Proton Pump Inhibitors (PPIs) and Histamine-2 Antagonists (H2As)

Month/Year of Review: November, 2012
PDL Class: Gastrointestinal- H2-Antagonists and PPI’s
End date of literature search: November 12, 2012

Date of Last Review: May 2009
Source Document: DERP Report

Current Status of PDL Class:

- **Preferred Agents:**
  - **H2-Antagonists:** Cimetidine tablets, cimetidine HCL solution, famotidine tablets, ranitidine.
  - **PPI’s:** Omeprazole capsules/tablets, pantoprazole tablets

- **Non Preferred Agents:**
  - **H2-Antagonists:** Nizatidine
  - **PPI’s:** Lansoprazole, dextansoprazole (Dexilant®), rabeprazole (Aciphex®), esomperazole (Nexium®), omeprazole/sodium bicarbonate (Zegrid®)

 Previous Conclusions¹:

**H2-Antagonists:**
- Evidence does not support a difference in efficacy or harms
- Cimetidine has the most adverse events, ranitidine has the second most adverse events
- Consider inclusion of at least one agent from the H2-Antagonist class with special consideration for famotidine or ranitidine for pediatric use

**PPIs:**
- The evidence does not demonstrate a clinical difference in efficacy to justify selection of any PPI as clinically superior to the other drugs in the class.
- There are no clinically demonstrable differences amongst the PPIs whether treatment is for GERD, peptic ulcer, non-steroidal ulcer, duodenal ulcer, or eradication of Helicobacter Pylori.
- No evidence supports differences in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities.

**Current PA Criteria:**
- Criteria in place for PPI’s to promote PDL options, restrict chronic use to patients who failed H2-Antagonists, preferred PPIs or who have severe disease and restricts BID use to patients with severe disease, H.pylori or pediatric patients (Appendix A).
Conclusions:
- Patient should be re-evaluated for benefit and risk while being on long term PPI therapy for potential adverse events.
- No new evidence consistently supports a difference in efficacy or safety between agents.

Recommendation:
- No further review needed. Evaluate comparative costs in executive session.

Methods:
A MEDLINE Ovid search was conducted using proton pump inhibitors, H2-Angstonists, GERD, peptic ulcers and H.Pylori. The search was limited to meta-analysis, English language, and to studies conducted in humans since last DERP review in May 2009. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews (See Appendix B for Review Abstracts)
- In September 2011, the Agency for Healthcare Research and Quality published an update of its report “Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease.” The review found moderate strength of evidence that PPIs are superior to H2A’s in the resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks. There was moderate strength of evidence demonstrating no significant differences between PPIs for relief of GERD symptoms at 4 weeks to 6 months. Based on 12 randomized controlled trials, there was moderate strength evidence that there were no consistent differences in doses and dosing regimens with different PPIs in relation to symptom resolution and esophagitis healing rates and no consistent difference in symptom relief and esophagitis healing rates between PPIs and over-the-counter dosage of PPIs approved for the treatment of frequent heartburn.

- There were two meta-analyses by Janarthanan S et al. and Deshpande et al. who investigated the association of Clostridium difficile-associated diarrhea (CDAD) and Clostridium difficile infection (CDI) with the use of PPIs respectively. The analysis done by Janarthanan reviewed of 23 studies including close to 300,000 patients who met the inclusion criteria. The results showed a 65% (summary risk estimate 1.69 with a 95% confidence interval (CI) from 1.395 to 1.974; P<0.000) increase in the incidence of CDAD among patients on PPIs. By study design, whether case–control study (17) or cohort study (6), there was still a significant increase in the incidence of CDAD among PPI users. The risk estimates were 2.31 (95% CI from 1.72 to 3.10; P<0.001) and 1.48 (95% CI from 1.25 to 1.75; P<0.001) for cohort and case–control studies, respectively. The authors concluded there was sufficient evidence to suggest that PPIs increase the incidence of CDAD. It was recommended by the authors that the routine use of PPIs for gastric ulcer prophylaxis should be more prudent and establishing a guideline for the use of PPI may help in the future with the judicious use of PPIs. This review used the Beff and Egger tests to evaluate the publication bias evaluation and the Duval and Tweedie “trim-and-fill” method for a sensitivity analysis. Desphandhe et al. conducted a similar meta-analysis on plausible link between CDI and PPIs use. Two investigators screened articles independently for inclusion criteria, data extraction, and quality assessment; disagreements were resolved based on consensus with a third
investigator. Data were combined by means of a random-effects model and odds ratios were calculated. Subgroup and sensitivity analyses were performed based on study design and antibiotic use. The results from Thirty studies (25 case-control and 5 cohort) reported in 29 articles met the inclusion criteria (n = 202,965). PPI therapy increased the risk for CDI (odds ratio, 2.15, 95% confidence interval, 1.81–2.55), but there was significant heterogeneity in results among studies (P < .00001). This association remained after subgroup and sensitivity analyses, although significant heterogeneity persisted among studies. The authors also concluded PPI therapy was associated with a 2-fold increase in risk for CDI. Unlike Janarthanan S et al study, this analysis included observational studies that investigated the risk of CDI associated with PPI therapy and used CDI as an end point. Due to the observational nature of the analyzed studies, the authors were not able to study the causes of this association.

