Original Research

Proton Pump Inhibitor Use and Adverse Effects in South Atlantic Hospitals

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Abstract

Background
Proton pump inhibitors (PPI) have transformed the management of acid-related gastrointestinal disorders, becoming one of the top-selling medications in the United States. There is no doubt that PPIs have a significant therapeutic impact on patients with gastroesophageal reflux disease and gastrointestinal bleeding. However, evidence is mounting that PPIs are overprescribed, leading to more patients possibly experiencing adverse effects. There is a great deal of ongoing debate surrounding the significance and impact of these adverse effects.

Methods
We conducted a study in 9 HCA hospitals in the southeastern United States to determine the number of patients who started on PPIs during their admission from July 2017 to July 2019 and, of these patients, how many were discharged on PPIs. We also explored whether PPIs were prescribed in conjunction with diagnoses consistent with appropriate use as defined by the National Institute for Health and Clinical Excellence (NICE) guidelines during their admissions. This appropriate use was evaluated based on ICD-10 codes entered during patient stays. Furthermore, we evaluated whether PPI patients had developed some known adverse effects including hypomagnesemia, pneumonia, and *Clostridium difficile*-associated diarrhea.

Results
Our data showed that of the 52 712 patients included in the study, 53.1% (27 993) received PPIs without evidence of an appropriate diagnosis based on ICD-10 codes. Appropriate use ranged between 36.1% and 62.8% for each hospital included.

Conclusion
PPIs were being overprescribed at the 9 hospitals included in the study according to the ICD-10 codes documented when compared to NICE guidelines. When compared with a normal, age-matched population, our results found increased rates of pneumonia and hypomagnesemia in patients being prescribed PPIs. This study suggests a need to improve hospital PPI prescribing practices to limit the non-indicated administration of PPIs and the resulting increased incidence of adverse effects.

Keywords
adverse drug effects; inappropriate prescribing; indications; inpatients; proton pump inhibitors (PPI)

Introduction
Since the advent of proton pump inhibitors (PPIs) in the 1980s, the treatment of different acid-related gastrointestinal disorders has been revolutionized, and they have become one of the highest-selling medicines.[1] With an estimated 11 billion dollars in sales annually in the United States (US), this class of antisecretory therapy falls behind only statins in total cost expenditure.[2] PPIs are the most potent

antisecretory agents of hydrochloric acid in the gastric lumen and act by inhibiting H-K ATPase, the final step of gastric acid secretion by parietal cells.

There is a common belief that PPIs have very low toxicity, high efficacy levels, and are perceived to be safe and cost-effective.[3] However, evidence shows that these medications can lead to multiple adverse side effects.[1] Due to adverse effects and decreased effectiveness with long-term use, the National Institute for Health and Clinical Excellence (NICE) guidelines were developed to recommend the dose and duration of PPI usage for different clinical indications, henceforth referred to as appropriate use or evidence-based use.[4] Most PPI indications only need short-term medical treatment, rarely beyond 4 to 8 weeks.[5] In a minority of conditions (severe Barrett's esophagus, gastrinoma, eosinophilic esophagitis, etc), protracted PPI use may be required.[6]

However, the inappropriate prescription of PPIs continues to rise yearly and significantly adds to healthcare costs while increasing the incidence of adverse effects.[7] For instance, a longitudinal study from the US showed a PPI drug cost of $3 013 069 US dollars during the first 30 days post-discharge in the study's patients, with 69% lacking appropriate medical indications.[8]

PPI overutilization in the inpatient setting is often a result of inappropriate stress ulcer prophylaxis (SUP) in non-intensive care unit patients or failure to discontinue SUP prior to hospital discharge.[2] Based on current evidence and guidelines, only critically ill patients who meet specific criteria should receive empiric acid-suppressive therapy.[9]

When PPIs are inappropriately prescribed, they can contribute to polypharmacy, prescribing cascades, adverse reactions, medication errors, and drug interactions.[10] Potential consequences of prolonged PPI therapy include hypergastrinemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy, causing rebound acid hypersecretion. PPIs have been linked via retrospective studies to an increased risk of adverse effects, including *C. diff*-associated diarrhea, community-acquired pneumonia, bone fracture, nutritional deficiencies, and interference with the metabolism of antiplatelet agents.[2] A meta-analysis of 23 cohort and case-control studies involving almost 300 000 patients identified a 65% increase in the relative risk of *C. diff*-associated diarrhea.[11] Studies also suggest that PPIs increase the risk of *Campylobacter* and *Salmonella* gastroenteritis and alter the gut microbiome.[12,13] Malabsorption of vitamin B12 and other nutrient elements may result from developing atrophic gastritis and achlorhydria, but the adverse effects on nutritional status have not yet been determined.

