Update on the Management of Acid-Related Disorders: A Canadian Perspective

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INTRODUCTION

Dyspepsia is the main manifestation of acid-related conditions: functional or non-ulcer dyspepsia (FD/NUD), gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD) and gastric, esophageal or pancreatic cancer. The prevalence of dyspepsia in Canada has been estimated at approximately 29% and may be as high as 50% in Western countries. It significantly decreases health-related quality of life and in Canada, over $670 million is spent on medication alone.

Dyspepsia is a symptom complex rather than a disease and its definition has evolved over the last decade. It is difficult to establish a unifying definition of dyspepsia since subjective symptoms and their interpretation vary between patients, physicians and even culture and language. The Canadian Dyspepsia (CanDys) Working Group defines dyspepsia as “a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, and which may include any of the following symptoms: heartburn, acid regurgitation, excessive burping and/or belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion or early satiety.”

The majority of patients with symptoms of upper gastrointestinal (GI) discomfort will present to the community pharmacy or family physician seeking...
advice and/or a diagnosis. It is therefore crucial that pharmacists recognize the typical signs and symptoms and more importantly the alarm features for appropriate recommendations and referral. Pharmacists are in a prime position to identify patients who have an acid-related gastrointestinal disorder, to assess their level of risk for complications, to educate patients on self-management, and to optimize care through collaboration with patients and physicians.

DETECTION & MANAGEMENT OF GASTROINTESTINAL ACID-RELATED DISORDERS

A) Uninvestigated dyspepsia

Prior to investigational work-up, patients with dyspeptic symptoms are considered to have uninvestigated dyspepsia. The CanDys Working Group, consisting of a multidisciplinary group of specialists, family physicians and pharmacists, developed a clinical management tool (CMT) based on best available evidence and expert opinion for patients who present with new-onset or recurrent dyspepsia. This tool provides the primary-care physician with five key questions to stratify and manage patients based on clinical features and symptoms (Fig 1). A unique feature of this tool is that it highlights and prompts the physician to address the importance of possible non-GI causes of dyspeptic symptoms, which will require further investigation. The alarm symptoms requiring urgent investigation include vomiting, evidence of gastrointestinal blood loss or anemia, abdominal mass or involuntary weight loss, dysphagia, odynophagia and chest pain. These symptoms may be suggestive of an organic cause and pharmacists should advise patients to contact their physicians immediately for further investigation.

B) GERD

Gastroesophageal reflux disease (GERD) is defined as “reflux of gastric contents into the esophagus causing symptoms sufficient to reduce quality of life and/or esophageal injury.” It is the most common gastrointestinal and acid-related disorder in Canada. In a survey of over 1,000 Canadians, 17% reported heartburn in the preceding three months and 13% had moderate to severe symptoms on a weekly basis. Quality of life is significantly affected, with patients reporting a poorer quality of life than those with diabetes, hypertension, mild heart failure or arthritis.

The typical presentation of GERD includes heartburn and regurgitation. Heartburn may wax and wane, and is usually worsened by lying down and ingestion of food. In a recent Canadian study (CADET-PE), reflux esophagitis was by far the most common endoscopic finding in patients with uninvestigated dyspepsia regardless of the dominant symptom reported. Most patients with typical GERD symptoms do not undergo investigation; therefore the term “heartburn-dominant uninvestigated dyspepsia” encompasses GERD. Reflux disease can also produce atypical symptoms (extra-esophageal manifestations) such as shortness of breath and wheezing, cough, pharyngitis, hoarseness, and chest pain (see Table 1).

Symptoms of acid reflux are likely due to poor gastric emptying and contact of esophageal mucosa with acid and pepsin. Structural and physiological mechanisms such as the lower esophageal sphincter (LES), bicarbonate in saliva, and esophageal peristalsis form the body’s anatomic defence against reflux. LES dysfunction due to transient relaxations and decreased tone, esophageal peristaltic dysfunction and abnormal gastric emptying may play a role in the development of GERD. A number of factors may alter natural defence mechanisms and increase the risk of reflux:
- Lifestyle factors (e.g. smoking, large...
meals, fatty foods, caffeine, pregnancy, obesity, body position and estrogen)
• Medications that lower LES pressure or cause direct GI irritation (Table 2)
• Hiatus hernia (increased esophageal exposure to gastric contents)

The severity of symptoms and degree of mucosal damage correlates with duration of exposure of the esophagus to gastric acid (duration of time pH<4).3 Therapies that prolong gastric acid suppression are therefore desirable for faster symptom relief and improved healing rates.