- In 2011 Kwok et al conducted a meta-analysis on the risk of fractures with acid-suppressing medications. The review included 12 studies with total 1,521,062 patients. Pooled analysis of PPI use showed significant risk for spine fractures (4 studies, OR 1.50, 95% CI 1.32–1.72, p < 0.001, I² = 0%) but this was not significant for H2RA (3 studies, OR 1.05, 95% CI 0.92–1.19, p = 0.50, I² = 0%). Similarly for hip fractures, there was a significant risk of fractures with PPIs (10 studies, OR 1.23, 95% CI 1.11–1.36, p < 0.001, I² = 72%), but not for H2RAs (9 studies, OR 1.12, 95% CI 0.99–1.27, p = 0.06, I² = 75%), respectively. Analysis of fractures overall (based on all 12 studies covering a mixture of fracture types) yielded an OR of 1.20 (95% CI 1.11–1.30, p < 0.001, I² = 78%) for PPIs, and OR of 1.08 (95% CI 1.00–1.18, p = 0.06, I² = 82%) for H2RA. However, aside from the risk of spine fractures, all the other analyses were limited by substantial heterogeneity. One study that reported on a direct comparison between acid-suppressing medications found an increased risk with PPIs vs. H2RA for hip fractures, OR 1.34 (95% CI 1.14–1.38). The authors concluded some evidence for a modest association between PPI use and risk of fractures, which was not seen with H2RA exposure. The association is most consistent for spine fractures, while there is substantial heterogeneity in the magnitude of risk for other fractures. Clinicians who are concerned about patients with high fracture risk may wish to consider the option of H2RAs instead of PPIs. The authors performed random effects meta-analysis of odds ratios (OR) according to fracture type and conducted subgroup analyses by duration of exposure. Heterogeneity was assessed using the I² statistic.

- A 2011 Cochrane review by Rostom A et al evaluated the effectiveness of common interventions for the prevention of NSAID induced upper GI toxicity. Randomized controlled clinical trials (RCTs) of prostaglandin analogues (PA), H2-receptor antagonists (H2RA) or proton pump inhibitors (PPI) for the prevention of chronic NSAID induced upper GI toxicity were included. Two independent authors extracted data regarding population characteristics, study design, methodological quality and number of participants with endoscopic ulcers, ulcer complications, symptoms, overall drop-outs, drop outs due to symptoms. Heterogeneity was evaluated using a chi square test, and the I square statistic. Forty-one RCTs met the inclusion criteria. All doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800 ug/day was superior to 400 ug/day for the prevention of endoscopic gastric ulcers (RR 0.17, and RR 0.39 respectively, P=0.0055). A dose response relationship was not seen with duodenal ulcers. Misoprostol caused diarrhea at all doses, although significantly more at 800 ug/day than 400 ug/day (P=0.0012). Misoprostol also reduced the risk of clinical ulcer complications. Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40; 95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol. The authors concluded Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic fractures.
duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40; 95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol.

