

Class Update: Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Month/Year of Review: March 2015

Date of Last Review: Proton Pump Inhibitors: March 2014
Histamine-2 Receptor Antagonists: January 2013

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:

The Health Evidence Review Commission (HERC) is limiting the funding for treatment of gastro-esophageal reflux disease (GERD) to 8 weeks on the OHP Prioritized List of Health Services. Prior Authorization (PA) criteria are in place for non-preferred PPIs to promote PDL options. There is currently open access to preferred PPIs and H2RAs.

Research Questions:

- What is the comparative effectiveness of different proton pump inhibitors (PPIs) in patients being treated for symptoms of gastro-esophageal reflux, gastro-esophageal reflux disease (GERD), peptic (gastric or duodenal) ulcer disease (PUD) or non-steroidal anti-inflammatory drug (NSAID)-induced ulcers?
- What is the comparative effectiveness of different histamine-2 receptor antagonists (H2RAs) in patients being treated for symptoms of gastro-esophageal reflux or GERD?
- What is the comparative safety of different PPIs in patients being treated for symptoms of gastro-esophageal reflux, PUD or NSAID-induced ulcers?
- What is the comparative safety of different H2RAs in patients being treated for symptoms of gastro-esophageal reflux?
- Is there evidence that long-term treatment (>8 weeks) of GERD or symptoms of gastro-esophageal reflux with a PPI is more effective than short-term treatment (≤8 weeks)?
- Are there specific sub-populations in which a specific PPI or H2RA may be more effective or associated with increased harms?

Previous Conclusions and Recommendations:

Proton Pump Inhibitors

- Patients should be re-evaluated for benefits and risks while on long-term PPI therapy for potential adverse events.
- There is no consistent difference in efficacy or safety between PPIs to justify selection of any PPI as clinically superior to the other drugs in the class.
- No evidence supports differences in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities.

Histamine 2-Receptor Antagonists

- Evidence does not support a difference in efficacy or harms.
- Cimetidine is associated with more adverse events; ranitidine has the second most adverse events.
- Consider inclusion of at least one H2RA with special consideration for famotidine or ranitidine for pediatric use.

Conclusions and Recommendations:

- There is high quality evidence that there is no difference in effectiveness between PPIs for healing and maintaining remission of erosive gastro-esophagitis based on endoscopy, relieving symptoms of heartburn for up to 8 weeks, or treatment of PUD or NSAID-induced ulcers.
- There is high quality evidence that there is no difference in efficacy between H2RAs for the management of gastro-esophageal reflux or GERD.
- There is moderate quality evidence that there are no differences in harms between different PPIs or between H2RAs. In general, long-term use of PPIs are associated with severe adverse effects that are not associated with H2RAs
 - No association between outpatient use of H2RAs and risk for *Clostridium difficile*-associated diarrhea was found; this evidence conflicts with previous evidence that suggested an association with chronic PPI use does exist.
 - Patients on long-term PPI therapy should receive an annual re-evaluation to determine need for continued therapy secondary to increased harms, including osteoporosis, *Clostridium difficile*-associated diarrhea and certain nutritional deficiencies. However, the accumulating evidence from better designed, prospective clinical studies cannot substantiate the initial concerns for adverse cardiovascular effects of PPI use in patients on clopidogrel originally seen in the retrospective cohort studies.
- There is high quality evidence that there is no difference between long-term treatment of PPIs and short-term treatment of PPIs for erosive gastro-esophagitis based on endoscopy.
- There is insufficient evidence for long-term treatment of PPIs for symptomatic GERD as most studies evaluating PPIs for the management of GERD are limited to 8 weeks' duration.
- There is insufficient evidence to suggest long-term PPI use significantly decreases incidence of esophageal adenocarcinoma and/or high-grade dysplasia in patients with Barrett's esophagus. The role of PPIs in Barrett's esophagus remains uncertain due to conflicting observational data.
- There is moderate quality evidence that there is no difference in safety or efficacy between PPIs in managing symptoms of reflux in the pediatric population aged 1 year and older. Evidence for use of H2RAs is limited to ranitidine. There is insufficient evidence for use of these agents in infants.
- Low quality evidence suggests PPIs and H2RAs in Cystic Fibrosis patients improves gastrointestinal symptoms and fat absorption but there is insufficient evidence of their effect on nutritional status, lung function, quality of life or mortality.
- Use current evidence and data presented in the PPI/H2RA Drug Use Evaluation to guide new PA criteria.
- Evaluate comparative drug costs for both classes in the executive session.