Lifestyle modification appears to have limited effectiveness for patients with severe and frequent GERD and well-designed controlled trials are needed to make any definitive conclusions regarding clinical efficacy.3 Despite the sparseness of controlled data, clinical experience suggests that patients with mild symptoms would likely benefit from strategies such as elevating the head of the bed, avoiding lying down within two hours of eating, avoiding food and medication triggers, reducing weight, quitting smoking, and decreasing coffee and alcohol consumption.3,7

Various comparative trials have shown that over-the-counter antacids alone or combined with low-dose histamine-2 receptor antagonists (H3RAs; e.g. ranitidine 75 mg or famotidine 10 mg) and antireflux agents such as algicin acid and are effective for symptom relief in mild GERD.3,7,8 There is suggestion that antacids provide quick relief and OTC H3RAs provide a longer duration of relief.3,7 There are very few well-designed studies comparing OTC H3RAs and antacids; however, due to the availability and safety profile of these agents, they are reasonable alternatives for patients with very mild and infrequent symptoms, particularly if symptoms are associated with meals or triggered by certain foods.3

Prokinetic or promotility agents such as cisapride, metoclopramide and domperidone have been studied in the treatment of GERD. These agents have been proposed to improve peristalsis and LES tone. Cisapride is the only prokinetic agent that has shown clinical efficacy; however, it is no longer available on the market in Canada and is now only available through the special access program due to concerns about prolongation of QT interval, ventricular tachycardia and death. Due to the paucity of clinically relevant data, these agents are not recommended alone or in combination with anti-secretory agents for the long-term maintenance treatment of GERD.3,11

The 2004 Canadian GERD Consensus guidelines recommend that a once-daily proton pump inhibitor (PPI) should be used for the empirical treatment of GERD unless symptoms are mild and infrequent (i.e. fewer than three times per week).3 This recommendation is supported by a meta-analysis of 13 trials in more than 3,000 patients where PPIs were approximately twice as effective as H3RAs.12 Furthermore, 2 recent Canadian studies showed that PPIs provide the highest rate of relief during the first 2-4 weeks of therapy compared to H3RAs.13,14

The CADET Heartburn-Dominant (CADET-HR) study13 compared heartburn relief in patients with uninvestigated dyspepsia with PPI or an H3RA. Three-hundred and ninety patients were randomized to either omeprazole 20 mg daily or ranitidine 150 mg twice daily for the first 4-8 weeks, with an escalation in therapy to omeprazole 40 or 20 mg, respectively if symptoms persisted. Results indicated that a PPI provides better symptom relief at 4 weeks, but no difference was observed for subsequent relapses during a 6-month treatment-free follow-up period. Forty-seven percent (47%) of patients on ranitidine required escalation therapy due to inadequate heartburn relief, compared to 26% of patients who had started with omeprazole. At 4 weeks, the difference in heartburn relief was 27.8% in favour of PPI-start strategy (55.1% vs. 27.3%, p<0.001). The difference in median times to sustained heartburn resolution was 24 days in favour of PPI (5 vs. 29 days), and at 4 weeks the PPI-start strategy was better in achieving additional heartburn relief and sustained effect (NNT = 4).

The multi-centre CADET-HN study15 comparing omeprazole, ranitidine, cisapride, or placebo in H pylori-negative primary-care patients with dyspepsia was recently published, providing

### TABLE 1: Extraesophageal manifestations of GERD

<table>
<thead>
<tr>
<th>ENT</th>
<th>Pulmonary</th>
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<tbody>
<tr>
<td>Cough</td>
<td>Asthma</td>
</tr>
<tr>
<td>Globus (sensation lump in</td>
<td>Cough</td>
</tr>
<tr>
<td>the throat)</td>
<td>Chronic bronchitis</td>
</tr>
<tr>
<td>Hoarseness/voice changes</td>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>Laryngeal cancer</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Otitis media</td>
<td>Chest pain</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Dental erosions</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Sleep apnea</td>
</tr>
<tr>
<td>Vocal cord granulomas</td>
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</tbody>
</table>

### TABLE 2: Medications that may worsen GERD

<table>
<thead>
<tr>
<th>Drugs that ↑ LES pressure</th>
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<tbody>
<tr>
<td>Anticholinergic agents</td>
</tr>
<tr>
<td>Barbiturates</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Caffeine and derivatives (aminophylline, theophylline)</td>
</tr>
<tr>
<td>Dihydropyridine calcium channel blockers</td>
</tr>
<tr>
<td>Estrogen</td>
</tr>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Narcotics (meperidine, morphine)</td>
</tr>
<tr>
<td>Nicotine (smoking)</td>
</tr>
<tr>
<td>Nitrites</td>
</tr>
<tr>
<td>Progesterone</td>
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</tbody>
</table>

Drugs that irritate the esophageal mucosa

<table>
<thead>
<tr>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
</tr>
<tr>
<td>Iron</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Potassium chloride</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
</tbody>
</table>

more evidence that PPIs provide better symptom relief compared to H2RAs and motility agents. Five-hundred and twelve patients were randomized to 4 weeks of treatment with omeprazole 20 mg daily, ranitidine 150 mg twice daily, cisapride 20 mg twice daily or placebo followed by on-demand therapy for an additional 5 months. The study’s primary outcome measure was the Global Overall Severity (GOS) score at 4 weeks, measuring dyspepsia symptoms. At baseline, included patients reported at least moderate symptom severity (GOS at least 4/7). A score of 1 or 2 defined treatment success. Treatment success at 4 weeks was omeprazole 51.1%, ranitidine 36%, cisapride 30.5% and placebo 23.3% (NNT = 4, omeprazole vs. placebo; NNT = 7, omeprazole vs. ranitidine). At 6 months there were no statistically significant differences between groups in terms of symptom relief.