This study aimed to determine if admitted patients were prescribed PPIs for appropriate indications. Appropriate use rates were compared at a group of hospitals in the Southeastern US to elucidate the relationship between PPI use and the incidence of pneumonia, hypomagnesemia, and *C. diff* infection compared to an average population. It was hypothesized that PPIs were being prescribed for non-evidence-based reasons and that overprescription might be causing an increased incidence of pneumonia, hypomagnesemia, or *C. diff* infection.

Methods

A retrospective study was conducted at 9 Southeastern hospitals using data from July 2017 to July 2019 (N = 52 712). Participants were 18 years of age and older who received PPIs while admitted to an inpatient service. Patients with a history of a PPI prior to the inpatient stay were excluded. For evidence-based PPI indications, 84 ICD-10 codes were used based on NICE guidelines and FDA-approved indications for PPI use, as shown in **Table 1**. Hypomagnesemia, pneumonia, and *C. diff* infection rates in these patients were also examined. Results were analyzed using regression analysis.

Results

Of the 52 712 patients, 27 993 received PPIs without evidence (53.1%), ranging from 37.2-63.9% at each hospital. At the 365-bed North Florida hospital, at which a quality improvement study has subsequently been started, 58% (n = 4414) of patients had PPI prescriptions without evidence-based reasons. **Table 2** shows the number of people at each hospital who received inpatient PPIs and whether or

Table 1. ICD-10 Codes: Evidence-Based Indications for PPI Use

K20: Esophagitis	K25.3: Acute gastric ulcer without hemorrhage or perforation	K28.1: Acute gastrojejunal ulcer with perforation	K29.61: Other gastritis with bleeding
K20.0: Eosinophilic esophagitis	K25.4: Chronic or unspecified gastric ulcer with hemorrhage	K28.2: Acute gastrojejunal ulcer with both hemorrhage and perforation	K29.7: Gastritis, unspecified
K20.8: Other esophagitis	K25.5: Chronic or unspecified gastric ulcer with perforation	K28.3: Acute gastrojejunal ulcer without hemorrhage or perforation	K29.70: Gastritis without bleeding
K20.9: Esophagitis, unspecified	K25.6: Chronic or unspecified gastric ulcer with both hemorrhage and perforation	K28.4: Chronic or unspecified gastrojejunal ulcer with hemorrhage	K29.71: Gastritis with bleeding
K21: Gastroesophageal reflux disease	K25.7: Chronic gastric ulcer without hemorrhage or perforation	K28.5 Chronic or unspecified gastrojejunal ulcer with perforation	K29.8: Duodenitis
K21.0: Gastroesophageal reflux disease with esophagitis	K25.9: Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforation	K28.6: Chronic or unspecified gastrojejunal ulcer with both hemorrhage and perforation	K29.80: Duodenitis without bleeding
K21.9: Gastroesophageal reflux disease without esophagitis	K26.0: Acute duodenal ulcer with hemorrhage	K28.7: Chronic gastrojejunal ulcer without hemorrhage or perforation	K29.81: Duodenitis with bleeding
K22.1: Ulcer of esophagus	K26.1: Acute duodenal ulcer with perforation	K28.9: Gastrojejunal ulcer, unspecified as acute or chronic, without hemorrhage or perforation	K29.9: Gastroduodenitis, unspecified
K22.10: Ulcer of esophagus without bleeding	K26.2: Acute duodenal ulcer with both hemorrhage and perforation	K29.0: Acute gastritis	K29.90: Gastroduodenitis without bleeding
K22.11: Ulcer of esophagus with bleeding	K26.3 Acute duodenal ulcer without hemorrhage or perforation	K29.00: Acute gastritis without bleeding	K29.91: Gastroduodenitis with bleeding
K22.2: Esophageal obstruction	K26.4: Chronic or unspecified duodenal ulcer with hemorrhage	K29.01: Acute gastritis with bleeding	K52.81: eosinophilic gastritis or gastroenteritis (K52.81)
K22.3: Perforation of esophagus	K26.5: Chronic or unspecified duodenal ulcer with perforation	K29.2: Alcoholic gastritis	E16.4: Zollinger-Ellison syndrome
K22.4: Dyskinesia of esophagus	K26.6: Chronic or unspecified duodenal ulcer with both hemorrhage and perforation	K29.20: Alcoholic gastritis without bleeding	A04.8: *Helicobacter pylori (H. pylori)*
K22.5: Diverticulum of esophagus, acquired	K26.7 Chronic duodenal ulcer without hemorrhage or perforation	K29.21: Alcoholic gastritis with bleeding	B96.3: *H. pylori* as cause of disease classified elsewhere
K22.6: Gastroesophageal laceration-hemorrhage syndrome	K26.9: Duodenal ulcer, unspecified as acute or chronic, without hemorrhage or perforation	K29.3: Chronic superficial gastritis	A06.1: Intestinal ulcer amebic A06.1
K22.7: Barrett's esophagus	K27.0: Acute peptic ulcer, site unspecified, with hemorrhage	K29.30: Chronic superficial gastritis without bleeding	K63.3: Intestinal ulcer, perforating K63.1