Background:

Dyspepsia describes a range of symptoms that arise from the upper gastrointestinal (GI) tract, but it has no universally accepted definition.¹ These symptoms, which typically present for 4 weeks or more, include upper abdominal pain or discomfort, heartburn, gastric reflux, nausea or vomiting.¹ Gastro-esophageal reflux can also cause a variety of gastroesophageal symptoms (i.e., heartburn and regurgitation) but can also cause extraesophageal symptoms (i.e., chronic cough, hoarseness, sore throat) and can overlap substantially with other disorders such as dyspepsia, irritable bowel syndrome, respiratory disorders or somatoform disorders.² Patients with GERD can also present with dysphagia, upper GI bleeding, chest pain and epigastric pain – “red flag” symptoms that should be clarified by immediate appropriate diagnostic evaluation. GERD is a multifactorial disorder related mainly to failure of the anti-reflux mechanisms. The pathophysiologic components of GERD, which can be either alone or combined, can include: a mechanically defective lower esophageal sphincter (LES); transient

LES relaxation; a hiatal hernia; insufficient esophageal peristalsis; delayed gastric emptying or impaired esophageal clearance. Several factors such as stress, obesity, pregnancy, diet or drugs can also play a role in the pathophysiology of GERD.

Epidemiologic data on GERD are not reliable largely because data are based on subjective symptoms such as heartburn and regurgitation. Using these data, prevalence ranges between 0.1% and 20% in industrial countries. The natural course of GERD is chronic but the majority of patients with GERD will remain within the initial level of severity of disease at diagnosis; about 4-7% of patients progress and develop further complications. Endoscopy is the most important diagnostic investigation to prove the presence of GERD, which can distinguish between non-erosive reflux disease (NERD) and erosive reflux disease (ERD) and Barrett's esophagus (BE).²

The primary goals of medical therapy for GERD are to control heartburn, heal gastroesophageal mucosal injuries and improve patient quality of life. Patients should avoid large meals and lying down within 3 hours after eating. Ingestion of fatty or spicy foods, chocolate, coffee, peppermint, citrus fruits and juices, tomato, carbonated drinks and alcohol may also increase reflux events and GERD symptoms. Weight loss also reduces risk for GERD and makes acid suppressant therapy more effective. Antacids are well tolerated, safe and effective in reducing heartburn and controlling acid regurgitation in patients with mild reflux disease. Proton pump inhibitors and H2RAs represent the mainstay of GERD medical treatment and provide healing and symptomatic relief in patients with esophageal syndromes.² An 8-week course of PPIs is recommended for symptomatic GERD.³ Zollinger-Ellison syndrome and other related conditions often require longer duration of PPI therapy because of the presence refractory ulcers in the upper GI tract.³

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes since the last DURM review were conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. Time limits included restricting evidence published since the PPI class was last reviewed by the P&T committee in March 2014 and the H2RA class in January 2013. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Effectiveness of PPIs and H2RAs

PPIs and H2RAs in the Adult Population

The pathogenesis of NERD and its response to treatment may differ from GERD with esophagitis. A Cochrane systematic review was performed in order to summarize, quantify and compare the efficacy of short-term use of PPIs and H2RAs in adults with GERD, treated either empirically without diagnosis by

endoscopy or in those with NERD. A total of 1,314 participants were studied in 24 double-blind, parallel group studies of one to 12 weeks' duration. Fifteen trials were eligible for inclusion in the endoscopy group, 15 trials were eligible for inclusion in the NERD group and 4 trials included both groups. Use of antacids was permitted in most of the studies. In the empiric group, the risk for heartburn remission, the primary efficacy variable studied, was significantly lower for PPIs than for the H2RAs in placebo-controlled studies (relative risk (RR) 0.37; 95% CI, 0.32 to 0.44 vs. RR 0.77; 95% CI, 0.60 to 0.99, respectively). In head-to-head studies, PPIs were also significantly more effective than H2RAs (RR 0.66; 95% CI, 0.60 to 0.73). In patients with NERD, the risk for heartburn remission was relatively equal between PPIs and H2RAs in placebo-controlled studies (RR 0.71; 95% CI, 0.65 to 0.78 vs. RR 0.84; 95% CI, 0.74 to 0.95, respectively). Thus, PPIs appear to be more effective at relieving symptoms than H2RAs when used for empiric treatment of GERD but the difference in efficacy between these two drug classes narrows when used in specifically patients with NERD.⁴ In-class differences between PPIs and H2RAs were not evaluated.

A similar meta-analysis evaluating PPIs was conducted in patients diagnosed with NERD. A total of 6,072 participants were studied in 17 RCTs ranging from 4 weeks to 6 months' duration. Seven studies involving 1,882 participants compared a PPI with a H2RA on the rate of symptomatic relief of NERD which showed PPIs to be significantly superior to H2RAs (RR 1.629; 95% CI, 1.422 to 1.867). The superiority of PPIs was maintained in sub-group analyses comparing short-term with long-term duration of treatment and with high dose PPI compared with low dose. Eleven studies involving 5,416 participants compared a PPI to placebo on the rate of symptomatic relief of NERD which showed PPIs to be significantly superior to placebo (RR 1.903; 95% CI, 1.573 to 2.302), with similar results comparing short-term with long-term duration of treatment and with high dose compared to low dose PPIs. There was no significant difference between PPIs and H2RAs in the rate of adverse events reported in these studies (RR 0.928; 95% CI, 0.776 to 1.110). In addition, there was no significant difference between PPIs and placebo in the rate of adverse events reported (RR 1.000; 95% CI, 0.896 to 1.116). In addition, sub-group analyses comparing short-term with long-term duration of PPI treatment and high dose PPIs compared with low dose PPIs did not reveal a significant difference in reported adverse events relative to placebo. There were no significant differences in rate of symptomatic relief of NERD using higher doses of PPIs (54.4%; 95% CI, 43.3 to 59.5%) versus lower doses (56.3%; 95% CI, 39.5 to 73.2%), nor were there any differences when PPIs were used long-term (51.4%; 95% CI, 43.3 to 59.5) versus short-term (51.5%; 95% CI, 43.2 to 59.8). Unfortunately, lengths of these durations were not explicitly defined. Individual response rates between PPIs were not significantly different (see **table 1**). Unfortunately, results from the meta-analysis are limited by significant heterogeneity between the studies ($I^2=96.8\%$). Only 3 of the 17 RCTs provided adequate sequence generation and no studies adequately concealed allocation. No obvious publication bias was identified.⁵