Evidence of erosive esophagitis (EE) on endoscopy accounts for up to two-thirds of patients with symptoms of reflux or 5 to 12% of the general population. The presence and severity of EE does not correlate with the severity of symptoms, however there is a correlation with complications such as esophageal strictures and Barrett’s esophagus (BE). Severity of EE has been graded using the LA classification system (see Table 3) based on endoscopic evidence. Multiple studies and meta-analyses provide evidence that PPIs in acute and long-term treatment provide significantly greater symptom relief and healing compared to H2RAs or cisapride in EE (absolute differences in healing rates of 30-40%). Standard dose PPIs (Table 4) have been compared in 24-hour intragastric pH studies. According to a 5-way crossover trial comparing esomeprazole 40 mg to all other agents at standard doses, esomeprazole provided a longer duration of acid suppression (pH>4). At this point, no unifying recommendations have been made regarding choosing one PPI over another since the clinical relevance of various direct comparisons is still under debate.

Barrett’s esophagus (BE), a metaplastic change from normal esophageal squa-
mous epithelium to columnar intestinal epithelium, is a serious complication of GERD. The incidence of BE increases with higher frequency (>3 times per week), severity and duration (>20 years) of GERD symptoms. BE has been associated with the development of esophageal adenocarcinoma; Canadian data show that the absolute risk of progression to adenocarcinoma in patients with long-standing GERD is approximately 0.4%.19 Although the likelihood of gastric or esophageal cancer is relatively low, the prevalence of cancer increases with age (>50) and with the severity, frequency and duration of GERD symptoms. North American gastroenterology guidelines recommend lifelong PPI therapy for BE patients along with periodic endoscopic surveillance.5,20 A strategy called “once in a lifetime” endoscopy has been developed for patients with chronic GERD, calling for endoscopy after 10 years of GERD symptoms to identify patients who have BE. Notwithstanding, life-long PPI treatment and “once in a lifetime” endoscopy has not been shown to reduce the incidence of gastric or esophageal cancer.19

For patients who fail to respond to standard-dose therapy and/or with severe esophagitis (LA Grade C or D, or stricture), some may obtain relief with double-dose or longer duration of PPI therapy.21,22 Recently, there have been some data to suggest that high-dose PPI therapy reduces symptoms in patients with extraesophageal manifestations of GERD such as non-cardiac chest pain (NCCP). Two meta-analyses showed that using higher doses of PPI (omeprazole 40/80 mg or lansoprazole 30 mg) for up to 4 weeks is a useful and potentially cost-saving strategy to diagnose and treat patients with NCCP. The small number of trials and patients included in these meta-analyses limit their generalizability; therefore more evidence is needed to confirm these results.23,24

C) Functional (non-ulcer) dyspepsia

The diagnosis of functional dyspepsia (FD), also referred to as non-ulcer dyspepsia (NUD) is defined as 12 weeks or more of persistent or recurrent dyspepsia within the last 12 months plus the absence of evidence that organic disease is likely to explain the symptoms (including evidence from upper endoscopy).2 This implies that a complete diagnostic evaluation has been completed and any obvious structural abnormality such as PUD or reflux esophagitis has been ruled out. Symptoms are frequently described as ulcer-like (e.g. burning) or dysmotility-like (e.g. nausea, bloating, early satiety, anorexia). Several pathophysiologic mechanisms have been proposed: motility abnormalities, visceral sensory abnormalities, psychological factors or chronic gastritis secondary to infection. One of the more prevalent theories currently being investigated is the possible relation between Hp infection and FD/NUD. Dyspepsia has been shown to occur after intentional Hp infection,25 suggesting a correlation; however, treatment results have been inconsistent and the role of Hp in non-ulcer dyspepsia remains controversial.26-28

Psychosocial factors (e.g. anxiety, depression and stress) have been shown in epidemiological studies to be more prevalent in patients with FD/NUD. A systematic review evaluated the effects of psychotherapy, cognitive behaviour therapy, relaxation therapy and guided imagery or hypnosis.26 The 3 trials included in the review showed improvement of symptoms at 12 weeks; however, the effect was no different after one year. Due to the heterogeneity of these studies, the results were not pooled and no specific recommendations were derived. Psychotherapy should be evaluated on an individual basis and considered in patients with a significant psychiatric condition or as an adjunct to medical management.

