Implications of Long-term Proton Pump Inhibitor Use: Promoting Step-Down Therapy for Management of Gastro-esophageal Reflux Disease in the Outpatient Setting

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Introduction/Background

Per the International Montreal Consensus, gastro-esophageal reflux disease (GERD) is defined as a "condition which develops when the reflux of stomach contents causes troublesome symptoms or complications" (1,2). GERD is the most common disease of the gastrointestinal tract with an estimated prevalence affecting 20% of the Western population (2,3,4). Approximately 44% of the US adult population or 61 million individuals experience heartburn at least once per month whereas 25 million individuals experience heartburn on a daily basis (5,6,7). According to the National Ambulatory Medical Care Survey, 38.53 million annual outpatient visits are related to GERD (5). GERD has implications beyond just heartburn and regurgitation as the chronic condition is associated with decreased work productivity and psychological well-being. GERD patients report lower quality of life scores than patients with untreated angina pectoris, chronic heart failure, or diabetes mellitus (2,5). Not only is the diagnosis of GERD often that of trial and error with empiric treatment but also therapeutic management as patient responsiveness to acid suppression therapy varies considerably with relief options including proton pump inhibitor (PPI), H2 receptor antagonists (H2RA), prokinetics, and antacids (2). Measures of outcomes in GERD management include symptom recurrence, quality of life, and cost of management.

The ABIM Foundation "Choosing Wisely" initiative in collaboration with the American Gastroenterological Association draws attention to the evidence based recommendation: "For pharmacological treatment of patients with gastro-esophageal reflux disease (GERD), long-term acid suppression therapy (proton pump inhibitors or histamine2 receptor antagonists) should be titrated to the lowest effective dose needed to achieve therapeutic goals." Often, patients are initiated on an indefinite, prolonged course of PPI therapy without regularly addressing adherence and following up on symptom progression over time. The risks of worsened symptom burden with reducing or discontinuing PPI therapy must be balanced with the uncertain risks of long-term PPI use.

Acquiring a patient history of heartburn, sour/bitter taste in the mouth, and acid regurgitation has 89% sensitivity and 94% specificity for GERD (5). Heartburn is classically defined as a burning sensation beginning in the upper abdomen or lower chest (retrosternal) that rises towards the neck (6,7). Regurgitation is classically defined as the effortless return of gastric contents into the pharynx without nausea, retching, or abdominal contraction (7). In these instances, empiric suppression therapy for 4-8 weeks with H2RA BID or PPI 30-60 minutes before the first meal of day is indicated (5). No gold standard for the diagnosis of GERD exists but 24 hour pH monitoring is accepted with 85% sensitivity and 95% specificity (5). Approximately 70% of patients have ENRD (endoscopy negative reflux disease) and 30% of patients have erosive reflux esophagitis (2). Endoscopy is useful for assessing complications of GERD such as peptic strictures, erosive esophagitis, Barrett's esophagus, and adenocarcinoma (2). Nearly 10-15% of GERD patients will develop Barrett's esophagus by columnar/intestinal metaplasia of whom 1-10% will develop adenocarcinoma (5). Warning signs/symptoms suggestive of complicated GERD with an indication for upper endoscopic workup encompass dysphagia, early satiety, GI bleeding, iron deficiency anemia, odynophagia, vomiting, weight loss (5,8).

Most often the mechanism of GERD acid reflux is most patients is associated with transient relaxation of the lower esophageal sphincter as well as other precipitators such as increased intra-abdominal pressure, hiatal hernias, and esophageal dysmotility as the reflux of gastric acid, pepsin, bile salts, and trypsin triggers classic symptoms (5,9). Atypical

signs/symptoms of GERD include asthma, chest pain, chronic cough, globus sensation, onset after age 45, recurrent laryngitis, and subglottic stenosis. Micro-aspiration of gastric contents into the larynx and bronchial tree as well as acid stimulation of vagal afferent neurons is believed to underlie such atypical presentations of GERD (10).

Patients often self-diagnose and self-medicate themselves for acid reflux at a rate of 50%. Nearly 1 out of 3 patients use OTC acid suppressants such as Tums, Rolaids, Maalox (10). Refractory acid reflux is often managed surgically with reduction of hiatal hernias and/or strengthening of the gastro-esophageal junction by open vs. laparoscopic Nissen fundoplication/gastric wrapping techniques (5,10). However, with a 20% postsurgical complication rate and subsequent 50% resumption of pre-operative acid suppression treatment rate, PPIs and H2RAs form the cornerstone of GERD management (10). Recent developments in endoscopic treatment include radiofrequency heating of gastroesophageal junction (Stretta procedure) and endoscopic gastroplasty (10).