Table 1. Rate of Symptomatic Relief in Patients with Non-erosive Reflux Disease Treated with Proton Pump Inhibitors.⁵

Proton Pump Inhibitor	Response Rate
Lansoprazole	52.1% (95% CI, 39.2 to 65.0%)
Omeprazole	52.1% (95% CI, 35.5 to 68.8%)
Pantoprazole	44.7% (95% CI, 36.9 to 52.6%)
Rabeprazole	60.8% (95% CI, 36.7 to 84.9%)

Safety of PPIs and H2RAs

Risk of Pre-cancerous Lesions with Long-term Use of PPIs

The safety of long-term use of PPIs is unclear. Long-term acid suppression results in hypergastrinemia, which has been associated with hyperplasia of the enterochromaffin cells lining the digestive tract. Indeed, the risk of development of gastric pre-malignant lesions with use of PPIs is inconsistent in the literature. A Cochrane systematic review was performed in order to assess the association for risk for the development of gastric pre-malignant lesions, such as atrophic gastritis, intestinal metaplasia, enterochromaffin-like cell hyperplasia, and dysplasia, in adult patients on PPIs for at least 6 months. A total of 1,789 participants in 7 RCTs were eligible for inclusion, though none of the studies assessed the development or progression of gastric pre-malignant lesions as a primary outcome. There was no apparent risk for the development of corporal atrophy or corporal intestinal metaplasia with long-term use of PPIs relative to non-PPI users (odds ratio (OR) 1.50; 95% CI, 0.59 to 3.80; $p=0.39$ and OR 1.46; 95% CI, 0.43 to 5.03; $p=0.55$, respectively). However, there was a significantly higher risk for the development of either diffuse (simple) (OR 5.01; 95% CI, 1.54 to 16.26; $p=0.007$) or linear/micronodular (focal) enterochromaffin-like cell hyperplasia (OR 3.98; 95% CI, 1.31 to 12.16; $p=0.02$) than non-PPI users. None of the included studies reported participants showing any dysplastic or neoplastic changes. There were an inadequate number of studies to assess whether use of PPIs for greater than 1 year was associated with higher risk relative to 6 months of PPI use. Thus, more studies are needed to determine if a significant risk for development of corpus gastric atrophy or intestinal metaplasia exists with long-term use of PPIs since current evidence remains imprecise.⁶

Risk of Adverse Cardiovascular Events with Concomitant Use of PPIs with Clopidogrel

Two systematic reviews recently assessed the concomitant use of clopidogrel with PPIs and its impact on clinical outcomes.^{7,8} The FDA published warnings of concomitant therapy of clopidogrel with PPIs, which were initially based on laboratory data and pooled data from retrospective cohort studies limited by substantial heterogeneity and high risk of bias. The former reported reduced *ex vivo* inhibition of platelet aggregation, indicative of a pharmacological interaction between certain PPIs and clopidogrel. Retrospective studies reported adverse clinical outcomes in cases of concomitant therapy, which seemed to correlate with the laboratory data. Clopidogrel is most commonly prescribed in the setting of coronary heart disease, such as acute coronary syndrome or after percutaneous coronary intervention. However, the two meta-analyses did not find any discernable differences in the clinical impact of individual PPIs when used concomitantly with clopidogrel. Each PPI had evidence of statistically significant harm with clopidogrel; however, significant cardiovascular harm was also found in patients on PPIs without clopidogrel relative to populations that do not use a PPI. In both analyses, pooling data solely from RCTs showed no risk of cardiovascular outcomes with concomitant use of PPIs and clopidogrel compared to PPIs users without clopidogrel.^{7,8}