The management of FD/NUD is often based on the predominant symptoms patients report. A plethora of data has been published and recently a Cochrane review analyzed 61 pharmacological intervention trials (antacids, bismuth salts, sucralfate, misoprostol, prokinetic agents, H2RAs and PPIs) for NUD.31 Due to trial limitations and significant heterogeneity, the management of NUD remains challenging and subjective. Nevertheless, indirect comparisons of the trials suggest that choice of therapy should be based on individual dyspepsia symptoms. Prokinetic agents were significantly better than H2RAs for symptoms of dysmotility such as nausea and early satiety, whereas H2RAs were better for heartburn. The evidence for antisecretory agents for reflux symptoms is strongest for PPIs as the studies were generally of higher methodological quality. However, due to the significant overlap in patients with symptoms of GERD and NUD, management of these patients mirrors that of GERD. More evidence is needed with clear delineation of patients and symptoms before any conclusions can be made.31

D) Peptic ulcer disease (PUD)

A peptic ulcer is a non-malignant lesion in the GI mucosa that may be acute, subacute or chronic. The major forms are duodenal ulcer (DU) and gastric ulcer (GU), and it is not uncommon for patients to develop both simultaneously. Lifetime prevalence is estimated to be 4-10% and is significantly higher in Hp-positive subjects - 10-20%.32-34

In general, a poor correlation exists between dyspeptic symptoms and presence of ulcers and there is no symptom complex that can adequately differentiate between GU, DU and NUD.35,36 Patients may experience minimal symptoms while others have severe initial presentation. Classic symptoms have been described as epigastric pain between the xiphoid process and the umbilicus or discomfort characterized by fullness, bloating, distention or nausea.35,36 Potential complications include hemorrhage (15-20%), perforation (5%), and gastric outlet obstruction (2%).36

Two decades ago, almost all peptic ulcers were considered to be idiopathic or due to excess gastric acid, stress or diet. Although acid injury is necessary for ulcers to form, acid secretion is normal in almost all patients with GU and increased in only one-third of patients with DUs. Today, it is well known that PUD is the end result of a number of etiological factors that disrupt GI defence. Hp infection and NSAIDs are now widely accepted as the major contributors to this disequilibrium.35,36 The remainder of this discussion attempts to update the reader on new guidelines or
clinical trials related to *H. pylori*, NSAIDs and the relationship between the two.

**i) H. pylori**

*H. pylori* infects ≥20% of the western world’s population; the incidence and prevalence varying with age and economic status. Factors associated with an increased prevalence include low socio-economic status, poor sanitary conditions and overcrowding. Up to 20% of those infected with *H. pylori* are found to have PUD, with >90% identification in DU and 70-85% in GU. Curing *H. pylori* infection will not only reduce the ulcer recurrence rate but also the risk of infection will not only reduce the Hp infection rate in many Canadian populations. As the incidence and prevalence of *H. pylori* seems to be decreasing in industrialized nations, including Canada, the role of accurate testing becomes increasingly important and primary care diagnostic tests that were once adequate need reappraisal. The 2004 Canadian *H. pylori* Study Group (CHSG) Consensus does not recommend stool antigen tests as an acceptable tool to diagnose infection in community-based practice based on lack of sufficient evidence and the need for dedicated and experienced laboratory staff. Serology was not considered to be accurate in many Canadian populations because, as the prevalence of infection declines, the predictive value of serology will become less reliable. For now, the urea breath test remains first choice when endoscopy is not indicated.

Since *H. pylori* was first cultured from the human GI tract in 1984, the relationship between it and GI ulcers has been explored in >3,000 RCTs, with a multitude of data supporting eradication rates of up to 96% with some regimens. Compared with acid suppression alone, *H. pylori* eradication therapy has been well proven to facilitate ulcer healing and reduce ulcer recurrence and complication rates several-fold. After successful eradication of *H. pylori*, recurrences of PUD are expected to be <5% annually. Given the proven importance of eradicating infection, finding the “ideal” regimen is vital. Single- and dual-agent therapy should not be used because of the unacceptably low eradication rates (<70%). CHSG guidelines suggest quadruple therapy for 10-14 days is as effective and well tolerated as 7-10 day PPI-based triple therapy regimens (see Table 6). However, given the complexity of a quadruple regimen, triple therapy with a PPI is often made first choice in practice. Newer evidence is emerging to suggest PPI-based triple regimens are more effective if administered for 14 days, although the increase in benefits is small (~5%).

**TABLE 6: Regimens for H. pylori eradication**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>Triple Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>PPI bid + clarithromycin 500 mg bid + (amoxicillin 1 g bid or metronidazole 500 mg bid)</td>
<td>Duration 7-14 days</td>
</tr>
<tr>
<td></td>
<td>Eradication rates of 80-90% in RCTs</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin 250 mg bid may be used in metronidazole-based regimens but is inadequate if combined with amoxicillin</td>
</tr>
<tr>
<td></td>
<td>Metronidazole is typically substituted for amoxicillin for penicillin allergic patients</td>
</tr>
<tr>
<td><strong>Quadruple Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>H2RA bid or PPI bid + Bismuth subsalicylate (525 mg) bid tid + metronidazole 250 mg bid or 500 mg tid + tetracycline 250 mg bid or 500 mg tid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ranitidine bismuth citrate was discontinued from the Canadian market in 2000.</td>
</tr>
<tr>
<td></td>
<td>Ranitidine should not be substituted for ranitidine bismuth citrate</td>
</tr>
<tr>
<td></td>
<td>Duration 14 days</td>
</tr>
<tr>
<td></td>
<td>Eradication rates of 75-85% in RCTs</td>
</tr>
</tbody>
</table>