- Another Cochrane review by Van Pinxteren et al⁹ compared the efficacy of short term use of PPI, H2RA in adults with GERD, treated empirically and in those with endoscopy negative reflux disease. Randomised controlled trials reporting symptomatic outcome after short-term treatment for GERD using proton pump inhibitors, H2-receptor antagonists or prokinetic agents. Participants had to be either from an empirical treatment group (no endoscopy used in treatment allocation) or from an endoscopy negative reflux disease (ENRD) group (no signs of erosive esophagitis). Thirty-two trials (9738 participants) were included: fifteen in the empirical treatment group, thirteen in the ENRD group and four in both. In empirical treatment of GERD the relative risk (RR) for heartburn remission (the primary efficacy variable) in placebo-controlled trials for PPI was 0.37 (two trials, 95% confidence interval (CI) 0.32 to 0.44), for H2RAs 0.77 (two trials, 95% CI 0.60 to 0.99) and for prokinetics 0.86 (one trial, 95% CI 0.73 to 1.01). In a direct comparison PPIs were more effective than H2RAs (seven trials, RR 0.66, 95% CI 0.60 to 0.73) and prokinetics (two trials, RR 0.53, 95% CI 0.32 to 0.87). In treatment of ENRD, the RR for heartburn remission for PPI versus placebo was 0.73 (eight trials, 95% CI 0.67 to 0.78) and for H2RA versus placebo was 0.84 (two trials, 95% CI 0.74 to 0.95). The RR for PPI versus H2RA was 0.78 (three trials, 95% CI 0.62 to 0.97) and for PPI versus prokinetic 0.72 (one trial, 95% CI 0.56 to 0.92). The authors concluded PPIs are more effective than H2RAs in relieving heartburn in patients with GERD who are treated empirically and in those with ENRD, although the magnitude of benefit is greater for those treated empirically.

New Treatment Guidelines
National Institute for Health and Clinical Excellence (NICE) guideline on management of acute upper gastrointestinal bleeding² (June 2012)
Summary of Major Recommendations on PPIs and/or H2As (The type of evidence supporting the recommendations is not specifically stated):
- Do not offer acid-suppression drugs (proton pump inhibitors or H₂-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding; offer proton pump inhibitors to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent hemorrhage shown at endoscopy.
- Offer acid-suppression therapy (H₂-receptor antagonists or proton pump inhibitors) for primary prevention of upper gastrointestinal bleeding in acutely ill patients admitted to critical care. If possible, use the oral form of the drug; review the ongoing need for acid-suppression drugs for primary prevention of upper gastrointestinal bleeding in acutely ill patients when they recover or are discharged from critical care.

The 2012 treatment guidelines on GERD by University of Michigan Health System³
Summary of Major Recommendations on Pharmacologic Intervention: H2RAs, PPIs, and prokinetics have proven efficacy in the treatment of GERD [I A]. Prokinetics are as effective as H2RAs but are currently unavailable [III A]. Carafate and antacids are ineffective [III A], but may be used as supplemental acid-neutralizing agents for certain patients with GERD [II D].
- **Non-erosive reflux disease (NERD):** *Step-up* (H2RA then as followed by a PPI if no improvement) and *step-down* (PPI then followed by the lowest dose of acid suppression) therapy are equally effective for acute treatment and maintenance [I B]. *On demand* (patient-directed) therapy is the most cost-effective strategy [I B].

- **Erosive esophagitis:** Initial PPI therapy is the treatment of choice for acute and maintenance therapy for patients with documented erosive esophagitis [I A].

- Take PPI's 30-60 minutes prior to breakfast (and dinner if two times per day [BID]) to optimize effectiveness [I B]. Use generic and over-the-counter (OTC) formulations exclusively, eliminating need for prior authorizations.

- Patients should not be left on acid suppressive therapy without re-evaluation of symptoms to minimize cost and the potential adverse events from medications [I B].

**New drugs:**
None

**New indications:**
June 2011: The indication for maintenance of healed erosive esophagitis for dexlansoprazole was expanded to include the relief of heartburn.

**New FDA safety alerts:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Alert Date</th>
<th>FDA Alert</th>
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<tbody>
<tr>
<td><em>Clostridium difficile</em>-associated diarrhea&lt;sup&gt;30&lt;/sup&gt;</td>
<td>02/28/2012</td>
<td>PPIs may be associated with an increased risk of <em>Clostridium difficile</em>-associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve. FDA is also reviewing the risk of CDAD in users of H2-Antagonists.</td>
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<tr>
<td>Low magnesium level associated with long-term PPI use&lt;sup&gt;11&lt;/sup&gt;</td>
<td>03/02/2011</td>
<td>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.</td>
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<tr>
<td>Avoid concomitant use of Plavix® and omeprazole&lt;sup&gt;12&lt;/sup&gt;</td>
<td>10/27/2010</td>
<td>FDA issued a reminder that it continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole because the co-administration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity. This information was added to the drug label of Plavix in November 2009, and has been the source of continued discussion in the medical literature. Patients at risk of heart attacks or strokes, who are given Plavix to prevent blood clots, will not get the full anti-clotting effect if they also take omeprazole. Omeprazole is found in prescription products (Prilosec, Zegerid, and generic products) and over-the-counter products (Prilosec OTC, Zegerid OTC, and generic products). FDA wishes to emphasize additional facts that may be a source of confusion among healthcare professionals: With regard to the proton pump inhibitor (PPI) drug class, this recommendation applies only to omeprazole and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP 2C19) that is crucial for conversion of Plavix into its active form.</td>
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Pantoprazole (Protonix) may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of Plavix than omeprazole.