The first meta-analysis found a higher incidence of short- and long-term major adverse cardiovascular events (MACE) among patients using PPIs in retrospective studies. Mortality was reported in 23 trials, of which 17 (74%) of them reported no risk difference for patients on PPIs. In the other six studies, the effect ranged from a reduced risk in one study (hazard ratio (HR) 0.68; 95% CI, 0.47 to 0.96) to an increased risk in five studies (RR 2.63; 95% CI, 1.17 to 5.94). Myocardial infarction (MI) was reported in 25 trials, of which 11 (44%) reported a significantly increased RR for PPI users ranging from 1.19 to 4.58. The other 14 studies reported no difference in MI. Of the 25 studies reporting MACE, 12 studies (48%) showed a significantly increased risk when PPIs were combined with clopidogrel, with an effect that ranged from HRs of 1.20 to 4.58. The other 13 studies showed no effect on outcome. Studies specifically evaluating omeprazole and esomeprazole, two PPIs of particular interest due to their role in CYP2C19 metabolism, had significant heterogeneity. Notably, nearly all the prospective studies and, most importantly, the only two trials with random allocation of a PPI, reported no detrimental clinical effect of PPIs in clopidogrel users.⁷

The second meta-analysis found similar findings after evaluating RCTs (n=2), controlled observational studies (n=19) and post-hoc analyses of clinical trials (n=2) reporting MACE in patients receiving clopidogrel. Risk of composite MACE for clopidogrel and individual PPIs were similar. Omeprazole was associated with an OR of 1.24 (95% CI, 1.07 to 1.43) with significant heterogeneity ($I^2=74\%$); esomeprazole was associated with an OR of 1.32 (95% CI, 1.09 to 1.60) with significant heterogeneity ($I^2=76\%$); lansoprazole was associated with an OR of 1.39 (95% CI, 1.23 to 1.57) with less heterogeneity ($I^2=26\%$); pantoprazole was associated with an OR of 1.41 (95% CI, 1.21 to 1.64), also limited by significant heterogeneity ($I^2=75\%$); and rabeprazole was associated with a nonsignificant OR of 1.38 (95% CI, 0.78 to 2.45), also limited by significant heterogeneity ($I^2=76\%$). There was no evidence for any consistent difference between PPIs and the risk of MI or other major adverse cardiac events. A significant cardiovascular risk was found with PPI use alone compared to patients not receiving clopidogrel or PPIs (OR 1.28; 95% CI, 1.14 to 1.44; $I^2=77\%$). The significant heterogeneity between studies that described the cardiovascular effects of PPIs in the absence of clopidogrel stemmed from one study; however, the risk of PPI use alone remained significant even without the study included (OR 1.39; 95% CI, 1.32 to 1.46). But like the previous meta-analysis, when a sensitivity analysis was performed on RCTs, the pooled OR for MACE was no longer statistically significant (OR 1.04; 95% CI, 0.72 to 1.51; $p=0.83$ vs. OR 0.94; 95% CI, 0.47 to 1.87; $p=0.87$, respectively).⁸

Risk of Clostridium difficile Infection with Use of H2RAs

A meta-analysis was performed to assess the association between H2RA use and *Clostridium difficile* infection (CDI).⁹ The role of gastric acid suppression has recently gained interest as a risk factor for CDI. Earlier meta-analyses suggested an association between PPIs and CDI and the FDA issued a safety alert for possible increased risk of CDI with chronic PPI use in 2012.¹⁰ Any analytical study examining the association between H2RAs and the incidence of CDI in the adult population was eligible for inclusion in this meta-analysis. Thirty-five observations from 33 eligible studies were pooled using a random effects model. Most studies did not specify the type or duration of H2RA therapy. The pooled effect estimate was 1.44 (95% CI, 1.22 to 1.70; $I^2=70.5\%$). The pooled effect estimate for high quality studies was 1.39 (95% CI, 1.15 to 1.68; $I^2=72.3\%$). This association was consistent across different subgroups (by study design and country) and there was no evidence of publication bias. The number needed to harm (NNH) with H2RAs in the general population at 1 year was 4549 persons (95% CI, 2860 to 9097). The NNH with H2RAs at 14 days after hospital admission in patients receiving antibiotics was 58 persons (95% CI, 37 to 115), whereas the NNH was 425 persons (95% CI, 267 to 848) if they did not receive antibiotics. Therefore, risk of CDI is low overall with H2RAs but risk is highest in hospitalized patients receiving antibiotics.⁹

Subpopulations

Decreased Risk of Esophageal Adenocarcinoma with PPIs in Patients with Barrett's Esophagus

This incidence of esophageal adenocarcinoma (EAC) has increased by more than six-fold in the last 30 years. Barrett's esophagus (BE) is a precursor lesion for EAC and confers a 30-125-fold higher risk of EAC. Preclinical studies indicate PPIs may prevent or delay progression of dysplasia in BE. At the same time, PPI-related acid suppression-induced hypergastrinemia and subsequent proliferation have led to concerns about the oncogenic potential of long-term PPI therapy. The primary analysis of this systematic review focused on assessing the risk of progression to EAC and/or high-grade dysplasia (BE-HGD) in patients with BE among PPI users (and H2RA users) compared with non-users.¹¹ Seven observational studies (five cohort, two case-control studies) were identified that reported on the association between PPIs and risk of EAC and/or BE-HGD and two observational studies (one cohort and one case-control) reporting on the association between H2RAs and these outcomes. Use of a PPI at the time of BE diagnosis was associated with a decreased risk of EAC and/or BE-HGD in patients with BE (unadjusted OR 0.26; 95% CI, 0.10 to 0.71). This protective effect persisted when adjusted for concomitant use of NSAIDs, aspirin or statins (adjusted OR 0.44; 95% CI, 0.24 to 0.83) as well as presence of erosive esophagitis or reflux symptoms (adjusted OR 0.15; 95% CI, 0.04 to 0.55). Long-term exposure to PPIs (>2-3

