Magnitude and Economic Effect of Overuse of Antisecretory Therapy in the Ambulatory Care Setting

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Objectives: To determine the prevalence and economic effect of inappropriate proton pump inhibitor (PPI) use in an ambulatory care setting.

Study Design: Retrospective medical record review of random sample with subgroup analysis.

Methods: Patients were categorized according to appropriateness of pharmacotherapy based on documented upper gastrointestinal tract diagnoses, gastrointestinal or extraesophageal symptoms, or gastroprotection. Adverse events potentially associated with PPI use were identified.

Results: Of 946 patients in an ambulatory care setting, 35.4% were given PPI therapy for an appropriately documented upper gastrointestinal tract diagnosis, 10.1% received PPIs empirically for symptomatic treatment based on extraesophageal symptoms, 18.4% received PPIs for gastroprotection, and 36.1% had no documented appropriate indication for PPI therapy. In a subgroup analysis, 48.6% of patients across all 4 categories received PPIs without documentation of reevaluation of upper gastrointestinal tract symptoms, accounting for 1034 patient-years of PPI use. The total cost of inappropriate PPI use was $233,994 based on over-the-counter PPI costs and $1,566,252 based on average wholesale price costs. Potentially related adverse events in this cohort included *Clostridium difficile*–associated diarrhea (6 cases) and community-acquired pneumonia (1 case), but no cases of hip fracture or vitamin B_{12} deficiency were identified.

Conclusions: Proton pump inhibitors are often overused in the ambulatory care setting without documented valid indications. Inappropriate use of PPIs is associated with substantial cost expenditure and with the potential for adverse events.

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For author information and disclosures, see end of text.

Proton pump inhibitors (PPIs) have been proven to be superior to H_2 receptor antagonists in the treatment and symptomatic remission of nonerosive reflux disease and erosive esophagitis in numerous randomized controlled trials highlighted in current guidelines from the American Gastroenterological Association[1] and the American College of Gastroenterology.[2] Proton pump inhibitors account for more than $11.2 billion annually in US prescription costs,[3] with an estimated $3441 per patient per year attributable to direct and indirect expenditures for the treatment of gastroesophageal reflux disease (GERD).[4] This substantial expenditure for PPIs has led researchers to consider cost-effective strategies for antisecretory therapy (AST) use in the treatment of GERD, including on-demand and step-down therapy.[5-10] In addition, several studies[11-13] have addressed the concern that AST, predominantly with PPIs, is overused for intensive care unit and non–intensive care unit stress ulcer prophylaxis, leading to significant yet controllable cost expenditure.

Questions regarding the appropriateness of prescribing practices in primary care with regard to long-term PPI therapy have been raised for more than a decade.[14] Studies[15,16] have addressed the issue of overuse of AST in the ambulatory care setting by identifying the indications and duration of AST; however, cost expenditure and potential adverse effects associated with nonindicated PPI therapy were not reported. Recently, significant attention has focused on the potential adverse events associated with short-term and long-term PPI use. Evidence supports associations between PPI use and *Clostridium difficile*–associated diarrhea (CDAD)[17-22] and other enteric infections,[23,24] community-acquired pneumonia (CAP),[25-28] hip fracture,[29-31] vitamin B_{12} (cobalamin) deficiency,[32] interference with antiplatelet therapy,[33-37] and, most recently, spontaneous bacterial peritonitis (SBP) in patients with cirrhotic ascites.[38]

We hypothesized that a significant proportion of patients who are started on PPI therapy in the ambulatory care setting do not have a valid indication or use PPIs indefinitely without documented reevaluation to determine the appropriateness of continued therapy. Moreover, we suspect that this practice leads to preventable and significant cost expenditure and may place such patients at an increased risk for potential adverse events due to nonindicated PPI therapy.

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Take-Away Points

Proton pump inhibitor (PPI) therapy is significantly overused in the ambulatory care setting with regard to documentation of appropriateness of therapy.

- Patients often continue using PPI therapy indefinitely without reassessment of continued need for therapy.
- Ensuring appropriate use of PPI therapy should decrease pharmacotherapeutic expenditures and reduce associated adverse events, including *Clostridium difficile*–associated diarrhea, community-acquired pneumonia, hip fracture, vitamin B_{12} deficiency, and inhibition of antiplatelet therapy.