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<th>Possible increased risk of fractures with the use of PPIs</th>
<th>05/25/2010</th>
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<tr>
<td>Healthcare professionals and users of proton pump inhibitors should be aware of the possible increased risk of fractures of the hip, wrist, and spine with the use of prescription and over-the-counter PPIs, and weigh the known benefits against the potential risks when deciding to use them. The new safety information is based on FDA’s review of several epidemiological studies that reported an increased risk of fractures of the hip, wrist, and spine with proton pump inhibitor use. Some studies found that those at greatest risk for these fractures received high doses of proton pump inhibitors or used them for one year or more (see Data Summary section). The majority of the studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group.</td>
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03/23/2011 update: FDA has determined an osteoporosis and fracture warning on the over-the-counter (OTC) proton pump inhibitor (PPI) medication “Drug Facts” label is not indicated at this time. Following a thorough review of available safety data, FDA has concluded that fracture risk with short-term, low dose PPI use is unlikely. The available data show that patients at highest risk for fractures received high doses of prescription PPIs (higher than OTC PPI doses) and/or used a PPI for one year or more.
References:


Appendix A

Proton Pump Inhibitors (PPIs)

Goal(s):
- Promote PDL options.
- Restrict chronic use (greater than eight weeks) to patients who failed H2-antagonist, preferred PPIs or who have severe disease, e.g. Barrett’s, or Zollinger Ellison syndrome.
- Restrict BID use to patients with severe disease, H.pylori or pediatric patients.

Notes:
- This is a “global” PA.
- If an active PA for a PPI already exists, then any PPI will pay.
- A new PA is required if the dosing schedule changes, e.g., an active PA for once daily dosing restricts the PPI to once a day.
- BID dosing requires a new PA, however, the strength of the dose could be increased without an additional PA, e.g., a change from 20mg daily could be increased to 40 mg ONCE a day without an additional PA.

Length of Authorization: 2 weeks to lifetime (criteria specific)

Requires PA:
- Non-preferred drugs

Covered Alternatives
- Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml
- Individual components for treatment of H.pylori that are preferred products.

<table>
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<tr>
<th>ROUTE</th>
<th>HICL</th>
<th>BRAND</th>
<th>GENERIC</th>
<th>FORMULATIONS</th>
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<tr>
<td>ORAL</td>
<td>021607</td>
<td>Nexium</td>
<td>esomeprazole</td>
<td>Capsules, delayed-release: 20, 40mg</td>
</tr>
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<td></td>
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<td></td>
<td>Suspension, delayed-release pkts: 10, 20, 40mg</td>
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<tr>
<td>ORAL</td>
<td>008993</td>
<td>Prevacid</td>
<td>lansoprazole</td>
<td>Capsules, delayed-release: 15, 30 mg</td>
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<td></td>
<td></td>
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<td></td>
<td>Enteric coated granules for oral suspension, delayed release: 15, 30mg</td>
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<tr>
<td>ORAL</td>
<td>025742</td>
<td>Prevacid</td>
<td>lansoprazole +</td>
<td>Delayed release capsules + naproxen tablets kit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NapraPAC</td>
<td>naproxen</td>
<td>- 15 – 375, 15 -500</td>
</tr>
<tr>
<td>ORAL</td>
<td>004673</td>
<td>Zegerid</td>
<td>omeprazole</td>
<td>Packet for solution: 20, 40mg Capsules: 20, 40mg</td>
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<tr>
<td>ORAL</td>
<td>36085</td>
<td>Kapdex</td>
<td>Dexlansoprazole</td>
<td>Capsules, delayed-release: 30, 60mg</td>
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<td>ORAL</td>
<td>011590, 022008</td>
<td>Protonix</td>
<td>pantoprazole</td>
<td>Tablets, delayed-release: 20 mg, 40 mg Suspension, delayed-release: 40mg</td>
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<td>ORAL</td>
<td>011590</td>
<td>pantoprazole</td>
<td>pantoprazole</td>
<td>Tablets, delayed-release: 20 mg, 40 mg</td>
</tr>
<tr>
<td>ORAL</td>
<td>018847</td>
<td>Aciphex</td>
<td>rabeprazole</td>
<td>Tablets, delayed-release: 20 mg</td>
</tr>
</tbody>
</table>