PPIs are not only frequently overprescribed in the primary and secondary care settings, but also account for a significant proportion of pharmaceutical healthcare expenditure. PPIs are among the top five most prescribed medications in North America, accounting for more than $100 million annually in US Department of Veterans Affairs outpatient pharmacy expenditure (11). Primary indications for PPI use include not only symptomatic relief of GERD but also preventing strictures and healing esophagitis, peptic ulcer disease, eradication of *Helicobacter pylori*, treatment and prevention of gastroduodenal ulcers secondary to NSAID use, Zollinger-Ellison syndrome, and Barrett's esophagus (5,9,12,13). The mechanism of action of PPIs is binding to the cysteine molecule of proton pumps on the canalicular membrane of parietal cells to irreversibly inhibit acid production (2,12). Grade A evidence from the American Gastroenterological Association (AGA) suggests that PPIs are more effective than H2RAs in controlling reflux symptoms, both of which are more effective than placebo (1,10). The AGA recommends step-up to twice daily PPI therapy if patients are unresponsive or step-down to standard lowest effective dose with adequate symptomatic control (1). Twice daily dosing of PPI is recommended for atypical presentations of GERD with reflux chest pain and extra-esophageal reflux (1).

A recent Cochrane review of 34 randomized controlled trials (RCTs) demonstrated that PPIs are more effective than H2RAs such as famotidine and ranitidine as well as prokinetics such as domperidone and metoclopramide in relieving heartburn (6). The reported relative risk for heartburn remission was PPIs (RR 0.37, 95% CI 0.32-0.44), H2RAs (RR 0.77), prokinetics (RR 0.86) (6). Similarly, a meta-analysis of 7 placebo-controlled RCTs found that PPIs are superior to placebo with a NNT 14.6 (14). Standard doses of PPIs include lansoprazole 30mg daily, omeprazole 20mg daily, pantoprazole 40mg daily, rabeprazole 20mg daily, dexlansoprazole 30mg daily, esomeprazole 40mg daily (5). Enantiomers of PPIs such as esomeprazole which is the S-isomer of omeprazole are designed to have stereoselectivity for higher bioavailability and improved efficacy (5,9). A systematic review of 12 RCTs indicated that esomeprazole 40mg demonstrated higher healing rates than standard/double dose PPIs at 4 and 8 weeks for severe erosive esophagitis of Los Angeles classification C & D or equivalent (5).

Over the course of 1999-2004, PPI use in the US has increased whereas H2RA use has decreased and PPIs are more expensive at a rate of $120 per month compared to generic H2RAs at less than $20 per month (15). H2RA effectiveness declines over time as its pharmacokinetics are superior for rapid symptom relief compared to PPIs which are optimal for long-term use (6).

Complete symptomatic relief with standard 4 week PPI therapy occurs in 60-70% patients (16). A review of 12 RCTs demonstrated a dose ceiling effect whereby higher PPI doses do not exert greater clinical benefit than the lowest effective dose (4).

While the most common side effects of PPI use include headache, diarrhea, constipation, abdominal pain, the adverse effects of long term PPI use and long term safety profile remains inconclusive (1). Adverse implications of PPIs encompass statistically significant associations with hip fractures, increased susceptibility to community acquired pneumonia (CAP) and health-care acquired pneumonia (HCAP), *Clostridium difficile* colitis, malabsorption of magnesium, iron, vitamin B12, hypergastrinemia, altered bioavailability of other medications, and antiplatelet interactions (4,5,7,9,10,11,14,17,18). Nevertheless, considering widespread PPI use, the benefit of acid suppression generally outweighs the risk of adverse events with the lowest effective dose recommended to mitigate potential risks (10). Frequent drug-drug interactions with common medications include ketoconazole, digoxine, nifedipine, indinavir, aspirin, and methadone (10). In 2011, the FDA acknowledged the risk of hypomagnesemia in the setting of 4 documented case reports of PPI induced hypomagnesemia contributing to complications such as seizures, arrhythmia, hypotension, tetany, and death (19,20).