METHODS

The Veterans Affairs Ann Arbor Healthcare System is a large multispecialty teaching hospital located in southeastern Michigan. Our study population consisted of all Veterans Affairs Ann Arbor Healthcare System outpatients who had received a prescription for a PPI. A list of all such outpatients who received a PPI between February 2006 and January 2007 was generated using the pharmacy computer database; 7877 patients were identified. Because this project focused solely on identifying the potential for overuse of PPI therapy, we included only those patients who did not have a definable upper gastrointestinal (GI) tract diagnosis based on appropriate related *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes (**Table**). Of 7877 identified patients who received a PPI, 2474 (31.4%) did not have an *ICD-9-CM* code indicating an upper GI tract diagnosis. A random sample of 946 patients was selected from this population using the random-number generator from Excel (Microsoft Excel; Microsoft Corporation, Redmond, WA). Once identified, these patients were retrospectively evaluated from the earliest date for which a PPI prescription had been filled until May 2008 using computerized medical record and pharmacy data. Age, sex, indication for PPI therapy (if listed), type of PPI, start and stop dates of PPI therapy, adverse drug reactions, and refill data for each subject were abstracted into a secondary electronic database (Excel spreadsheets). Comorbid diagnoses were collated under the broad disease categories of GI, cardiovascular, renal, endocrine, pulmonary, psychiatric, urologic, hematology/oncology, infectious, orthopedic, neurologic, dermatologic, and rheumatologic. Subjects were categorized into the following 4 groups based on appropriateness of PPI therapy: (1) appropriate therapy for GI diagnosis (Table), (2) empiric treatment based on upper GI tract symptoms without a documented GI diagnosis (eg, empiric trial of PPI for extraesophageal symptoms of GERD), (3) gastroprotection (defined liberally in this study to include subjects receiving chronic warfarin sodium anticoagulation or concomitant therapy with nonsteroidal anti-inflammatory drugs or corticosteroids), or (4) no documented appropriate indication for PPI therapy.

The retrospective medical record review identified the initial indication for PPI therapy and documented the rationale for continuing or discontinuing therapy. Adverse events potentially related to PPI use were also abstracted, including CDAD, CAP, hip fracture, and vitamin B_{12} deficiency. Potential interactions with antiplatelet agents and the occurrence of SBP in patients with cirrhotic ascites were not recorded in this study. Pharmacy records were abstracted to determine when a PPI was initially prescribed and when prescription refills were dispensed. Cost data were based on the number of pills prescribed and the duration of treatment. Cost estimates were calculated using over-the-counter prices from Costco Wholesale Corporation (http://www.costco.com) and average wholesale price (AWP) data from the *2009 Red Book: Pharmacy's Fundamental Reference* (Thomson Reuters, New York, NY), assuming full adherence to medication prescriptions. These 2 cost figures provide a reasonable range for expenditure, it being understood that full AWP cost is rarely charged.

Inappropriate PPI use data were analyzed by descriptive reporting of counts of days/years of PPI use per patient. The total PPI consumption (days/years of PPI use) was based on actual prescription fills during the period of observation. The costs associated with inappropriate PPI use were calculated by multiplying the number of days/years of PPI use without an appropriately documented indication by the unit cost of PPI. Univariate (χ^2) and multivariate (logistic regression) analyses were performed to identify whether the presence or type of underlying diagnoses or comorbid conditions was associated with inappropriate PPI use. $P < .05$ was considered statistically significant.

RESULTS

Among 946 patients lacking administrative codes indicating a diagnosis requiring AST who were evaluated in our study, 2391 years (872,671 days) of PPI therapy were accumulated. The mean (SD) age of the subjects in this study was 66.8 (12.2) years, and 96.3% were male. Omeprazole was the most frequently prescribed PPI (98.9% of patients), followed by pantoprazole (0.9%).