### Approval Criteria

1. **What is the diagnosis being treated?**  
   - **Record ICD9 code**

2. **Is drug requested preferred?**  
   - **Yes:** Go to 4  
   - **No:** Go to 3

3. **Will the prescriber consider a change to a preferred product?**  
   - **Yes:** Inform provider of covered alternatives in class.  
   - **No:** Go to 4

4. **Is diagnosis**  
   a) Zollinger-Ellison (251.5)?  
   b) Barrett’s esophagus (530.85)?  
   c) Multiple Endocrine Adenoma (237.4)?  
   d) Malignant Mastoma (202.6)?  
   e) MEN Type I (258.01)?  
   - **Yes:** Approve for a life time; BID dosing OK.  
   - **No:** Go to 5

5. **Is the diagnosis dyspepsia (536.8)?**  
   - **Yes:** Pass to RPH, DENY (OHP coverage)  
   - **Diagnosis is below the line; preferred agents are available without PA.**  
   - **No:** Go to 6

6. **Has patient tried and failed Prilosec OTC 40mg/day for 8 week trial (2 weeks for H. Pylori)?**  
   - **Yes:** Go to 7  
   - **No:** Go to #12

7. **Is diagnosis H.Pylori?**  
   - **Yes:** Approve for 2 weeks – BID dosing OK  
   - **No:** Go to 8
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Yes: Approve for 8 weeks - BID dosing OK</th>
<th>No: Go to 9</th>
</tr>
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<tbody>
<tr>
<td>8</td>
<td>Is diagnosis active GI bleed? <em>(531.0-531.2, 532.0-532.2, 533.0-533.2, 534.0-534.2)</em></td>
<td>-</td>
<td></td>
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<td>9</td>
<td>Is diagnosis Gastric or Duodenal Ulcer <em>(531.3-531.9, 531.3-532.9, 533.3-533.9, 534.3-534.9)</em> and/or does patient have 2 or more of the following risk factors: &lt;br&gt; - &gt; 65 years &lt;br&gt; - requires &gt; 3 mths of NSAIDs, aspirin or steroids &lt;br&gt; - on anticoagulation (warfarin, enoxapirin, etc.) &lt;br&gt; - History of GI Bleed or Ulcer?</td>
<td>Yes: Approve QD for 1 year, if previously failed an 8 week QD trial at highest dose approve BID for 1 year.  May approve BID dosing for pediatrics &lt;12 years old</td>
<td>No: Go to 10</td>
</tr>
<tr>
<td>10</td>
<td>Is the diagnosis symptomatic GERD <em>(530.81, 530.10 – 530.19)</em></td>
<td>Yes: Approve QD dosing for 1 year; if previously failed an 8 week QD trial at highest dose approve BID for 1 year.  May approve BID dosing for pediatrics &lt;12 years old</td>
<td>No: Go to 11</td>
</tr>
<tr>
<td>11</td>
<td>Is diagnosis &lt;br&gt; a) Ulcer of esophagus <em>(530.2x)</em>  &lt;br&gt; b) Stricture &amp; stenosis of esophagus <em>(530.3)</em>  &lt;br&gt; c) Perforation of esophagus <em>(530.4)</em></td>
<td>Yes: Approve up to BID for 1 year.</td>
<td>No: Go to 13</td>
</tr>
<tr>
<td>12</td>
<td>Is the request for Prevacid Solutab or Zegerid for tube administration?</td>
<td>Yes: Approve QD dosing for 1 year. May approve BID dosing for pediatrics &lt;12 years old.</td>
<td>No: Pass to RPH. Deny and recommend omeprazole 20 mg QD or BID.</td>
</tr>
<tr>
<td>13</td>
<td>All other diagnoses will need to be evaluated by a pharmacist for appropriateness and OHP line coverage.</td>
<td>- Diagnoses above the line and where PPI is appropriate can be covered. &lt;br&gt; - Diagnoses below the line and where PPI is appropriate should be denied as not covered. &lt;br&gt; - Diagnoses above the line but where PPIs are not appropriate should be denied and not medically appropriate.</td>
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Appendix B:


BACKGROUND: Gastroesophageal reflux disease (GERD) is one of the most common health conditions affecting Americans. Despite the availability of medical, surgical, and endoscopic options, optimal management strategies remain unsettled.