PPI use has considerable public health implications as PPIs are estimated to account for 4.7% of hip fractures, which have a 20% mortality rate within the first year after sustaining the hip fracture and osteoporotic fracture costs ranging from $17-25.3 billion annually (21,22,23). A systematic meta-analysis of 11 observational studies found PPI use was associated with a significant increase in hip fracture risk (RR 1.30, 95% confidence interval 1.19-1.43), increase in spine fracture risk (RR 1.56, 95% CI 1.31-1.85) as well as any site fractures risk both with short term use of less than one year and long term use (21). H2RAs are not associated with increased fracture risk but exhibit weaker acid suppression. Similarly, a case control study with the General Practice Research Database of UK patients to demonstrated the risk of hip fractures associated with PPI use (22). The adjusted odds ratio associated with more than 1 year of PPI therapy (AOR 1.44, 95% CI 1.30-1.59) had a significant dose response effect as the strength of association increased with duration of PPI use (22). Long-term high dose PPIs (AOR 2.65, 95% CI 1.80-3.90, $p<0.001$) had a stronger association to fracture risk in men compared to women (22). The crude incidence rate of hip fractures was 4.0/1000 person years in the setting of more than 1 year PPI use vs. 1.8/1000 in controls (22). Likewise, a systematic review and meta-analysis of 10 controlled observational studies indicated PPIs are associated with hip fracture (OR 1.25, 95% CI 1.14-1.37), vertebral fracture (OR 1.50, 95% CI 1.32-1.72), and wrist/forearm fracture (OR 1.09, 95% CI 0.95-1.24) with both high and low dose PPI use (23).

Potential mechanisms for PPI associated predisposition to fractures include inhibition of osteoclastic H+K+ATPase pumps which impairs bone resorption, impaired calcium absorption secondary to hypochlorhydria, and vitamin B12 deficiency associated peripheral neuropathy and homocysteinemia interfering with collagen cross-linking both of which enhance fall risk (20,21,22,23). Such results must be interpreted with caution due to potential unmeasured/residual confounding factors such as the fact that PPIs are more often prescribed to older adults and many patients are simultaneously exposed to other medications such as corticosteroids, bisphosphonates, calcium and vitamin D supplementation as well as weight bearing activity and variable nutrition intake (21,22).

Additional reported PPI risk includes potential development of gastric pre-malignant lesions such as atrophic gastritis, intestinal metaplasia, and enterochromaffin-like (ECL) cell hyperplasia. A review of 7 RCTs encompassing 1789 participants indicated per lower quality

evidence suggested that PPI maintenance therapy is associated with diffuse (simple) ECL hyperplasia (OR 5.01, 95% CI 1.54-16.26, p=0.007) or linear/micronodular ECL hyperplasia (OR 3.98, 95% CI 1.31-12.16, p=0.02) (12). Such hyperplasia enhances the risk for dysplastic changes and subsequent gastric carcinoid formation. However, there is no clear evidence of PPIs inducing gastric atrophy or intestinal metaplasia. Additionally, unlike rat studies indicating carcinoid tumors with long-term PPI use, a review of 6 RCTs with a total of 785 patients found that maintenance PPI use is not associated with increased gastric atrophic changes or ECL hyperplasia for at least 3 years (24).

Nevertheless, prolonged PPI treatment may produce bowel symptoms and small intestinal bacterial overgrowth (SIBO) (7). A study of 42 patients at an outpatient GI unit in Naples receiving esomeprazole 20mg BID for 6 months found that at 8 weeks of PPI use, 43% patients experienced bloating, 17% flatulence, 7% abdominal pain, and 2% diarrhea. Glucose hydrogen breath test (GHBT) was positive in 26% patients in the setting of altered intestinal microflora and increased bacterial density by 1000 fold (7).

PPI induced achlorhydria not only contributes to malabsorption and B12 deficiency but also increased risk of gastrointestinal and respiratory microbial infections as a pH<4 exerts potent bactericidal effect (12,20). A meta-analysis of 6 nested, population-based, case-control studies totaling 1 million people demonstrated an increased risk of CAP associated with PPI use (OR 1.36, 95% CI 1.12-1.65) especially with short duration of use (11). Although recently hospitalized, immunocompromised, and high aspiration risk patients were excluded, potential confounders included age, gender, smoking status, and COPD. New PPI users have twice the risk of developing CAP compared to non-users. Potential mechanisms of such findings include acid suppression inducing bacterial overgrowth in the stomach which then contributes to enhanced bacterial micro-aspiration as well as inhibition of both innate and adaptive immunity by impairing neutrophil, natural killer and cytotoxic T cell activity (11).