Despite the absence of administrative coding, review of medical records revealed documentation of an upper GI tract diagnosis requiring PPI therapy in 35.4% of the cohort (n = 335). Another 18.4% of patients (n = 174) received PPIs for gastroprotection, and 10.1% (n = 96) received PPIs empiri-

Table. Definable and Acceptable Upper Gastrointestinal Tract Diagnoses for Proton Pump Inhibitor (PPI) Therapy and Corresponding *ICD-9-CM* Codes

Diagnosis	*ICD-9-CM* Code
Diagnoses That Are Appropriately Treated with PPI Therapy	
Esophagitis	530
Esophageal ulcer	530.2
Esophageal stricture	530.3
Barrett's esophagus	530.85
Esophageal reflux	530.81
Heartburn	787.1
Gastric ulcer	531
Duodenal ulcer	532
Peptic ulcer disease	533
Gastroduodenal ulcer	534
Diagnoses That May Be Treated with PPI Therapy[a]	
Gastritis	535
Dyspepsia	536.8
Abdominal pain/epigastric	789.06
Abdominal pain/periumbilical	789.06

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification.*
[a]These are symptoms and not disease states; therefore, continuation of PPI therapy is not indicated, despite persistence of symptoms.

cally for symptoms; however, the remaining 36.1% of subjects (n = 341) had no documented appropriate indication for PPI therapy, despite an extensive analysis of the medical records (**Figure**). The mean duration of PPI therapy for appropriate indications as defined in our study (eg, appropriate diagnoses, gastroprotection, and symptomatic treatment) was 1013 days, while that for inappropriate or undocumented therapy was 823 days.

In addition, 48.6% of patients (n = 460) across all 4 categories received PPI therapy without documentation of reevaluation of symptomatic improvement or assessment of continued need for AST, accounting for 1034 patient-years of PPI use and $233,994 based on over-the-counter costs of omeprazole and $1,566,252 based on AWP costs of omeprazole. Among these 460 patients, 15.7% (n = 72) had an initial appropriate diagnosis, 7.8% (n = 36) had been prescribed empiric treatment based on upper GI tract symptoms, 2.4% (n = 11) had received PPI therapy for gastroprotection, and 74.1% (n = 341) had no documented indication for PPI therapy. These 341 patients accounted for 768 patient-years of inappropriate PPI use and $1,163,328 in AWP PPI costs over the study period.

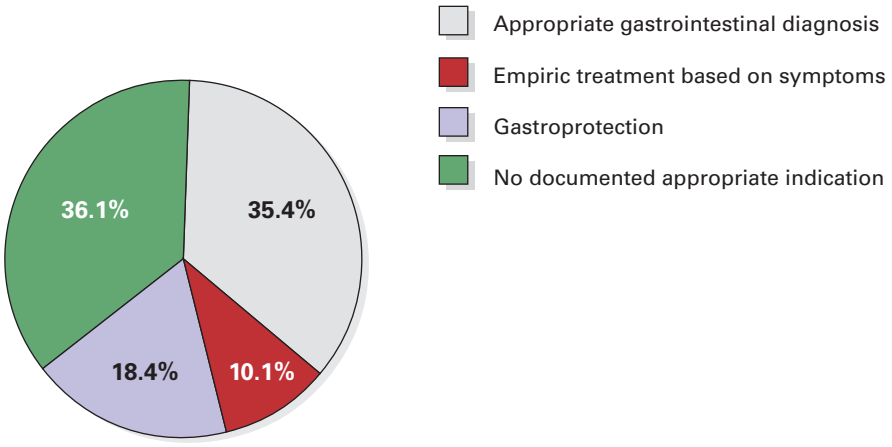
Among 174 patients who received PPIs for gastroprotection, 93.7% (n = 163) were taking warfarin, nonsteroidal anti-inflammatory drugs, or corticosteroids concomitantly, while the remaining 6.3% (n = 11) were not. These 11 patients accrued 25.7 patient-years of inappropriate PPI use and $38,929 in AWP PPI costs. Among 772 patients who did not receive PPIs for gastroprotection, 43.4% (n = 335) had an appropriate upper GI tract diagnosis, 12.4% (n = 96) received empiric treatment, and 44.2% (n = 341) had no documented indication for PPI therapy.