PURPOSE: The purpose was to systematically review and update our previous Comparative Effectiveness Review, which compared the effectiveness of different management options for adults with GERD.

DATA SOURCES: We searched MEDLINE®, Cochrane Central Register of Controlled Trials, and other relevant databases, as well as other existing systematic reviews.

STUDY SELECTION: Studies of various designs were sought, including comparative randomized controlled trials, nonrandomized and cohort studies, and systematic reviews.

DATA EXTRACTION: A standardized protocol was used to extract details on study design, diagnoses, interventions, outcomes, and quality.

DATA SYNTHESIS: In total, 166 studies met eligibility criteria. We found a moderate strength of evidence that laparoscopic fundoplication in patients whose GERD symptoms were already well controlled by medical treatments was at least as effective as continued medical treatment (and in some cases superior) in controlling GERD-related symptoms for the first 1 to 3 years following surgery. However, the rate of serious adverse events was generally higher in patients who underwent fundoplication compared with those who had medical treatment. We did not identify sufficient evidence to conclude whether medical or surgical treatment was more effective in preventing long-term complications of GERD, such as the development of Barrett’s esophagus or esophageal adenocarcinoma. We found a moderate strength of evidence that proton pump inhibitors were superior to histamine-2 receptor antagonists in resolving GERD symptoms at 4 weeks and promoting healing of esophagitis at 8 weeks. Evidence regarding the effectiveness of endoscopic procedures was insufficient. Evidence regarding the effectiveness of treatment of GERD on asthma symptoms was inconclusive.

LIMITATIONS: Studies directly comparing surgery to medical therapy generally had high dropout rates in long-term followup. There was a great deal of variability in the rigor with which the outcomes were evaluated across studies, particularly in subjective endpoints.

CONCLUSIONS: Medical therapy and laparoscopic fundoplication were similarly effective in improving GERD symptoms in patients whose symptoms were already well controlled by medical therapy for at least the first 1 to 3 years following surgery. Serious adverse events were more common after surgery. The effectiveness of endoscopic procedures remains substantially uncertain.

Clostridium difficile-Associated Diarrhea and Proton Pump Inhibitor Therapy: A Meta-Analysis
Abstract

Objectives: Clostridium difficile-associated diarrhea (CDAD) is a major cause of morbidity and increasing health-care costs among hospitalized patients. Although exposure to antibiotics remains the most documented risk factor for CDAD, attention has recently been directed toward a plausible link with proton pump inhibitors (PPIs). However, the results of studies on the association between CDAD and PPIs remain controversial. We have conducted a meta-analysis to summarize the association between PPIs and CDAD among hospitalized patients.

Methods: A systematic search of published literature on studies that investigated the association between PPIs and CDAD from 1990 to 2010 was conducted on Medline and PubMed. The identified articles were reviewed for additional references. The most adjusted risk estimates were extracted by two authors and summarized using random effects meta-analysis. We also conducted a subgroup analysis by study design. Publication bias was evaluated using the Begg and Egger tests. A sensitivity analysis using the Duval and Tweedie “trim-and-fill” method has also been performed.

Results: Twenty-three studies including close to 300,000 patients met the inclusion criteria. There was a 65% (summary risk estimate 1.69 with a 95% confidence interval (CI) from 1.395 to 1.974; P<0.000) increase in the incidence of CDAD among patients on PPIs. By study design, whether case–control study (17) or cohort study (6), there was still a significant increase in the incidence of CDAD among PPI users. The risk estimates were 2.31 (95% CI from 1.72 to 3.10; P<0.001) and 1.48 (95% CI from 1.25 to 1.75; P<0.001) for cohort and case–control studies, respectively.