Rebound acid hypersecretion following PPI therapy cessation is often an area of concern when discussing step-down or discontinuation of therapy. A systematic review of 8 studies demonstrated no strong evidence of clinically relevant rebound acid production (3). A randomized, double blind study enrolled 120 healthy volunteers to either 12 weeks placebo or 8 weeks esomeprazole 40mg daily followed by 4 weeks placebo. Nearly 44% of patients in the PPI group had worse symptoms of acidity in weeks 9-12 vs. 15% in the placebo group (p<0.001) (17). Such rebound acid hypersecretion may be secondary to the upregulation of H2 receptors, hypergastrinemia stimulating ECL cell histamine release, increased parietal cell mass, and upregulation of H+K+ATPase activity (3). The transient increase in blood and urine pH after gastric secretion is known as the alkaline tide phenomenon further highlighting the importance of gradual step down to enable reformation of H+K+ATPase and restore gastrin levels (17).

While the empiric step-up approach begins with H2RA for 8 weeks with transition to PPI if symptoms do not improve, several trials have demonstrated the effects of step-down to the lowest effective medication type and dosage with variable results. For instance, Piterman et al 2004 reported 70% of patients relapse after PPI step-down within 6 months whereas Inadomi et al 2001 reported 58% patients remained asymptomatic at one year after step-down (15). The DIAMOND (Dutch study on Initial Management of Newly Diagnosed Dyspepsia) double-blind, randomized, placebo-controlled trial of more than 600 patients compared 4 weeks of step-up acid suppression from antacid to H2 receptor antagonist to PPI with inadequate symptom relief vs. step-down from initial PPI therapy (8). Patients in the step-down arm reported higher rates of symptom relief at 2 and 4 weeks of therapy but there was no significant difference in symptoms

or quality of life score improvement at 6 month follow-up (8). Stepping up from antacid to PPI therapy is more cost-effective than stepping down from a PPI with statistically significant savings of 34 euros per patient (8). Similarly, in a study of PPI step-down in 71 subjects, 58% were asymptomatic after 1 year following PPI discontinuation with a decrease in management costs by 37% (25).

While step-down provides rapid initial relief, less treatment failure, and faster improvement in quality of life, the risks of overtreatment and higher initial cost are greater than that of the step-up approach which often has delayed symptomatic relief. Per Bak et al, an estimated 40% patients will experience symptom recurrence within 6 months of discontinuing PPI therapy (26). A recent study of 43 patients with reflux esophagitis randomized patients to either to one of three arms: step-down from 30mg daily lansoprazole to 8 weeks famotidine 20mg BID, dose reduction from 30mg daily lansoprazole to 15mg daily lansoprazole, and 15mg lansoprazole for 16 weeks (27). Nearly 50% of patients experienced heartburn recurrence and 78.6% of patients experienced regurgitation recurrence in the H2RA step-down group with impaired quality of life per the Psychological General Well-being Index (PGWB) (27). A Chicago Veterans' Affairs hospital step-down intervention transitioned 223 patients from lansoprazole 30mg BID to rabeprazole 20mg daily of whom 111 patients (50%) were successfully maintained on step-down and 23 patients (10%) entirely discontinued PPI therapy (28). Management of GERD with less intense acid suppression is a feasible option for some patients as this intervention demonstrated a comprehensive 28% reduction in pharmacy costs (28).

Likewise, in a retrospective population based cohort study in Republic of Ireland, cost savings occurred with implementing PPI generic substitution and step-down based on National Institute of Clinical Excellence (NICE) guidelines. PPI dose reduction resulted in 24% cost savings, PPI therapeutic switching to cheaper brand/generic equivalent with dose reduction 46% cost savings, and therapeutic substitution with H2RA 40% cost savings (18). Other interventions included a randomized, double-blinded taper of omeprazole in Sweden where discontinuation of PPI was successful in 27% long term PPI users and found to be associated with significantly better quality of life (29). The Tennessee Medicaid Program intervention requiring prior authorization for PPI prescriptions with valid indication for use such as erosive esophagitis, Barrett's esophagus, Zollinger-Ellison syndrome, GERD with h/o failure on H2RA resulted in the step-down of 71 patients from PPI to H2RA, and at 8 months follow up, 62.2% patients reported symptoms once per week or less (15). In a step-down study to single dose PPI in 117 patients, 79.5% did not report recurrent symptoms at 6 months and cost was decreased without compromising quality of life (30). A study of 82 patient and 26 general physician interviews demonstrated the importance of patient autonomy and awareness of uncertain effects of long-term PPI use as a common barrier to step-down is patient recognition that H2RAs are not as effective as PPIs (31).