years) was associated with a greater protective effect on EAC and/or BE-HGD risk (adjusted OR 0.45; 95% CI, 0.19 to 1.06) whereas short-term exposure (<2-3 years) was not significantly associated with EAC and/or BE-HGD (adjusted OR 1.09; 95% CI, 0.47 to 2.56). The observed cumulative incidence rates of EAC and/or BE-HGD in patients with BE overall, non-dysplastic BE and BE with low grade dysplasia were 10.2, 6.8 and 18.3 per 1000 patient-years, respectively. There was insufficient data from these studies to allow estimation of PPIs' effect on risk of progression to EAC alone or BE-HGD alone. There were also insufficient data to allow pooling based on type, dose or frequency of use of PPIs. In addition, there was considerable heterogeneity in the overall analysis ($I^2=81\%$). Recently, two nested case-control studies resulted in observational evidence that conflicts with this meta-analysis, adding a level of ambiguity to the role of PPIs in BE.^{12,13} Two studies reported on the association between H2RA use and the risk of EAC in patients with BE but neither of them individually observed a protective association.¹¹

PPIs and H2RAs in the Pediatric Population

The natural history of gastro-esophageal reflux in infancy is generally that of a functional, self-limiting condition that improves with age; less than 5% of children with vomiting or regurgitation continue to have symptoms after infancy. Older children and children with co-existing medical conditions may have a much longer course of symptoms. A Cochrane systematic review was performed in order to provide a robust analysis of currently available pharmacological interventions used to treat children with gastro-esophageal reflux. All safety and efficacy outcomes studied in RCTs on study participants from birth to 16 years of age were assessed with a primary focus on improvement in clinical symptoms. A total of 1,201 participants were studied in 24 trials 4-8 weeks in length, most of which received pharmaceutical industry support for manuscript preparation. Most of the studies assessing PPIs and H2RAs enrolled children greater than 12 months of age with limited evidence in children under 1 year of age. In addition, several different endpoints were assessed, study design varied, and study populations were heterogeneous in these trials precluding the ability for the authors to perform a meta-analysis of the data. In general, moderate-quality evidence suggested from these trials that PPIs can reduce gastro-esophageal reflux symptoms in children with confirmed erosive esophagitis, improve pH metrics and improve erosive changes on endoscopy, particularly in older children. No PPIs demonstrated statistical superiority over another PPI and evidence is weaker for the use of PPIs in infants. Evidence also suggested that H2RAs can reduce symptoms but methodological differences between studies evaluating H2RAs make it difficult to assess efficacy overall. One study showed high dose ranitidine was comparable to omeprazole in symptom relief, pH indices and endoscopic findings. The addition of a H2RA to a PPI did not offer additional improvement in symptoms. No serious adverse events were noted in the trials. Overall, evidence supports the short-term use of PPIs in children with gastro-esophageal symptoms. Evidence for the use of H2RAs other than ranitidine is more limited, however, and use of either of these drug classes is limited in infants. No within class differences in efficacy or safety were demonstrated.¹⁴

PPIs and H2RAs in the Cystic Fibrosis Population

Impaired pancreatic function in patients with cystic fibrosis (CF) may result in increased gastric acidity, leading to heartburn, risk for development of peptic ulcers and impairment of oral pancreatic enzyme replacement therapy. Orally administered pancreatic enzymes may be inactivated by gastric acid in people with CF with pancreatic insufficiency leading to fat and protein malabsorption. The administration of gastric acid-reducing agents such as PPIs and H2RAs have been used as an adjunct to pancreatic enzyme therapy to improve absorption of fat and GI symptoms in patients with CF. A Cochrane systematic review was performed in order to establish the evidence regarding potential benefits and safety of PPIs and H2RAs in CF. Primary outcomes included nutritional status as assessed by weight, height and other indices of growth; symptoms related to increased gastric acidity such as epigastric pain or heartburn; and complications of increased gastric acidity such as gastric or duodenal ulcers. Secondary outcomes included measures of fat absorption, lung function, quality of life, mortality and adverse effects related to these drugs. A total of 273 participating children and adults in 17 RCTs were eligible for inclusion: seven trials were limited to children and four trials were limited only to adults. Most trials were placebo-controlled but unfortunately, study design and insufficient data from these trials prohibited