**TABLE 7: Risk Factors for NSAID/ASA-Induced Ulcers and Upper GI Complications**

<table>
<thead>
<tr>
<th>Established</th>
<th>Possible</th>
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<tbody>
<tr>
<td>Advanced age (&gt;65 years)</td>
<td>NSAID-related dyspepsia</td>
</tr>
<tr>
<td>History of PUD or ulcer-related complication (e.g. upper GI bleeding)</td>
<td>Duration of NSAID use (however as little as one week exposure has been reported)</td>
</tr>
<tr>
<td>High-dose NSAIDs</td>
<td>Concomitant use of corticosteroids</td>
</tr>
<tr>
<td>ASA (including low cardioprotective dosages)</td>
<td>Concomitant illness (e.g., cardiovascular disease, rheumatoid arthritis)</td>
</tr>
<tr>
<td>Coagulopathy or concomitant anticoagulant or antiplatelet Rx - markedly increase the risk of bleeding when used concurrently with NSAIDs or ASA.</td>
<td>Concomitant use of corticosteroids</td>
</tr>
<tr>
<td>There is evidence to suggest that antipatelet drugs such as clopidogrel and ticlopidine also increase the risk of GI bleeding when used in combination with NSAIDs or ASA.</td>
<td></td>
</tr>
<tr>
<td>Advanced age (&gt;65 years)</td>
<td>History of PUD or ulcer-related complication (e.g. upper GI bleeding)</td>
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Adapted from 33,52,56-59

March 2006
and amoxicillin, 0%; confirming published U.S. data.42,45,46

Cases in which the patient has undergone more than one treatment without successful eradication of Hp infection are typically difficult to manage with low likelihood of cure. CHSG suggests susceptibility testing for those who fail first-line therapy to guide selection of susceptibility testing for those who fail.47,48 CHSG recommends that result in significant morbidity and mortality.42 Given the widespread use of a PPI substantially reduces the risk of NSAID-related ulcers and complications annually.49-51 Risk factors for ulcers and complications secondary to NSAIDs are presented in Table 7. Additive risk is conferred when risk factors are combined.47

Prevention should be considered for those at increased risk for GI injury or those who would be at significant risk for morbidity/mortality if a complication developed. A number of strategies have been used to reduce the risk of NSAID-related ulcers and complications: buffering or enteric coating of the NSAID formulation; antacids; sucralfate; H2RAs; misoprostol; PPIs (see Table 8). There is insufficient evidence to support the use of buffer or enteric coating, antacids or sucralfate in reducing the risk of NSAID-related ulcers and their complications. H2RA co-therapy has been shown to be effective in reducing the risk of endoscopic duodenal but not gastric ulcers. Double-dose H2RA co-therapy was effective at reducing the risk of duodenal ulcer (DU) and GU.50-53,55-57,61,64,66,68,69

Misoprostol has been shown to reduce the risk of ulcer56,59,60 and serious ulcer-related GI complications.50,51 Misoprostol 800 mcg/day was superior to 400 mcg/day for the prevention of endoscopic gastric ulcers; a dose response relationship was not seen with duodenal ulcers.52,55,56,61 However, multiple daily dosing, its urotrophic effects, abdominal cramping, and dose-related diarrhea limit its use. The total daily misoprostol dosage may be reduced to minimize diarrhea, but dosages as low as 400 mcg/day may compromise its gastroprotective effect. Substantial data has proven concomitant use of a PPI substantially reduces the risk of DU and GU associated with non-selective NSAIDs compared to various other therapies56,57,59,61,64-66. Overall, H2RAs and PPIs are better tolerated than misoprostol, and reduced NSAID related dyspeptic symptoms.61

An alternative proposed approach has been to use COX-2 selective NSAIDs, as it was previously observed that NSAIDs with greater inhibition of COX-2 versus COX-1 appeared to be associated with a lower prevalence of GI ulceration and erosions on endoscopic evaluation.52,57,67,68 This review would not be complete without a brief discussion of the recent COX-2 trials, despite the fact that in late 2004, evidence became available associating COX-2 use with significant cardiovascular concerns, increased risk of heart attack and stroke, compared with placebo. Since the publication of this information celecoxib is the only remaining selective COX-2 agent on the Canadian market and is typically avoided in those at risk of cardiovascular events. Two large multicentre, double-blind trials, CLASS59 and VIGOR,68 examined the GI safety of COX-2 agents. Both trials used high doses of the specific COX-2 inhibitor and selected patients in the CLASS trial received low-dose ASA. Initial analysis of the CLASS and VIGOR trials indicated that both celecoxib and rofecoxib decreased the risk of developing upper GI clinical events and complications by ~50% when compared with traditional agents in patients not taking concomitant low-dose ASA. The beneficial effects of a COX-2 inhibitor may ablate the GI safety of these agents as suggested in the CLASS study post-hoc analyses.67 The utility of PPIs in combination with non-selective NSAID versus COX-2 selective inhibitors have been explored as a means to reduce the risk of recurrent bleeding in Hp-negative patients with a recent history of ulcer-related bleeding.61 Results suggest that using celecoxib monotherapy is as effective as adding a PPI to a non-selective NSAID among patients with a recent

