THE OREGON STATE DRUG REVIEW©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter

August 2015 Volume 5, Issue 5

Is Long-Term Proton Pump Inhibitor Treatment for GERD Worth the Risk?

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New Funding Placement of GERD Treatment

Proton Pump Inhibitors (PPI) are a major economic burden for the healthcare system; not necessarily because of the cost of the drugs but because of the overprescribing of these drugs for minor symptoms without clear indications, as well as the increasing long-term use of PPIs. PPIs and histamine-2 receptor antagonists (H2RA) were associated with nearly $500,000 annual net cost in the Oregon Health Plan (OHP) fee-for-service (FFS) program and $2.13 million annual net cost in the coordinated care organizations during the 2014 calendar year.[1] The Health Evidence Review Committee placed long-term (greater than 8 weeks) medical treatment of gastro-esophageal reflux disease (GERD) below the OHP funding line on the Prioritized List of Services effective January 1, 2015.[2] Dyspepsia continues to be a non-funded condition. However, other U.S. Food and Drug Administration (FDA) approved indications for PPIs and H2RAs (e.g., gastrointestinal ulcers, pathological hyper-secretory conditions, *Helicobacter pylori* eradication) remain funded.

This article will review the evidence for long-term PPI safety and efficacy, describe current FFS utilization trends, communicate FFS PPI policy changes, and present guidance to assist with weaning patients off of long-term PPIs.

Evidence for Long-term Safety and Efficacy of Proton Pump Inhibitors

Proton pump inhibitors are well tolerated and are generally thought to be safe. However, long-term use of PPIs is now commonplace despite lack of evidence for long-term safety or efficacy. Prescribers should consider the diagnosis prior to treatment. Clinical practice guidelines recommend only 4 weeks of PPI therapy for uninvestigated dyspepsia.[3,4] High quality evidence suggests only 8 weeks of PPI therapy is needed for GERD or erosive esophagitis, but diagnosis is dependent on endoscopy, and symptoms can be poorly correlated with endoscopic findings.[3,4] There is insufficient evidence for PPI use beyond 8 weeks for GERD, and patients who do not respond to 8 weeks of therapy should be referred for further evaluation. Despite lack of evidence, long-term maintenance therapy is sometimes recommended for cases of chronic, severe esophagitis.[3,4] However, symptoms typically fluctuate, and on-demand use of acid suppressants (ie, PRN dosing) has demonstrated to be effective and is the preferred method of treatment for chronic dyspepsia or GERD.[4,5]

Growing evidence demonstrates long-term use might not be as harmless as first considered, and the FDA periodically updates prescribing information of PPIs with new safety alerts (Table 1).[6] However, randomized controlled trials are not feasible for most of the potentially associated harms of PPIs. The majority of observed associations are based on observational cohort studies and case reports and requires careful interpretation.

Table 1. Post-marketing FDA Safety Alerts for Proton Pump Inhibitors.[6]

***Clostridium difficile* Infection**	An increased risk of *C. difficile*-associated diarrhea has been associated with PPI use.
Bone Fractures	An increased risk of osteoporosis and fractures of the hip, wrist and spine have been associated with long-term (1 year or longer) use of PPIs, high doses of PPIs, or multiple daily doses of PPIs.
Vitamin B-12 Deficiency	Long-term use of PPIs (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin due to sustained hypochlorhydria.
Low Magnesium	Use of PPIs for greater than 1 year increases risk of hypomagnesemia which may not be reversible with oral magnesium supplementation.

A systematic review evaluated all studies that investigated the risk of *Clostridium difficile* infection (CDI) between 1990 and 2010.[7] Together, 25 case-control studies and 5 cohort studies were identified, which presented very heterogeneous data.[7] Despite the heterogeneity, the results between case-control studies and cohort studies consistently demonstrated higher risk of CDI with PPI use. A meta-analysis of the data was performed and the investigators found PPI therapy was associated with a 2-fold increased risk of CDI (odds ratio [OR] = 2.15, 95% Confidence Interval [CI], 1.81 to 2.55).[7]

Evidence limited to 11 observational cohort or case-control studies composed of mostly older adults suggests use of PPIs is associated with a modest increased risk in hip fractures (relative risk [RR] = 1.30; 95% CI, 1.19 to 1.43) and spine fractures (RR 1.56; 95% CI, 1.31 to 1.85).[8] These associated risks persisted after stratifying data by sex or duration of PPI use.[8] PPI use for less than 1 year was associated with a RR for hip fracture of 1.39 (95% CI, 1.10 to 1.74) and PPI use greater than 1 year was associated with a RR of 1.24 (95% CI, 1.19 to 1.29).[8]

An association between chronic PPI use and iron and vitamin B-12 deficiency is still controversial.[9] Results from observational studies assessing chronic PPI use and iron deficiency are contradictory, and it is doubtful an association can be found with the available data.[9] Most studies assessing vitamin B-12 deficiency, however, suggest a definite association exists between chronic PPI use and vitamin B-12 deficiency or vitamin B-12 supplementation;[9] however, no meta-analysis has been performed to quantify whether the association is significant. None of the studies identified found an association between H2RA use and iron or vitamin B-12 deficiency.[9]