Table 1. ICD-10 Codes: Evidence-Based Indications for PPI Use, Cont'd

K22.70: Barrett's esophagus without dysplasia	K27.1: Acute peptic ulcer, site unspecified, with perforation	K29.31: Chronic superficial gastritis with bleeding	P78.0: Intestinal ulcer, perforating, newborn
K22.71: Barrett's esophagus with dysplasia	K27.2 Acute peptic ulcer, site unspecified, with both hemorrhage and perforation	K29.4: Chronic atrophic gastritis	K63.3: Intestinal ulcer primary, small intestine
K22.710: Barrett's esophagus with low-grade dysplasia	K27.3: Acute peptic ulcer, site unspecified, without hemorrhage or perforation	K29.40: Chronic atrophic gastritis without bleeding	K62.6: Intestinal ulcer rectum
K22.711: Barrett's esophagus with high-grade dysplasia	K27.4: Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage	K29.41: Chronic atrophic gastritis with bleeding	A18.32: Intestinal ulcer tuberculous
K22.719: Barrett's esophagus unspecified	K27.5: Chronic or unspecified peptic ulcer, site unspecified, with perforation	K29.5: Unspecified chronic gastritis	I86.8: Intestinal ulcer varicose
K25.0: Acute gastric ulcer with hemorrhage	K27.6: Chronic or unspecified peptic ulcer, site unspecified, with both hemorrhage and perforation	K29.50: Unspecified chronic gastritis without bleeding	K63.1: Intestinal ulcer with perforation
K25.1: Acute gastric ulcer with perforation	K27.7: Chronic peptic ulcer, site unspecified, without hemorrhage or perforation	K29.51: Unspecified chronic gastritis with bleeding	B37.81: Esophagitis, candidal
K25.2: Acute gastric ulcer with both hemorrhage and perforation	K27.9: Peptic ulcer, site unspecified, unspecified as acute or chronic, without hemorrhage or perforation	K29.6: Other gastritis	A18.83: Esophagitis tuberculous
K25.3: Acute gastric ulcer without hemorrhage or perforation	K28.0: Acute gastrojejunal ulcer with hemorrhage	K29.60: Other gastritis without bleeding	

not there was evidence for the PPIs to be prescribed.

Evaluation was done for pneumonia, hypomagnesemia, and *C. diff* rates among the patients being given PPIs compared to those not taking PPI. The normal population consisted of 3572 patients, matched for gender and age, not receiving PPIs from within the same geographic region. The combined results of the hospitals studied are shown in **Table 3**. The odds ratio (OR) was higher for pneumonia at 1.78, which was statistically significant (95% confidence interval (CI) 1.40-2.27, $P < .001$) for those taking PPIs. Hypomagnesemia had a higher adjusted OR of 2.830, which was also statistically significant (95% CI 1.25-6.38, $P = .012$). Patients on PPIs were 2.830 times as likely to end up with hypomagnesemia and 1.78 times more likely to have pneumonia than those not receiving PPIs. Patients on PPIs had an increased rate of *C. diff* compared to patients not on PPIs which was not statistically significant, with an adjusted OR of 2.032 ($P = .230$).