### TABLE 8: Strategies for Reducing GI Risk in Patients Receiving Chronic NSAID Therapy

<table>
<thead>
<tr>
<th>Risk</th>
<th>Definition</th>
<th>Suggested management</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>&lt;65 yr, no ASA, no prior ulcer or GI complication</td>
<td>Non-selective NSAID alone</td>
</tr>
<tr>
<td>Moderate</td>
<td>One to two risk factors (e.g., age &gt; 65 yr, high-dose NSAIDs, low-dose ASA)</td>
<td>Partially selective NSAID (e.g. meloxicam) plus PPI or misoprostol; or selective COX-2 inhibitor</td>
</tr>
<tr>
<td>High</td>
<td>≥3 risk factors or concomitant ASA, corticosteroids or warfarin</td>
<td>Selective COX-2 inhibitor plus PPI or misoprostol*</td>
</tr>
<tr>
<td>Very high</td>
<td>Prior ulcer or ulcer-related complication</td>
<td>Selective COX-2 inhibitor plus PPI or misoprostol* Consider avoiding non-selective NSAIDs and selective COX-2 inhibitors</td>
</tr>
</tbody>
</table>

*Not studied in prospective RCTs; theoretically useful. Level of risk represent general, but not complete agreement among experts. The preferred strategy for each group remains uncertain and some of the suggested strategies have not been investigated in appropriate clinical trials. Compiled from references 56,57,60-62,73-75.
history of ulcer bleeding. There is growing clinical use of combined COX-2 inhibitors with acid suppressive therapy or misoprostol, especially in those with very high risk of complications or previous history of PUD events. Although such combination may offer theoretically better GI protection, especially in very high risk circumstances, to date, there are no published outcome trials to establish the benefits of these combinations.

When an active ulcer is suspected or confirmed, therapy with the NSAID should be stopped whenever possible and smoking should be stopped to improve healing. PPIs are the preferred treatment as they provide a rapid rate of ulcer healing, especially in the setting of complicated, large ulcers. If chronic NSAID therapy must be continued, potential options include use of a COX-2 selective NSAID (e.g. celecoxib), reducing the dosage of the non-selective agent and/or adding concomitant therapy with PPIs or misoprostol. PPIs are the drugs of choice when the NSAID must be continued, as potent acid suppression is required to accelerate ulcer healing.

### H pylori interaction with ASA/NSAIDs

An interaction between H. pylori and NSAIDs is biologically plausible given their different mechanisms of disrupting gastric mucosal defense but published data did not always confirm this. A recent systematic review demonstrated synergism between H. pylori and NSAIDs for the development of PUD and ulcer bleeding. The risk of PUD was reported to be ~60-fold higher in H. pylori positive NSAID users compared with H. pylori-negative subjects not taking NSAID. Moreover, H. pylori infection was shown to increase the risk of ulcer bleeding by 1.8-fold, NSAID use by 4.85-fold, and the presence of both factors by 6.1-fold compared with the risk of bleeding among H. pylori-negative subjects not taking NSAID. Table 9 summarizes the published data in this area and current clinical practice. CHSG supports H. pylori testing and eradication for naive NSAID users. A similar strategy has also been suggested for naive ASA users, although the efficacy of such an approach has not been confirmed. In chronic ASA/NSAID users, recommendations depend on the risk of PUD complications and the type of NSAID.

### ROLE OF THE PHARMACIST

The management of GI acid-related disorders continues to evolve with a wealth of literature for both functional and organic acid-associated conditions. As pharmacists are often the first healthcare professionals encountered by the patient, we are uniquely positioned to identify, counsel and monitor patients requiring acute or chronic therapy for conditions related to gastric acid. Pharmacists should have a working knowledge of the pathophysiology of gastric acid-related diseases, risk stratification, potential under- and over-treated acid-disorders, as well as the efficacy and safety of the available pharmacological agents/regimens.

The patient interview should include a patient’s past medical and medication history, the nature and timing of symptoms and the presence of alarm features. Intervention through education, counselling and recommendation of initial non-prescription therapies such as antacids or H2RAs may be appropriate for patients at low risk. Collaboration with physicians is vital when pharmacists identify and refer patients with alarm symptoms. The patient should be educated regarding the disease state and its potential consequences.

Through medication reviews, pharmacists can identify:

- **Medications that are ulcerogenic or promote injury to the esophageal and/or gastric mucosa**;
- **Medications that exacerbate GERD**;
- **The pattern of both prescription and non-prescription NSAID use and patients who will require gastric protection**;
- **Patients who are experiencing recurrence or complications of PUD or GERD**;
- **Significant drug-drug interactions and adverse effects**;
- **Patients who are not adhering to a prescribed regimen**;
- **Optimal administration and scheduling of medications and alternative forms of oral dosing**.

The role of the pharmacist as patient advocate and educator cannot be overstated.