a meta-analysis from being conducted. Two placebo-controlled H2RA trials measured nutritional status which showed no significant improvements in height, weight and skinfold thickness between the treatment and control groups. Nine trials measured GI symptoms but none of the trials assessing a PPI or H2RA reported results. No trials assessed long-term complications of increased gastric acidity such as gastric or duodenal ulcers. For secondary outcomes, 7 trials reported significant improvement in measures of fat malabsorption; and two trials reported no significant improvement in nutritional status. No trials were identified assessing the effectiveness of PPIs or H2RAs in improving quality of life, long-term complications of increased gastric acidity or mortality. Lung function was reported to improve only narratively in two trials. Thus, limited evidence suggests PPIs and H2RAs in CF patients result in improvement in GI symptoms and fat absorption but there is insufficient evidence to suggest these drugs have an effect on nutritional status, lung function, quality of life or mortality. Participants in studies assessing PPIs and H2RAs tolerated the drugs well; only one participant was forced to withdraw from a study because of possible neurological complications due to cimetidine.¹⁵

New Guidelines:

National Institute for Health and Care Excellence

In 2014, NICE developed guidance for the management of dyspepsia and symptoms suggestive of GERD. Dyspepsia in primary care is broadly defined to include people with recurrent epigastric pain, heartburn or acid reflux, with or without bloating, nausea or vomiting. According to the guideline, lifestyle changes are core to the treatment of dyspepsia, which includes healthy eating, weight loss and smoking cessation. Known precipitants of dyspepsia should be avoided if possible, including smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Alternative therapy to medications known to cause dyspepsia (see **table 2**) should be considered.¹

Table 2. Drugs Associated with Increased Risk of Dyspepsia.¹

Calcium Channel Blockers	Nitrates	Theophylline	Bisphosphonates	Corticosteroids	Non-steroidal Anti-inflammatory Drugs
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Empirical, standard-dose PPI therapy for 4 weeks should be offered to patients with dyspepsia. Dosing of PPIs using language described by NICE are defined in **table 3**. Choice of a PPI should be based on cost, tolerability of the PPI, possible interactions with other drugs, and patient preference. Patients receiving PPI therapy for dyspepsia symptoms should reduce therapy to the lowest effective dose and reduce frequency by trying “as-needed” use when appropriate, and returning to self-treatment with an antacid. Patients who need long-term management of dyspepsia symptoms should have their condition reviewed annually and be encouraged to try stepping down or stopping therapy unless there is an underlying condition that necessitates continuing treatment.¹

Table 3. Proton Pump Inhibitor Doses Relating to NICE Evidence Synthesis and Recommendations.¹

Proton Pump Inhibitor	Standard Dose	Low Dose (on demand)	Double Dose
Esomeprazole	20 mg once daily	Not available	40 mg once daily
Lansoprazole	30 mg once daily	15 mg once daily	30 mg twice daily
Omeprazole	20 mg once daily	10 mg once daily	40 mg once 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

Patients with a diagnosis of GERD should be managed similarly to uninvestigated dyspepsia and be offered a standard-dosed PPI for 4 or 8 weeks. Again, the dose should be tapered to the lowest effective dose and patients are encouraged to manage symptoms only when needed. Patients with severe esophagitis should be given a standard-dose PPI for 8 weeks to allow for adequate healing. If initial treatment for healing severe esophagitis fails, switching to another standard-dose PPI or increasing the current PPI to a double-dose regimen may be considered, though evidence is lacking. In cases of severe esophagitis, long-term maintenance therapy of a standard-dose PPI may be required.¹

If the patient is diagnosed with PUD secondary to *Helicobacter pylori*, the bacteria must be eradicated using recommended 7-day therapy including a PPI, amoxicillin and either clarithromycin or metronidazole. However, if the patient has a NSAID-induced peptic ulcer, the NSAID must be discontinued and the patient started on a standard-dose PPI or H2RA therapy for 4 to 8 weeks. For patients continuing to take NSAIDs after a peptic ulcer is healed, the potential harms from NSAID treatment should be discussed and the need for NSAID treatment should be reviewed at least every 6 months with the patient. Reducing the dose of the NSAID, switching to a COX 2-selective NSAID, substituting the NSAID with acetaminophen or switching to low dose ibuprofen should be considered. A PPI should be continued indefinitely in all patients on NSAIDs at high risk for NSAID-induced ulcers (i.e., previous ulcers).¹

National Institute for Health and Care Excellence

In 2015, NICE developed guidance for the management of GERD in children. According to the guideline, gastro-esophageal reflux is a normal physiological process that usually happens after eating in healthy infants and children. In contrast, GERD occurs when the effect of the reflux leads to symptoms severe enough to merit medical treatment. In clinical practice, the terms gastro-esophageal reflux and GERD are used interchangeably in this population and there is no reliable and accurate diagnostic test to confirm whether the condition is simply gastro-esophageal reflux or GERD. In no wise are acid-suppressing drugs, such as PPIs or H2RAs ever recommended to treat overt regurgitation in infants and children occurring as an isolated symptom. Several non-pharmacological management options are presented in the guideline, depending on the age and circumstances of the infant or child, and should be initiated before starting medicine in this population. A 4-week trial of a PPI or H2RA may be considered for those who are unable to describe their symptoms (e.g., infants or young children) and have overt regurgitation with at least one of the following: unexplained feeding difficulties (e.g., refusing feeds, gagging or choking); distressed behavior; or delayed growth. In addition, a 4-week trial of a PPI or H2RA may be considered in children and young people with persistent heartburn, retrosternal pain or epigastric pain. In all cases, response to therapy should be assessed at 4 weeks and the patient referred to a specialist or endoscopy if symptoms have not resolved or recur after stopping treatment. A PPI or H2RA should be continued in patients with endoscopy-proven reflux esophagitis along with continued reassessments.¹⁶