Predictors of successful response to PPI step-down from long term, daily dosing to less than daily dose in placebo-controlled trials included female gender and adequate symptom control on daily PPI based on the Quality of Life in Reflux and Dyspepsia questionnaire (32). Predictors of step-down failure included heartburn predominant symptoms, younger age, and longer duration of PPI use (5,30). In a study of 293 patients given 8 weeks of esomeprazole 20mg daily followed by step down to on-demand esomeprazole 20mg for 26 weeks to take if symptomatic only, predictors of step-down failure included irritable bowel syndrome (adjusted

HR 2.1, 95% CI 1.5-3.8, p=0.01) and daily reflux symptoms (AHR 2.7, 95% CI 1.9-4.2, p=0.001) as IBS patients often demonstrate higher esophageal sensitivity to acid (33).

Purpose

The purpose of this study was to inspire both patient and provider attention to the uncertainty of adverse effects as well as cost implications of long-term PPI use in the outpatient setting for the management of GERD as well as encouraging patient-provider dialogue regarding step-down therapy in the setting of well-controlled acid reflux symptoms. Considering the EMMC promotes the ABIM Foundation "Choosing Wisely" initiative in many areas of medicine, this study was designed to focus on the American Gastroenterological Association evidence based recommendation: "For pharmacological treatment of patients with gastro-esophageal reflux disease (GERD), long-term acid suppression therapy (proton pump inhibitors or histamine2 receptor antagonists) should be titrated to the lowest effective dose needed to achieve therapeutic goals."

Methods

Chart review of the EMMC Family Medicine Center Centricity Outpatient Electronic Medical Records was completed with assistance from preceptor Dr. Pritham. The following search criteria were applied: Active patients + active PPI use on medication list + date of last office visit on or after 7/1/2014. As of 12/17/2014, 527 patients met the aforementioned criteria and every fifth patient was randomly in alphabetical order. The charts of 50 patients in total were reviewed to assess the current acid suppression therapy regimen, diagnosis/problem list for which the PPI is indicated, progression of symptoms, and history of changes to the therapy regimen including both step-up and step-down. Additionally, the last three clinic visit encounter notes were reviewed for each patient to assess if GERD was re-visited during the encounter.

Data – *chart review document attached*

Results

Pertinent results acquired from chart review include 28% of patients demonstrated improved GERD/acid reflux symptoms during the most recent office visit during which GERD was discussed, however of these patients, only 1 patient received a step-down intervention whereas the remainder of patients continued their existing PPI and/or H2RA regimen. Furthermore, 70% of patients were not asked about their GERD/acid reflux symptoms over the course of the last 3 office visits to the clinic. Nearly 64% of patients' GERD or reflux symptom status or degree of symptomatic control was not updated on their problem history during the entire year of 2014 or no description of symptoms were ever recorded in the past. Surprisingly, 14% of patients did not have a diagnosis listed on their problem list which would correspond to an indication for PPI use. Overall, 28% of patients had received some form of step-down therapy over the course of their acid suppression regimen, most often in the form of step-down from PPI to H2RA.

Discussion

Per interview with [Name Withheld], PharmD Associate Professor of Pharmacy Practice, School of Pharmacy at Husson University, Bangor, ME:

Often patients are placed on PPIs during hospitalization which are not discontinued upon discharge and are subsequently continued in the outpatient setting due to PCP reluctance to discontinue medications prescribed by gastrointestinal specialists. Nearly 40% patients in the UK initiated on PPI during hospitalization were not reviewed for indications to continue such medications post-discharge (Cahir). Additionally, most patients are using OTC products which have weaker formulations for cost-effectiveness such as the use of microencapsulation techniques. It is "exceedingly rare to see a de-escalation of PPI therapy as it is rarely observed" in the Bangor community as the step-down approach is not being implemented on a wide scale. Rebound acid following discontinuation of PPI is often worse than initial symptoms and confounding variables of adverse effects seen in observational studies such as overweight/obese BMI and smoking status make it difficult to assess benefits vs. risks. There is often push back from patients on changing their medication regimen yet there is significant potential for drug-drug interactions causing exaggerated side effects as well as pharmaco-economic implications.