### TABLE 9: Strategies for approaching H. pylori status in the setting of NSAID Therapy

<table>
<thead>
<tr>
<th>H. pylori Test- &amp; Treat Approach</th>
<th>Long-Term PPI Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Naïve to ASA/NSAIDs</strong></td>
<td></td>
</tr>
<tr>
<td>a) Naïve ASA users</td>
<td>✔</td>
</tr>
<tr>
<td>b) Naïve NSAIDs users</td>
<td>✔ with evidence</td>
</tr>
<tr>
<td>c) Chronic ASA users</td>
<td></td>
</tr>
<tr>
<td>a) With a recent ulcer complication</td>
<td>✔</td>
</tr>
<tr>
<td>b) At high risk for ulcer complication</td>
<td>✔ with evidence</td>
</tr>
<tr>
<td>c) At low risk for ulcer complication</td>
<td>X</td>
</tr>
<tr>
<td><strong>Chronic NSAIDs users</strong></td>
<td></td>
</tr>
<tr>
<td>a) With a recent ulcer complication</td>
<td>✔</td>
</tr>
<tr>
<td>b) At high risk for ulcer complication</td>
<td>✔ with evidence</td>
</tr>
<tr>
<td>c) At low risk for ulcer complication</td>
<td>X</td>
</tr>
</tbody>
</table>

Adapted from 56,70,83-89
disease and severity, with dyspepsia the most common presenting symptom of all acid-related disorders. Proton pump inhibitors remain the cornerstone of medical therapy. The majority of patients will need empiric therapy after a thorough clinical history and symptom description is established. This educational module attempts to highlight important information and evidence-based updates on the management of uninvestigated dyspepsia, GERD and PUD and how this information can be applied to the Canadian population.

Pharmacists are in a unique and key position, through patient education and collaboration with other health-care providers to optimize the care of patients with acid-related disorders.

REFERENCES


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QUESTIONS

1. Which case best characterizes a patient with heartburn that a pharmacist should refer to a physician for further medical evaluation?
   a) 50-year-old man who awakens at night with heartburn, coughing, and choking
   b) 20-year-old student complaining of indigestion after eating pizza
   c) 40-year-old woman who has heartburn once a month
   d) 35-year-old man taking OTC H2RAs for one week

2. What alarm features should trigger investigation according to the Clinical Management Tool of the CanDys Uninvestigated Dyspepsia guidelines? Choose the best answer.
   a) Diarrhea, vomiting, anemia, odynophagia
   b) Vomiting, bleeding/anemia, abdominal mass/weight loss, dysphagia
   c) Shortness of breath, chest pain, weight loss, tinnitus
   d) Night sweats, heartburn, regurgitation, shortness of breath

3. Dyspepsia is one of the most common symptom complexes in patients with acid-related disorders.
   a) True
   b) False

4. Which statement(s) regarding the epidemiology and impact of GERD is/are TRUE?
   I. A significant percentage of adults report monthly heartburn symptoms.
   II. Patients with GERD report significant impairment in quality of life.
   III. Extraesophageal presentations should rule out GERD.
   IV. Heartburn and regurgitation are the cardinal symptoms of GERD.
   a) I, II, and III
   b) II and III
   c) I and III
   d) I, II and IV

5. Which statement(s) regarding the mechanisms of disease of GERD is/are FALSE?
   I. The main cause of GERD is contact of the esophageal epithelium with the acidic contents of the stomach.
   II. GERD symptoms may be caused by a combination of lower esophageal sphincter dysfunction, esophageal dysmotility and/or delay in gastric emptying.
   III. The severity of GERD symptoms is directly related to the degree or severity of erosive esophagitis.
   IV. Drug therapy targeting the underlying motility disorder of the esophagus is largely successful.
   a) I, II, and III
   b) III and IV
   c) I and III
   d) IV only

6. Which statement(s) regarding the clinical presentation and diagnosis of GERD is/are TRUE?
   I. Endoscopy and biopsy are the gold standard for diagnosis of GERD.
   II. All patients with GERD have erosive esophagitis.
   III. Dysphagia, weight loss, and hematemesis are alarm symptoms that should immediately prompt further testing for complications of GERD, such as stricture, ulcer or adenocarcinoma.
   a) I, II, and III
   b) II and III
   c) I and III
   d) IV only

IV. GERD is considered a progressive disease, with progression of both symptoms and esophagitis in all patients.
   a) I, II, and III
   b) I and III
   c) II and IV
   d) III only

CASE STUDY

ND is a 47-year-old male who presents to his family doctor with a three-month history of epigastric discomfort. His vitals are normal and his examination is unremarkable. He is approximately 290 lbs, approximately 30% over his ideal body weight and has an erratic eating schedule due to his job. He had been taking OTC antacids and famotidine 40 mg for approximately two months but has not experienced any significant relief. He denies any bleeding, vomiting or NSAID use.

7. How should the primary care physician respond to this patient?
   a) Treat the patient with eradication regimen that includes antibiotics since H pylori can be the culprit.
   b) Suggest lifestyle modifications, prescribe a PPI for four weeks and then reassess.
   c) Refer the patient to a gastroenterologist for endoscopy.
   d) Suggest lifestyle modifications and continue OTC antacids and/or H2RAs for symptomatic relief.