The American Journal of Gastroenterology

The American Journal of Gastroenterology published a guideline for the diagnosis and management of GERD in adults in 2013. The GRADE system was used to evaluate the strength of the recommendations and the overall level of evidence. Similar non-pharmacological measures are recommended in the management of GERD, including weight loss and routine elimination of foods known to trigger reflux. An 8-week course of PPIs is the therapy-of-choice for symptom relief and healing of erosive esophagitis (*Strong Recommendation, High Level of Evidence*). There are no major differences in efficacy between different PPIs (*Strong Recommendation, High Level of Evidence*). Therapy with a PPI should be initiated at once daily dosing, before the first meal of the day (*Strong Recommendation, Moderate Level of Evidence*). For patients with a partial response to once daily therapy, tailored therapy with adjustment of dose timing or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, or sleep disturbance (*Strong Recommendation, Low Level of Evidence*). In

patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief (*Conditional Recommendation, Low Level of Evidence*). Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after a PPI is discontinued and in patients with complications including erosive esophagitis and Barrett's esophagus (*Strong Recommendation, Moderate Level of Evidence*). For patients who require long-term PPI therapy, it should be administered at the lowest effective dose, including "as needed" or intermittent therapy (*Conditional Recommendation, Low Level of Evidence*). Treatment with a H2RA can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief (*Conditional Recommendation, Moderate Level of Evidence*). Bedtime H2RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but H2RAs may be associated with the development of tachyphylaxis after several weeks of use (*Conditional Recommendation, Low Level of Evidence*).¹⁷

The European Association of Endoscopic Surgery

The European Association of Endoscopic Surgery issued a consensus statement on recommendations for the management of GERD. A Grade of Recommendation (GoR) was assigned based on a recommendation's level of evidence (A = 'must'; B = 'should'; C = 'can'). The degree of consensus was also expressed as the percentage of agreement for a certain recommendation by the expert panel (ExC) and the scientific community (SCC).²

According to the guideline, GERD (including ERD and NERD) is associated with significant impairment of quality of life. Thus, the goals of medical therapy in GERD are to control heartburn, heal gastroesophageal injuries and improve quality of life (*GoR A; ExC 100%; SCC 100%*). Acid suppressive drugs such as PPIs and H2RAs are effective in patients with esophageal syndromes. However, PPIs are more powerful than H2RAs in providing mucosal healing and symptomatic relief (*GoR A; ExC 100%; SCC 100%*). Though H2RAs continue to be a mainstay of GERD treatment, H2RAs have shown lower efficacy than PPIs in acid suppression, but given in divided doses may be effective in some patients with less severe forms of GERD. However, it is important to note that continuous use of H2RAs is associated with the development of tachyphylaxis, thus limiting their long-term use and efficacy. Proton pump inhibitors potently reduce gastric acid secretion and provide the most powerful symptomatic relief and heal esophagitis in the majority of patients. Standard doses of omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole have shown comparable rates of healing and remission of erosive esophagitis. In patients with a partial or unsatisfactory response to a once daily PPI dose, twice daily PPI dosing may help improve symptom relief (*GoR B; ExC 100%; SCC 98%*). Data supporting twice daily dosing of PPIs and H2RAs rather than standard dosing for improving mucosal healing and symptom relief are weak and largely based on expert opinion. The current treatment for Barrett's esophagus includes PPIs in single or double doses or antireflux surgery and aims to control GERD-related symptoms and to prevent complications such as ulcers, bleeding and strictures. However, antireflux surgery may be more effective than medical therapy for Barrett's esophagus and should be considered, particularly in young patients (*GoR C; ExC 100%; SCC 89%*). Antireflux surgery has the advantage of correcting LES failure and the frequently associated hiatal hernia, as well as controlling abnormal gastric and duodenal reflux in 80-90% of patients. However, some data suggests escalating PPI doses may have a comparable rate of symptom control as surgery.²

New Safety Alerts:

New FDA PPI labeling additions to CONTRAINDICATIONS, WARNINGS and PRECAUTIONS include hypersensitivity reactions resulting in acute interstitial nephritis and cyanocobalamin (vitamin B-12) malabsorption leading to nutritional deficiency secondary to daily long-term use (e.g., longer than 3 years). **Table 4** lists current FDA safety alerts found in PPI labeling.

Table 4. Current FDA Safety Alerts for Proton Pump Inhibitors.