Discussion

In many instances, PPIs are extremely beneficial drugs and are well tolerated with few to no side effects in most individuals. However, due to the scale of use of PPIs, many patients are exposed to potential side effects. PPIs are not currently recommended as empiric therapy for non-critical care inpatients who do not already take PPIs on an outpatient basis. This study found that PPIs were being overprescribed at all 9 hospitals included in the study according to the ICD-10 codes documented when compared to NICE guidelines. When compared with a normal, age-matched population, our results found increased rates of pneumonia and hypomagnesemia in patients being prescribed PPIs, 2 well-known side effects of these medications. There was a non-statistically significant increase in rates of *C. diff* infection in the group

Table 2. Data for South Atlantic Division Hospitals

		413 Bed S GA	135 Bed S SC	350 Bed NE GA	190 Bed Cent GA	371 Bed NE SC	454 Bed NE FL	231 Bed SE GA	365 Bed NE FL	321 Bed E SC	Total
Without evidence	Count	3465	575	4487	2151	5660	3576	757	4144	3178	27 993
	% within hospital	49.3%*	37.2%	63.9%†	58.1%‡	54%	49.8%	63.2%	58%‡	42.9%	53.1%
With evidence	Count	3561	972	2530	1553	4831	3608	441	2998	4225	24 719
	% within hospital	50.7%	62.8%	36.1%	41.9%	46.0%	50.2%	36.8%	42%	57.1%	46.9%
Total	Count	7026	1547	7017	3704	10 491	7184	1198	7142	7403	52 712
	% of total	13.3%	2.9%	13.3%	7.0%	19.9%	13.6%	2.3%	13.5%	14.0%	100%

Abbreviations: S =South; GA = Georgia; SC = South Carolina; NE = North-East; Cent = Central; FL = Florida; SE = South-East; E = East.
*, †, ‡, no statistical significance between values with the same marking

prescribed PPIs, likely due to the relatively small sample size. This study suggests a need to improve hospital PPI prescribing practices to limit the non-indicated administration of PPIs and the increased incidence of adverse effects experienced by those patients.

Limitations

This retrospective study examined hospitals in 1 region of the US. All hospitals were in the same hospital system, limiting the generalizability of the results. We determined if PPIs were being prescribed for an approved reason using ICD-10 codes entered during their admission, but some patients may have had appropriate indications that were never coded. Since this is a retrospective study, we cannot determine the decision-making process when these medications were prescribed. Furthermore, we may not have included all the patients experiencing side effects, especially hypomagnesemia, since those side effects may have been treated but never coded. Prospective studies would be needed to further understand the potential mortality and morbidity caused by hypomagnesemia and pneumonia.

Conclusion

Our study was unable to prove a statistically significant relationship between PPI use and *C. diff* infection due to our sample size. A study with a larger sample size would be able to determine the relation between inpatient PPI administration and *C. diff* infection with greater confidence. We plan to use our findings to promote more conservative use of PPIs within 1 of the studied hospitals with the goal of decreasing adverse effects experienced by patients who do not have an evidence-based indication for PPIs. We may also reanalyze our data to determine if inappropriate PPI use increases the length of stay in the hospital due to side effects compared to patients who did not receive these medications.

Conflicts of Interest

The authors declare they have no conflicts of interest.

The authors are employees of HCA Florida Orange Park Hospital, a hospital affiliated with the journal's publisher.

Table 3. Rates for Pneumonia, Hypomagnesemia, and *C. diff* in Patients on PPIs Compared to Normal Population

	P value	Adj OR	95% CI
Pneumonia	.001	1.785	1.401-2.274
Hypomagnesemia	.012	2.830	1.254-6.386
C. diff	.230	2.032	0.639-6.460

Abbreviations: *C. diff* = *Clostridium difficile* infection; OR = odds ratio; CI = confidence interval

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