Among 96 subjects who received an empiric trial of PPI therapy based on extraesophageal symptoms, 37.5% (n = 36) had no documented assessment of response, accruing 52.3 patient-years and $79,221 in AWP PPI costs over the study period. Among 335 patients who were prescribed PPI therapy for an appropriately documented upper GI tract diagnosis, 21.5% (n = 72) had no documented assessment of response, accruing 188 patient-years and $284,773 in AWP PPI costs.

The mean (SD) number of comorbid diagnoses per patient, as defined by the aforementioned disease categories, was 4.5 (1.1). The most common comorbid conditions were related to cardiovascular disorders, including hypertension and hyperlipidemia (65.0%), whereas the least common comorbidities were related to orthopedic conditions (0.1%). There was no statistical association between PPI use and comorbid conditions to demonstrate any potential cause-and-effect relationship.

Observed adverse clinical outcomes potentially associated with PPI therapy included CDAD (6 cases) and CAP (1 case), but no cases of hip fracture or vitamin B_{12} deficiency

■ **Figure.** Prevalence of Proton Pump Inhibitor Therapy in the Ambulatory Care Setting of a Veterans Affairs Hospital Internal Medicine Clinic



were identified. Adverse reactions potentially associated with concomitant use of PPIs and antiplatelet therapy and the occurrence of SBP in patients with cirrhotic ascites were not assessed.

DISCUSSION

In a single-center review of 7877 patients prescribed PPIs over a 1-year period, 31.4% did not have an *ICD-9-CM* code associated with an upper GI tract disease diagnosis. Our extensive review of the primary medical records for 946 of these patients confirmed that 36.1% had no indication for AST. Among patients prescribed an empiric trial of PPIs for presumed GI symptoms, 48.6% continued taking PPIs without reassessment of response to the empiric trial. In addition, prescription refills for PPIs were given without documentation of persistence of upper GI tract symptoms, and substantial costs were incurred based on inappropriate PPI therapy. Observed clinical outcomes in this retrospective cohort study that were potentially associated with PPI use included 6 cases of CDAD and 1 case of CAP.

Our study highlights the common practice of overuse of PPIs for upper GI tract conditions, specifically the commencement of therapy and the failure of physicians to readdress the need for continuous therapy. Previous research on potential overuse of AST in managed care settings reported an estimated 6% to 24% incidence of patients taking AST without an appropriately documented indication,[39] well before the notion that PPIs may be overused and contribute to excess expenditure became widespread.[40]

A study conducted by Jacobson and colleagues[15] sought to determine patterns of use of PPIs and H_2 receptor antagonists in clinical practice and used pharmacy billing data to identify patients who were taking AST for more than 90 days. Although their study evaluated a substantially larger cohort of 168,727 adult patients, they determined that an appropriate upper GI tract diagnosis was documented in 61% of the study population (eg, GERD in 38% and dyspepsia in 42%) compared with 35.4% in our cohort, with an almost identical criteria list for acceptable upper GI tract diagnoses. In their study, 55% of subjects were female, whereas almost all of our subjects were male. The mean age of their subjects was 52 years, while that in our study was 66.8 years.

Although 39% of patients in the study by Jacobson et al[15] lacked appropriate documentation for any upper GI tract diagnosis, almost one-half had documented symptoms of extraesophageal manifestations of potential upper GI tract disease. A total of 19% of subjects had diagnoses that the authors thought could represent atypical GERD or dyspepsia, compared with 10.1% in our study. The study by Jacobson and colleagues did not define or evaluate a subgroup analysis with regard to gastroprotection using PPIs.