Conclusions: There is sufficient evidence to suggest that PPIs increase the incidence of CDAD. Our meta-analysis shows a 65% increase in the incidence of CDAD among PPI users. We recommend that the routine use of PPIs for gastric ulcer prophylaxis should be more prudent. Establishing a guideline for the use of PPI may help in the future with the judicious use of PPIs. Further studies, preferably prospective, are needed to fully explore the association between PPIs and CDAD.
Association Between Proton Pump Inhibitor Therapy and *Clostridium difficile* Infection in a Meta-Analysis

**Background & Aims:** In the past decade, there has been a growing epidemic of *Clostridium difficile* infection (CDI). During this time, use of proton pump inhibitors (PPIs) has increased exponentially. We evaluated the association between PPI therapy and the risk of CDI by performing a meta-analysis.

**Methods:** We searched MEDLINE and 4 other databases for subject headings and text words related to CDI and PPI in articles published from 1990 to 2010. All observational studies that investigated the risk of CDI associated with PPI therapy and used CDI as an end point were considered eligible. Two investigators screened articles independently for inclusion criteria, data extraction, and quality assessment; disagreements were resolved based on consensus with a third investigator. Data were combined by means of a random-effects model and odds ratios were calculated. Subgroup and sensitivity analyses were performed based on study design and antibiotic use.

**Results:** Thirty studies (25 case-control and 5 cohort) reported in 29 articles met the inclusion criteria (*n* = 202,965). PPI therapy increased the risk for CDI (odds ratio, 2.15, 95% confidence interval, 1.81–2.55), but there was significant heterogeneity in results among studies (*P* < .00001). This association remained after subgroup and sensitivity analyses, although significant heterogeneity persisted among studies.

**Conclusions:** PPI therapy is associated with a 2-fold increase in risk for CDI. Because of the observational nature of the analyzed studies, we were not able to study the causes of this association. Further studies are needed to determine the mechanisms by which PPI therapy might increase risk for CDI.

**Meta-analysis: Risk of fractures with acid-suppressing medication.**
Chun Shing Kwok, Jessica Ka-Yan Yeong, Yoon Kong Loke School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ, UK. *Bone* Volume 48, Issue 4, 1 April 2011, Pages 768–776

**Abstract**

**Aims:** Recent studies have suggested an increased risk of fractures with proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs). We planned to perform a meta-analysis of fractures in patients taking PPIs and H2RAs.

**Methods:** We searched MEDLINE and EMBASE in September 2010 for observational studies reporting on the risk of fractures with acid-suppressing medication (PPIs and H2RA). We also checked the references lists of included studies and regulatory authority websites for additional data. We performed random effects meta-analysis of odds ratios (OR) according to fracture type and conducted subgroup analyses by duration of exposure. Heterogeneity was assessed using the *I*² statistic.
Results: Our review included 12 studies covering 1,521,062 patients. Pooled analysis of PPI use showed significant risk for spine fractures (4 studies, OR 1.50, 95% CI 1.32–1.72, p < 0.001, I² = 0%) but this was not significant for H2RA (3 studies, OR 1.05, 95% CI 0.92–1.19, p = 0.50, I² = 0%). Similarly for hip fractures, there was a significant risk of fractures with PPIs (10 studies, OR 1.23, 95% CI 1.11–1.36, p < 0.001, I² = 72%), but not for H2RAs (9 studies, OR 1.12, 95% CI 0.99–1.27, p = 0.06, I² = 75%), respectively. Analysis of fractures overall (based on all 12 studies covering a mixture of fracture types) yielded an OR of 1.20 (95% CI 1.11–1.30, p < 0.001, I² = 78%) for PPIs, and OR of 1.08 (95% CI 1.00–1.18, p = 0.06, I² = 82%) for H2RA. However, aside from the risk of spine fractures, all the other analyses were limited by substantial heterogeneity. One study that reported on a direct comparison between acid-suppressing medications found an increased risk with PPIs vs. H2RA for hip fractures, OR 1.34 (95% CI 1.14–1.38).

Conclusion: There is some evidence for a modest association between PPI use and risk of fractures, which was not seen with H2RA exposure. The association is most consistent for spine fractures, while there is substantial heterogeneity in the magnitude of risk for other fractures. Clinicians who are concerned about patients with high fracture risk may wish to consider the option of H2RAs instead of PPIs.


Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications in North America and Europe. However, there is overwhelming evidence linking these agents to a variety of gastrointestinal (GI) toxicities.

Objectives: To review the effectiveness of common interventions for the prevention of NSAID induced upper GI toxicity.

Search methods: We searched MEDLINE from 1966 to May 2009, Current Contents for six months prior to May 2009, EMBASE to May 2009, and the Cochrane Controlled Trials Register from 1973 to May 2009. Recent conference proceedings were reviewed and content experts and companies were contacted.