8. ND returns to the clinic for follow-up. The physician gives the patient a urea breath test and he tests negative for H pylori. His symptoms have lessened, but have not completely
resolved. What recommendation would be appropriate to provide to the primary care physician?

a) Treat the patient with an eradication regimen that includes antibiotics since *H pylori* can be the culprit despite a negative test.

b) Refer the patient to a gastroenterologist for endoscopy.

c) Continue current management and reassess after another four weeks.

d) Add H$_2$RA to the current regimen for four weeks and reassess.

9. Which statement(s) regarding Barrett’s esophagus and esophageal adenocarcinoma is/are TRUE?

I. Barrett’s esophagus is associated with long-standing (chronic) reflux and a risk factor for esophageal adenocarcinoma.

II. The risk of adenocarcinoma is extremely high, especially in patients with Barrett’s esophagus.

III. Treatment of GERD with PPIs has been shown to decrease the incidence of Barrett’s esophagus.

IV. Patients who have had chronic reflux for more than 10 years should receive a “once in a lifetime” endoscopy to assess for Barrett’s esophagus.

a) I, II and III

b) II and III

c) I and IV

d) all of the above

10. Since few trials have directly compared different PPIs, whether the different pharmacokinetic properties of these drugs translate into significant clinical differences is unknown.

a) True

b) False

11. Clinical studies indicate that the most effective acid-suppression medications belong to which class of drugs?

a) Antacids

b) PPIs

c) H$_2$RAs

d) Sucralfate

12. Proton pump inhibitors have been shown to play a significant role in:

a) Eradicating *H pylori* in the context of a triple therapy with antibiotics;

b) Protecting against NSAID-induced duodenal ulcers, not gastric ulcers;

c) None of the above.

d) (a) and (b)

13. *H pylori* is a pathogen associated with the development of:

a) GERD

b) NSAID-induced ulcers

c) PUD

d) All of the above

14. Mark, a 39-year-old construction worker, had symptoms of PUD and was found to be *H pylori* positive. He received triple therapy treatment with lansoprazole + clarithromycin + amoxicillin (HP-PACÆ) for 2 weeks and his symptoms resolved. Future treatment options for Mark include:

a) Intermittent PPI or H$_2$RA for recurrent symptoms.

b) Diovol PRN.

c) Chronic acid suppression with H$_2$RA or PPI.

d) No treatment.

15. Which statement about therapy with NSAIDs is TRUE?

a) COX-2 inhibitors have not been associated with risk of cardiovascular events.

b) Standard dose H$_2$RAs are effective in reducing the risk of NSAID-induced gastric ulcers.

c) Patients >65 starting on meloxicam therapy should receive PPI or misoprostol co-therapy, or switch to celecoxib.

b) Low-dose ASA is not associated with an increased risk of upper Gl bleeding.

16. Which statement about prophylaxis in patients treated with NSAIDs is FALSE?

a) Co-therapy with a PPI has been shown to reduce the incidence of gastroduodenal ulcers.

b) Standard dose H$_2$RAs (e.g. famotidine 20 mg bid) are not indicated in the prevention of gastric ulcers.

c) Low-dose misoprostol (e.g. 200 mcg bid) is as effective as a PPI with a low incidence of side effects.

d) PPI therapy has been shown to be effective for treating NSAID-associated Gl ulcer complications.

17. Martha, a 47-year-old school teacher, presents with a recent onset of heartburn, gnawing, abdominal pain that has been causing discomfort. She denies vomiting, blood in her stool or recent weight loss. She takes HCTZ 25 mg daily for hypertension and recently naproxen 550 mg intermittently for lower back pain. What is the best initial treatment option?

a) Check *H pylori* serology status.

b) Stop intermittent naproxen use and suggest acetaminophen.

c) Treat empirically with sulcrafate.

d) Refer to GI specialist for upper endoscopy.

18. Burt is a 68-year-old retired engineer presenting with a recent history of epigastric symptoms. He has experienced a 10-pound weight loss in the past 3 months. Upon further examination, he is found to have a heme-positive stool. What is the best approach?

a) Check *H pylori* stool antigen.

b) Check *H pylori* serology.

c) Endoscopy

d) Empiric triple therapy with PPI + 2 antibiotics

19. For the prevention of DU recurrence after initial ulcer healing, which statement below about *H pylori* eradication treatment is TRUE?

a) *H pylori* eradication treatment in addition to acid suppressive therapy is superior to acid suppressive therapy alone.

b) PPI therapy is superior to *H pylori* eradication.

c) Neither strategy is very effective.

d) There is no significant difference between the 2 treatment options.

20. Simon, a 32-year-old stockbroker, presents to the clinic with burning mid-epigastric discomfort that is relieved with Tums, which he has been using daily. *H pylori* testing is positive by urea breath testing. Simon has no known drug allergies. Treatment options include:

a) PPI + amoxicillin + metronidazole x 10 days

b) PPI + levofloxacin + amoxicillin x 10 days

c) PPI + amoxicillin + clarithromycin x 7 days

d) Ranitidine HCl + amoxicillin + tetracycline x 14 days
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