Our study had several limitations. It was conducted at a Veterans Affairs outpatient clinic, and as a result the cohort was almost exclusively middle-aged men with multiple medical comorbidities. Because the data were abstracted via retrospective medical record review from each outpatient visit, it is possible that upper GI tract symptoms or indications for PPI therapy were not reported and not documented, yet in a substantial percentage of cases, already noted, a PPI was prescribed. It is probable that some of the patients in the cohort categorized as having no appropriately documented indication for PPI therapy (more than one-third of all patients in this study) could have had GERD or GERD-like symptoms and were prescribed a PPI initially. We suspect that over time PPI prescriptions were simply refilled without discussion of

continuation or resolution of GERD symptoms. Moreover, because many patients with GERD have adequate symptom control using PPIs, physicians may have assumed stability and not addressed or commented on this issue in their medical record documentation. Nonetheless, no documentation among our cohort of 946 patients was made of any attempt at on-demand or step-down therapies, which have been proven to be efficacious and cost-effective in the management of upper GI tract disorders.[5-10]

The incidence of reported adverse events with a potential relationship to PPI therapy was 0.7%, or 7 of 946 patients. Because a retrospective study can only show association and not true causality, any direct potential relationship would have been difficult to prove. Only 6 of 946 patients (0.6%) in our study had CDAD. One study to date has adequately evaluated risk of community-acquired CDAD in patients receiving PPI therapy. Dial and colleagues[18] performed 2 population-based case-control investigations in the United Kingdom among patients who had not been hospitalized within the previous year. They found an odds ratio (OR) for community-acquired CDAD associated with current PPI use of 2.9 (95% confidence interval [CI], 2.4-3.4). By comparison, hospital-based studies[19-22] examining the risk of CDAD associated with PPI use have found ORs ranging from 2.1 (95% CI, 1.4-3.4) to 3.6 (95% CI, 1.7-8.3). The incidence of CDAD in our study may be artificially low, as it is unclear from medical record review whether all patients who reported diarrhea were tested for C *difficile* toxin while receiving chronic PPI therapy. Nonetheless, this potential causal relationship remains a challenge to prove as a direct factor.

There was only 1 documented case of CAP (0.1%) in our study. Our medical record review included 946 patients over a multitude of durations, which makes this incidence surprising in a population of middle-aged male veterans. Investigators examining risk of CAP in patients taking PPIs have found ORs of 4.5 (95% CI, 3.8-5.1) in one study[25] and 1.5 (95% CI, 1.3-1.7) in another study.[26] Sarkar and colleagues[27] performed a nested case-control study and determined the following risk of CAP associated with current PPI therapy: OR of 6.53 (95% CI, 3.95-10.80) if started within 2 days of CAP diagnosis, OR of 3.79 (95% CI, 2.66-5.42) if started within 7 days of diagnosis, and OR of 3.21 (95% CI, 2.46-4.18) if started within 14 days of diagnosis. Most worrisome was the risk of CAP associated with initiation of PPIs 0 to 7 days before diagnosis, with an OR of 5.0 (95% CI, 2.1-11.7). In the only such study conducted in the United States, Herzig and colleagues[28] found a lower risk of CAP development associated with current PPI therapy, with an OR of 1.3 (95% CI, 1.1-1.4). Therefore, starting patients on PPI therapy increases risk of CAP during initial days of therapy, yet failing to reassess patients for necessity of PPI therapy or continuing them on PPI therapy for longer periods of time has not been shown to significantly increase risk.

There were no cases of hip or other osteoporotic fracture reported in our study cohort. Yang and colleagues[29] performed a nested case-control study in the Netherlands that found an OR of hip fracture with PPI use for 1 year of 1.22 (95% CI, 1.15-1.30), for 2 years of 1.41 (95% CI, 1.28-1.56), for 3 years of 1.54 (95% CI, 1.37-1.73), and for 4 years of 1.59 (95% CI, 1.39-1.80). Vestergaard and colleagues[30] performed a case-control study in Denmark that demonstrated the following risks associated with PPI use within the last year: fracture OR of 1.18 (95% CI, 1.12-1.43), hip fracture OR of 1.45 (95% CI, 1.28-1.65), and spine fracture OR of 1.60 (95% CI, 1.25-2.04). Targownik and colleagues[31] performed a retrospective matched cohort trial in Canada that showed an OR of hip fracture after 5 or more years of PPI use of 1.62 (95% CI, 1.02-2.58), an OR of hip fracture after 7 or more years of PPI use of 4.55 (95% CI, 1.68-12.29), and an OR of any osteoporosis-related fracture after 7 or more years of PPI use of 1.92 (95% CI, 1.16-3.18).

