predictable pattern of gastric pH values (2.14, 3.30, and 4.47 respectively).[121] However, the contribution of genetic polymorphism has not been evaluated systematically in any major trials of PPIs.

Modest and inconsistent increases in digoxin levels are seen with PPIs because of their inhibitory effects on ATP-dependent glycoprotein, an intestinal transporter involved in digoxin efflux.[116,117] The consequent increase in the bioavailability of digoxin is likely to be of limited clinical significance.[118] Other drugs that have been hypothesized to interact with PPIs via a similar mechanism include nifedipine, tacrolimus, ketoconazole, and amitriptylline.[118]

The interaction profile of individual PPIs will be discussed in the remainder of this section with a view to understanding the clinical relevance of these interactions.

Omeprazole

Omeprazole is the oldest and best studied of the PPIs with regard to interactions. Theoretical interactions have been suggested with carbamazepine, diazepam, digoxin, phenytoin, methotrexate, nifedipine, and warfarin.[117] The interaction with diazepam may produce a 25% to 50% reduction in diazepam clearance and may be of clinical significance in some situations.[118] Kinetic studies have shown reduction in plasma clearance of phenytoin.[122] The clinical significance of this theoretical interaction is questionable since, in one study, no significant changes in phenytoin levels were found in a small group of patients with epilepsy.[118,123] Case reports of omeprazole/phenytoin interactions are exceedingly rare.[124]

Omeprazole decreases the metabolism of warfarin; a few isolated case reports of increased prothrombin time have been reported.[118] While caution is warranted, there are a few factors that warrant consideration in the evaluation of the clinical significance of this interaction. Warfarin exists as two enantiomers. *R*-warfarin is less pharmacologically active than *S*-warfarin. Only *R*-warfarin is metabolized by CYP2C19, therefore only the metabolism of this enantiomer is affected by omeprazole. Randomized studies have not shown clinically significant drug interactions between warfarin and omeprazole.[125] Case reports of such an interaction are rare (0.09 per million packages supplied).[124] It is interesting to note that the rate for warfarin interactions for omeprazole was no higher than reported for lansoprazole and pantoprazole (both at 0.11 interactions per million packages supplied).[124]

In summary, while caution and monitoring should be considered, the majority of omeprazole drug interactions have limited clinical significance.

Lansoprazole

Investigation into the interactions of lansoprazole with diazepam, oral contraceptives, prednisone, theophylline, phenytoin, and warfarin has failed to reveal significant effects.[118,119] Although not well studied, a potential interaction with tacrolimus should be noted because of the potential for considerable harm from increased tacrolimus bioavailability.[119,126]

Pantoprazole

Pantoprazole has less inhibitory activity on the CYP450 enzyme system than omeprazole and lansoprazole and as such is associated with fewer reports of drug interactions.[117,119] No significant

interactions have been found with carbamazepine, diazepam, metoprolol, phenytoin, theophylline, or warfarin.[119,120] Pantoprazole can also be metabolized outside of the CYP450 system by sulfotransferase (Figure 9). Pantoprazole can raise digoxin levels, but this is not related to CYP450 enzyme systems and is of limited clinical significance.[117,127]

Rabeprazole

While rabeprazole is metabolized via the CYP2C19 and CYP3A4 pathways, its primary route of metabolism is through non-enzymatic reduction.[117,118] As such, rabeprazole may be less likely to cause interactions with other medications. Rabeprazole can raise digoxin levels but this is not related to CYP450 enzyme systems and is of limited clinical significance.[117,118]

Esomeprazole

Esomeprazole was the last PPI to enter the Canadian market. Since it is simply the S-enantiomer of omeprazole, its interaction profile can be expected to be similar. It has been shown to produce similar effects on the metabolism of diazepam (45% decrease in clearance).[118,128] Like omeprazole, esomeprazole has been shown to increase phenytoin plasma levels, but a clinically significant interaction in individuals with epilepsy has not been demonstrated.[118,128] Esomeprazole also produces limited inhibition of the metabolism of R-warfarin, an effect that is not likely to be clinically significant.[118,128] Finally, clarithromycin has been shown to reduce the metabolism of esomeprazole and double its bioavailability by interfering with its metabolism though the CYP3A4 pathway.[118,128] On balance, it appears that the risk of clinically significant drug interactions with esomeprazole is low and approximately the same as that seen with omeprazole.[119,128]

5.4 Summary

The absolute magnitude of risk associated with PPI drug interactions is low.[119,124] Although the majority of interactions with PPIs have not been shown to be clinically significant, consideration should be given in patient populations at greatest risk, such as the elderly, and patients receiving medications with a low therapeutic index.[117,118]

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