Per interview with [Name Withheld], MD, Family Medicine Resident:

Patients with GERD/acid reflux symptoms are often initiated on either a PPI or H2RA considering patient specific severity of symptoms. Although PPIs only require 4 weeks to take effect, patients are provided 3 months of PPI use before symptoms are re-assessed. After 3 months of use and adequate symptom control, an attempt to step-down is initiated by either decreasing the dose or transitioning to H2RA. In the event that a patient fails step-down therapy, they are returned to their original PPI dose.

Per interview with S.G. 53 year old male patient presenting for follow up on GERD:

H/o obesity (BMI 34.11), GERD, HLD, depression, anxiety, and organic erectile dysfunction, 35 pack year smoking history, daily alcohol use presented for refill of pantoprazole 40mg daily. Patient was asked if he has ever been asked to step-down his regimen either by dosage or H2RA use which he denied. At the visit, he declined any current heartburn or regurgitation symptoms but noted new onset dysphagia to solid foods only and globus sensation in mid-sternal area due to which step-down was not further pursued and patient was referred for upper endoscopy workup of peptic strictures vs. obstructive malignancy in the setting of alcohol and tobacco use history. Patient was additionally educated on lifestyle interventions to reduce GERD symptoms.

Patient Education Slides – *located at end of powerpoint*

Future Directions

Considering the efficacy of lifestyle modifications with AGA Grade B fair evidence supporting weight loss if overweight or obese as well as elevation of the head of the bed by 4-8 inches, such approaches can be applied synergistically with acid suppression therapy to better enable step-down. Among these interventions include educating patients to avoid large, late meals as well as avoid reflux precipitants such as acidic, spicy, and high fat content foods, tomato or citrus based products, alcohol, caffeine, chocolate, onions, garlic, peppermint, and carbonated drinks. Patients may be further instructed to avoid recumbency 2-3 hours after meals as well as remain cognizant of medications that potentiate GERD symptoms including calcium channel blockers, alpha and beta agonists, theophylline, nitrates, and sedatives. Other lifestyle modifications include avoiding tight clothing around the waist, smoking cessation, moderation of alcohol, as both alcohol and nicotine contribute to decreased LES pressure and esophageal

irritation. Limited evidence exists to support alternative therapies such as licorice root, ginseng, vinegar, and acupuncture.

Further evidence is needed to assess the efficacy of antisecretory therapies and optimal use of medications in specific settings; role of diagnostic testing including endoscopy, esophageal manometry, ambulatory pH monitoring in evaluation of patients with GERD; management approaches to atypical GERD patients including patients with reflux chest pain and extraesophageal reflux syndromes such as asthma, laryngitis, cough; and potential adverse effects warranting work up with bone density studies, calcium supplementation for which currently there is insufficient evidence.

Limitations of the study include small sample size, chart review of past 3 visits of which some were acute visits, and potential for brief follow up of reflux symptoms without documentation in the EMR. Patients may not be appropriately dosing PPIs prior to meals or may be continuing inappropriate PPI use without proper indications especially in the setting of potential undocumented OTC PPI use.

Multi-faceted initiatives are vital to promoting changes in existing PPI use trends including pharmacy driven step-down orders, limiting PPI use for stress ulcer prophylaxis for non-ICU patients, and chart review of medication on discharge. An intriguing study of the PROMISe III trial in Australian pharmacies enabled a computerized clinical decision support prompt in pharmacy-dispensing software to promote PPI step-down by encouraging patients to discuss this therapeutic option with PCPs. Nearly 73 out of 185 pharmacies were randomly selected to have a prompt activated upon dispensing high dose 40mg daily esomeprazole or pantoprazole. The prompt group demonstrated a PPI intervention rate of 1.67/100 prescriptions vs. 0.17/100 in control ($p<0.001$) with 34 instances of PPI step-down in 28 days of which 28 occurred in PPI prompt pharmacies (34). Cost savings upon extrapolation was 497,000 euros in the first year across over 5000 Australian pharmacies (34). With a patient centered medical model approach to family medicine, PPI step-down therapy draws attention to the importance of patient empowerment with the information to make informed decisions regarding their health.

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