The potential association between PPIs and hypomagnesemia was investigated in a systematic review and meta-analysis.[10] Data from 9 studies with more than 100,000 patients were analyzed.[10] Patients using PPIs had higher rates of hypomagnesemia versus patients who did not use PPIs (27.1% vs. 18.4%, respectively; OR = 1.78; 95% CI, 1.08 to 2.92).[10] Though there appears to be an association between regular use of PPIs and hypomagnesemia, significant heterogeneity between the studies analyzed limit the interpretation of these results.[10]

The cardiovascular risk associated with PPIs outside high-risk cohorts has not been adequately studied. Recently, however, a novel population data-mining approach for pharmacovigilance was performed on multiple medical record data sets of adult patients with GERD diagnoses.[11] Patients were matched and balanced to controls based on several covariates.[11] The data demonstrated a positive association between GERD patients exposed to PPIs and risk for myocardial infarction (OR = 1.16; 95% CI, 1.09 to 1.24).[11] The investigators approached yielded 97.5% specificity and 39% sensitivity in discerning a true association, which according to the investigators, provided 89% accuracy.[11] When data were analyzed in a separate prospective cohort, increased risk for cardiovascular mortality among PPI users was also found despite the investigators accounting for cardiovascular comorbidities (hazard ratio [HR] = 2.00; 95% CI, 1.07 to 3.78).[11] There were no such associations found between GERD patients exposed to H2RAs.[11]

Studies conducted since 1987 that investigated the association between PPIs and community-acquired pneumonia (CAP) were systematically reviewed.[12] Two retrospective cohorts and 7 case-control studies were available totaling over 120,000 pneumonia cases.[12] Use of PPIs was associated with increased risk of CAP (OR = 1.39; 95% CI, 1.09 to 1.76).[12] A stronger association was observed with higher doses of PPIs (OR = 1.50; 95% CI, 1.33 to 1.68).[12] Interestingly, the highest risk was for short-term PPI use.[12] No association between long-term PPI use (>180 days) and CAP was found.[12]

It has been suggested that long-term use of PPIs could promote the development of pre-cancerous lesions in the stomach, which might then increase the

occurrence of stomach cancers in PPI patients. However, there is no clear evidence to support these suggestions, though increased thickening of the stomach lining (hyperplasia) has been observed with long-term PPI use.[13] Such a condition can rarely lead to benign gastric carcinoids.[13]

Findings of PPI Drug Use Evaluation in Oregon Health Plan

The Oregon Pharmacy and Therapeutics Committee reviewed FFS PPI and H2RA utilization patterns for calendar year 2014.[14] PPIs accounted for 90% of all acid suppression claims and 84% were for preferred generics (omeprazole and pantoprazole).[14] The preferred H2RA (ranitidine) was associated with 8% of claims and the remaining 2% were associated with generic famotidine and cimetidine.[14] Over 75% of all patients (n=6712) were on acid suppression therapy longer than 8 weeks.[14] Funded OHP conditions were associated with just 14% of patients on continuous long-term PPI therapy and treatment averaged over 230 days per patient in 2014.[14]

Given the extensive long-term use by OHP FFS patients, lack of associated funded diagnosis and known risks associated with PPIs, the current prior authorization (PA) policy will limit use of all PPIs beyond 8 weeks to documented funded diagnoses effective July 1, 2015.[15] Current patients on long-term PPIs will be automatically approved for 1 year to allow for tapering. Preferred H2RAs will remain with open access due to their low overall utilization and established safety profile. Updated PA criteria allows some exceptions for use of PPIs under the OHP.[15]

Strategies to Wean Off Proton Pump Inhibitors

It is well understood that rebound acid hypersecretion following cessation of PPIs can occur. However, there is insufficient evidence to suggest this is a consistent phenomenon.[16] Studies evaluating rebound acid hypersecretion are of low-quality and have yielded contradictory results based on duration of therapy.[16] Therapy for up to 4 weeks found no evidence of rebound acid hypersecretion while therapy for 8 weeks or longer found evidence of hypersecretion.[16] The clinical importance of this acid rebound following the treatment with acid-suppressive therapy is unclear, but it may make it more difficult to discontinue PPIs. Thus, tapering off a PPI seems more logical than abruptly discontinuing a PPI, especially after long-term therapy.

There is a lack of consensus and guidelines on how to best discontinue long-term PPI therapy. A small number of discontinuation strategies have been investigated in patients with dyspepsia or non-erosive esophagitis, but very few studies have evaluated a specific discontinuation method and their effect on successful long-term discontinuation rates.[17] Studies with the highest long-term success rates (range, 30-60% at 12 months) used a brief 2- or 3-week PPI taper using a half-dose once daily or a full-dose on alternate days, in addition to providing patients with both oral and written education on symptom management and offering alternate drug therapy for breakthrough symptoms.[17] Studies assessing abrupt discontinuation of the PPI without a taper had much less successful permanent discontinuation rates.[17] It is unknown if tapering regimens longer than 3 weeks lead to improved discontinuation rates. Certainly, randomized clinical trials comparing different PPI discontinuation strategies are needed to inform this practice.

Regardless of the discontinuation strategy, screening for *H. pylori* infection and other appropriate diagnostic workups, if not previously performed, will identify patients less likely to tolerate PPI withdrawal and ensure appropriate treatment is initiated. In addition, providing written and verbal education about lifestyle and environmental strategies[18] and alternative treatment options to manage dyspepsia (eg, H2RAs and/or antacids) will ease the transition off the PPI. OHP patients have open access to preferred drugs like ranitidine and calcium carbonate.[19]

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