Selection criteria: Randomized controlled clinical trials (RCTs) of prostaglandin analogues (PA), H2-receptor antagonists (H2RA) or proton pump inhibitors (PPI) for the prevention of chronic NSAID induced upper GI toxicity were included.

Data collection and analysis: Two independent authors extracted data regarding population characteristics, study design, methodological quality and number of participants with endoscopic ulcers, ulcer complications, symptoms, overall drop-outs, drop outs due to symptoms. Dichotomous data were pooled using RevMan 5.0. Heterogeneity was evaluated using a chi square test, and the I square statistic.

Main results: Forty-one RCTs met the inclusion criteria. All doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800 ug/day was superior to 400 ug/day for the prevention of endoscopic gastric ulcers (RR 0.17, and RR 0.39 respectively, P=0.0055). A dose response relationship was not seen with duodenal ulcers. Misoprostol caused diarrhea at all doses, although significantly more at 800 ug/day than 400 ug/day (P=0.0012). Misoprostol also reduced the risk of clinical ulcer complications. Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40;95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol.
Authors' conclusions: Misoprostol, PPIs, and double dose H2RAs are effective at preventing chronic NSAID related endoscopic gastric and duodenal ulcers. Lower doses of misoprostol are less effective and are still associated with diarrhea. In patients with previous NSAID bleeds, a COX-2 inhibitor alone is equivalent to a NSAID+PPI, though the re-bleeding rates with both strategies are still relatively high. A strategy of a COX-2 inhibitor+PPI appears to offer the greatest GI safety in high risk patients.

Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-esophageal reflux disease-like symptoms and endoscopy negative reflux disease

Abstract

Background: Approximately 25% of adults regularly experience heartburn, a symptom of gastro-oesophageal reflux disease (GORD). Most patients are treated empirically (without specific diagnostic evaluation e.g. endoscopy). Among patients who have an upper endoscopy, findings range from a normal appearance, mild erythema to severe oesophagitis with stricture formation. Patients without visible damage to the esophagus have endoscopy negative reflux disease (ENRD). The pathogenesis of ENRD, and its response to treatment may differ from GORD with oesophagitis.

Objectives: Summarise, quantify and compare the efficacy of short-term use of proton pump inhibitors (PPI), H2-receptor antagonists (H2RA) and prokinetics in adults with GORD, treated empirically and in those with endoscopy negative reflux disease (ENRD).

Search methods: We searched MEDLINE (January 1966 to November 2008), EMBASE (January 1988 to November 2008), and EBMR in November 2008.

Selection criteria: Randomized controlled trials reporting symptomatic outcome after short-term treatment for GORD using proton pump inhibitors, H2-receptor antagonists or prokinetic agents. Participants had to be either from an empirical treatment group (no endoscopy used in treatment allocation) or from an endoscopy negative reflux disease group (no signs of erosive oesophagitis).

Data collection and analysis: Two authors independently assessed trial quality and extracted data.

Main results: Thirty-two trials (9738 participants) were included: fifteen in the empirical treatment group, thirteen in the ENRD group and four in both. In empirical treatment of GORD the relative risk (RR) for heartburn remission (the primary efficacy variable) in placebo-controlled trials for PPI was 0.37 (two trials, 95% confidence interval (CI) 0.32 to 0.44), for H2RAs 0.77 (two trials, 95% CI 0.60 to 0.99) and for prokinetics 0.86 (one trial, 95% CI 0.73 to 1.01). In a direct comparison PPIs were more effective than H2RAs (seven trials, RR 0.66, 95% CI 0.60 to 0.73) and prokinetics (two trials, RR 0.53, 95% CI 0.32 to 0.87). In treatment of ENRD, the RR for heartburn remission for PPI versus placebo was 0.73 (eight trials, 95% CI 0.67 to 0.78) and for H2RA versus placebo was 0.84 (two trials, 95% CI 0.74 to 0.95). The RR for PPI versus H2RA was 0.78 (three trials, 95% CI 0.62 to 0.97) and for PPI versus prokinetic 0.72 (one trial, 95% CI 0.56 to 0.92).

Authors' conclusions: PPIs are more effective than H2RAs in relieving heartburn in patients with GORD who are treated empirically and in those with ENRD, although the magnitude of benefit is greater for those treated empirically.