FDA Safety Alert	
<i>Clostridium difficile</i>-associated diarrhea	PPIs may be associated with an increased risk of <i>Clostridium difficile</i> -associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve.
Low magnesium levels	Prescription PPIs may cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods of time (in most cases, longer than one year). In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.
Cyanocobalamin (vitamin B-12) deficiency	Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- and achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.
Acute interstitial nephritis	Acute interstitial nephritis has been observed in patients taking PPIs. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue the PPI if acute interstitial nephritis develops.
Bone fractures	Several published observational studies in adults suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (1 year or longer). Patients should use the lowest and shortest duration of PPI therapy appropriate for the condition being treated.

New Formulations or Indications:

None identified.

Randomized Controlled Trials:

One relevant clinical trial was identified from the literature search (see **Table 5**). The full abstract is included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Quality*
Moraes-Filho, et al. MC, DB, PG, RCT	Pantoprazole 40 mg/day vs. Esomeprazole 30 mg/day for 4 weeks	Adults w/ erosive GERD	Complete remission of GERD at 4 weeks based on confirmed endoscopic healing and relief of symptoms based on ReQuest-GI questionnaire, which assesses GI-related symptoms associated with GERD	Pantoprazole 170/278 (61.2%) Esomeprazole 165/270 (61.1%) P = not significant	Good

Abbreviations: DB = double blind; GERD = gastro-esophageal reflux disease; GI = gastrointestinal; MC = multi-centered; PG = parallel group; RCT = randomized controlled trial

*Quality of each study is ranked as “Good”, “Fair” or “Poor” based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

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Appendix 1: Current Status on Preferred Drug List

Preferred	Non-Preferred
Proton Pump Inhibitors	
Omeprazole capsule Pantoprazole tablet	Dexlansoprazole Esomeprazole Lansoprazole Omeprazole packet; suspension; tablet Omeprazole/sodium bicarbonate Pantoprazole packet Rabeprazole
Histamine-2 Receptor Antagonists	
Cimetidine tablet Famotidine tablet Ranitidine syrup, tablet	Cimetidine solution Famotidine suspension Famotidine/calcium carbonate/magnesium hydroxide Nizatidine Ranitidine capsule; tablet

Appendix 2: Abstracts of Clinical Trials

Moraes-Filho J, Pedroso M and Quigley E. Randomised clinical trial: daily pantoprazole magnesium 40 mg vs. esomeprazole 40 mg for gastro-oesophageal reflux disease, assessed by endoscopy and symptoms. *Alimentary Pharmacology and Therapeutics*. 2014; 39: 47-56.

Background:

Pantoprazole magnesium (pantoprazole-Mg) may display extended inhibition of the proton pump with the potential for improved clinical efficacy in gastro-oesophageal reflux disease (GERD).

Aim:

To compare the efficacy of pantoprazole-Mg and esomeprazole in GERD.

Methods:

Gastro-oesophageal reflux disease (Los Angeles grades A–D) patients were randomised to 4 weeks of treatment with pantoprazole-Mg (n=290) or esomeprazole (n=288), both 40 mg once daily, in this multicentre (14 Brazilian sites in 9 cities), double-blind study, with an additional 4 weeks' treatment in non-responding patients. Severity of oesophagitis (at endoscopy) and GERD-related symptoms (ReQuest-GI) were assessed. The primary end point was the proportion of patients in complete remission (ReQuest-GI score < 1.73 plus endoscopic healing) at week 4.

Results:

Complete remission occurred in 61% of patients in each treatment group at 4 weeks (primary endpoint) and in 81% and 79% of patients in the pantoprazole-Mg and esomeprazole groups at 8 weeks, with no significant differences. Mucosal healing rates were high and not significantly different. At 8 weeks, symptom relief with pantoprazole-Mg was significantly greater than that with esomeprazole (91.6% vs. 86.0%, $P=0.0370$) because of continued improvement in symptoms with pantoprazole-Mg from week 4 to week 8 ($P=0.0206$).

Conclusions:

Pantoprazole-Mg 40 mg was at least as effective as esomeprazole 40 mg for complete remission and the mucosal healing rate was high. Symptom relief with pantoprazole-Mg continued to improve from 4 to 8 weeks and was greater than that with esomeprazole at week 8, suggesting an extended period of treatment effect.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 3 2015

- 1 exp Omeprazole/ 6374
- 2 pantoprazole.mp. 1287
- 3 exp Dexlansoprazole/ 45
- 4 exp Esomeprazole/ 704
- 5 exp Lansoprazole/ 1651
- 6 exp Rabeprazole/ 771
- 7 1 or 2 or 3 or 4 or 5 or 6 7664
- 8 limit 7 to (english language and yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)) 39

Ovid MEDLINE(R) without Revisions 1996 to January Week 3 2015

- 1 exp Cimetidine/ 1442
- 2 exp Famotidine/ 729
- 3 exp Ranitidine/ 1815
- 4 exp Nizatidine/ 124
- 5 1 or 2 or 3 or 4 3730
- 6 limit 5 to (english language and yr="2013 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)) 31