There were no cases of vitamin B_{12} deficiency reported in our cohort of 946 patients. However, our medical record review did not include a separate and extensive review of documentation of laboratory testing verifying serum cobalamin levels, but rather relied solely on diagnosis summaries. Studies[41,42] from the 1990s estimated the prevalence of vitamin B_{12} deficiency in Americans to be 5% to 15%, whereas more current data estimate the rate to be 39% or higher.[43] Valuck and Ruscin[32] performed a retrospective case-control trial that found an OR of 4.46 (95% CI, 1.49-13.33) for vitamin B_{12} deficiency associated with the use of PPIs or H_2 receptor antagonists for 12 months or longer. We are suspicious that a modest percentage of our study cohort had a cobalamin deficiency, given the cohort's mean age and numerous comorbidities. Therefore, we are unable to determine if there is a true cause-and-effect relationship between long-term PPI use and cobalamin deficiency in our cohort.

Our study did not record or examine the suspected effects of PPI therapy on antiplatelet agents. Recent investigations have evaluated the potential interaction of the antiplatelet agent clopidogrel bisulfate in patients concomitantly treated with PPIs, suggesting that PPIs decrease antiplatelet effects due to competitive inhibition of the cytochrome P450 2C19 enzyme.[33] Gilard and colleagues[34] conducted a double-blind, randomized, placebo-controlled trial among patients with coronary artery disease undergoing coronary artery stent implantation in which all patients received aspirin and clopidogrel and were randomized to receive omeprazole or placebo. They determined that omeprazole use significantly decreased

the effects of clopidogrel on platelet activation, yet no clinical outcomes were examined in their study. Siller-Matula and colleagues[35] evaluated patients with coronary artery disease undergoing percutaneous coronary intervention and receiving both clopidogrel and PPI therapy, and found no statistically significant difference between findings among patients who received pantoprazole or esomeprazole versus those who received no PPI therapy. Results of their study suggested that the suspected PPI–clopidogrel interaction may not be a class effect. Ho and colleagues[37] examined a cohort of US veterans after hospitalization for acute coronary syndrome and found that the use of clopidogrel plus PPIs was associated with a 25% increased risk of death from or rehospitalization for acute coronary syndromes compared with the use of clopidogrel without PPIs; no increased risk of all-cause mortality was noted.

Proton pump inhibitors suppress gastric acid secretion and allow for bacterial colonization of the upper GI tract, with potential for development of bacterial overgrowth and translocation. Bajaj and colleagues[38] performed a retrospective case-control study among 70 patients with cirrhotic ascites and determined that 69% of patients with SBP had used PPIs before hospitalization versus only 31% of patients without SBP. They concluded that PPI use was independently associated with SBP in this cohort (OR, 4.31; 95% CI, 1.34-11.7). They also observed that 47% of patients who used PPIs had no documented indication for AST.

We conclude that PPIs are often overused in the ambulatory care setting without documented valid indication for treatment of upper GI tract disorders or for continuation of therapy. This hypothesis stems from the observation that GERD and dyspepsia are often of minimal severity in the absence of upper GI tract alarm symptoms and are frequently overlooked in follow-up examinations, with healthcare providers reflexively refilling prescriptions and not reassessing symptoms. Our study did not discover a significant incidence of adverse effects potentially related to PPI therapy in contrast to numerous retrospective studies across the globe. Additional research to prove a cause-and-effect relationship between PPI therapy and CDAD, CAP, osteoporotic fracture, vitamin B_{12} deficiency, inhibition of antiplatelet therapy, and SBP in patients with cirrhotic ascites needs to be performed, as there is a paucity of even associative data in US trials.

Potential interventions to minimize inappropriate use of PPI therapy in the absence of documented disease or symptoms include prompt-based reminder systems to trigger a direct discussion between provider and patient regarding symptomatic improvement, worsening, or stability that are centered on a proven cost-effective on-demand or step-down approach to therapy. Such a system could also minimize reflexive refilling of PPI prescriptions in the outpatient setting. The use of pharmacists and mid-level providers could also aid in this task, with the ultimate goal of decreasing resource expenditure and minimizing the potential risk of adverse events.

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