RECENT SAFETY DATA: IMPLICATIONS FOR USE OF PROTON PUMP INHIBITORS

Key Takeaways for Pharmacists

- Proton pump inhibitors (PPIs) have a well-studied safety profile that has been verified in multiple long-term randomized controlled trials, as well as decades of clinical experience.
- Very small theoretical risks with PPIs have been identified in observational studies of patients receiving therapy over months to years; these studies do not apply to short-term treatment, as is recommended with over-the-counter (OTC) use.
- No causal relationship has been established between the use of PPIs and the risk of chronic kidney disease or dementia.

Talking Points for Patients

- Heartburn is a common symptom; in North America, heartburn is experienced at least once per week by an estimated 18% to 28% of adults. A variety of OTC treatment options are available for heartburn management.
- Frequent heartburn is defined as heartburn that occurs consistently at least 2 days per week.
- PPIs are an effective treatment option for frequent heartburn, with around-the-clock acid-reducing effects.
- OTC PPIs may be used for up to 3 courses of 14 days yearly (every 4 months) for control of frequent heartburn; if symptoms persist or worsen, make an appointment with a physician.
- In the United States, PPIs have been available over the counter for 13 years and have been in clinical use for over 27 years.
- Discuss any concerns about PPIs with your pharmacist or other health care provider.

PRACTICAL INFORMATION FOR TODAY'S PHARMACIST®

Pharmacy Times®

CLINICAL UPDATE

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Recent Safety Data: Implications for Use of Proton Pump Inhibitors

Heartburn is a condition characterized by a burning sensation felt behind the sternum that travels up toward the neck. In some cases, heartburn may be accompanied by regurgitation of acidic stomach contents into the mouth. These symptoms may occur more often at night, while lying recumbent, or during exercise. It is important to recognize that heartburn is not limited to painful esophageal symptoms; heartburn may also affect social functioning, work productivity, and sleep quality.[1-3]

In North America, heartburn is experienced at least once per week by an estimated 18% to 28% of adults.[4] Of those with symptoms, it has been estimated that about one-fourth experience heartburn symptoms on a daily basis and another 20% of heartburn sufferers experience symptoms 3 to 6 times per week.[5]

In managing this common condition, pharmacists are a valuable source of information on the appropriate use of over-the-counter (OTC) medications. According to a recent survey conducted by *Pharmacy Times*®, pharmacists make more than 1.6 million recommendations per month related to the use of acid-reducing medications, including proton-pump inhibitors (PPIs).[6]

DEVELOPMENTS IN THE MANAGEMENT OF HEARTBURN

Before approval of the first PPI, treatment options for heartburn associated with serious medical problems (eg, esophagitis, ulcers) were limited. Due to the lack of effective pharmacologic options, cases such as these were often managed via surgical intervention.[7,8]

The management of heartburn changed with the introduction of the first PPI in 1989.[9] The safety and efficacy of PPIs are supported by a large body of evidence accumulated over the past 27 years. Although retrospective studies have previously linked PPI use with bone fracture, pneumonia, and *C. difficile*-associated diarrhea,[10] the overall safety of these widely used medications has been demonstrated in controlled trials spanning thousands of patient-years of use.[11-13] In a study of nearly 12,000 patients receiving an average of 26 weeks of PPI therapy, 119 potential medication-related adverse events were observed, the vast majority of which were limited to nausea/vomiting, diarrhea, dizziness, or headache.[11,12] Similarly, a study of PPI safety in 230 patients over a mean follow-up period of 6.5 years reported 0.52 adverse events per year over approximately 1500 patient-years of treatment.[13]

Q&A with GARY W. FALK, MD, MS

Pharmacy Times® (*PT*) consulted with Gary W. Falk, MD, MS, Co-Director of the Esophagology and Swallowing Center at the Hospital of the University of Pennsylvania, in order to gain his perspective on current issues related to PPI use. Commentary from Dr Falk is interspersed throughout this supplement.

***PT*®:** How can health care professionals communicate an appropriate balance of the benefits and risks and address concerns with PPI therapy so that patients can make an informed decision?

Dr Falk: The best thing to do is to review the studies and place them in context. I point out the following:

- These studies show an association and do not prove cause and effect.
- These studies have methodologic limitations.
- Statistical significance does not equal clinical significance.
- The safety record of PPIs over many years is excellent.
- If a PPI is needed, it should be used in the lowest dose needed to control symptoms.
- If a PPI is not needed, it should not be used.

ADDRESSING CONCERNS REGARDING DATA FROM STUDIES PUBLISHED IN 2015 AND 2016

Data from observational studies published in 2015 and 2016 have led to concerns about PPIs. Typically, observational studies are used by scientists to generate hypotheses for subsequent testing in prospectively designed randomized clinical trials.[14,15] For pharmacists, maintaining an awareness and understanding of these studies remains an important priority, as they may be approached by patients with questions or concerns regarding PPI use.

TABLE. HAZARD RATIOS AND ODDS RATIOS[17,18]

Statistic	Description	Example
Hazard ratio (HR)	The instantaneous probability that an outcome will occur in 1 group versus another group at any given point in time	If the HR that a patient will be cured with treatment A versus treatment B is 2.0, at every time point, patient A is twice as likely to be cured as patient B.
Odds ratio (OR)	The ratio of the probability that an outcome will occur to the probability that the outcome will not occur	If the probability of a cure with treatment A is 60%, and the probability of a cure with treatment B is 30%, the odds ratio of cure with treatment A versus treatment B is 0.6/0.3, or 2.

Practical Relevance

In practice, ORs are generally interpreted in the same way as HRs. The difference between an OR and an HR tends to be small if the magnitude of an association is small or the efficacy difference between treatments is small. In interpreting ORs, it is important to remember that ORs always tend to be larger than HRs generated with the same data, which may exaggerate the perceived magnitude of an association or treatment effect.

RECENT DATA: DEMENTIA

Recent data suggesting a link between PPI use and dementia include observational analyses by Haenisch et al (2015) and Gomm et al (2016), as well as a meta-analysis of observational data conducted by Wijarnpreecha et al (2016).

Haenisch 2015

Researchers Haenisch et al evaluated a potential association between the use of PPIs and dementia by analyzing data from 3327 patients 75 years or older enrolled in a study conducted in Germany. The risk of developing dementia in patients using PPIs was evaluated. Through statistical techniques, researchers attempted to adjust for several potential confounding factors, including medical comorbidities and the presence or absence of a gene that is associated with an increased risk of developing dementia (*ApoE4*).[16]

In an unadjusted analysis, use of PPIs was associated with an increased risk of dementia (HR, 1.38; 95% CI, 1.04-1.83; P = .02). (See the TABLE[17,18] for more information on hazard ratios.) A secondary analysis statistically adjusted for possible confounding variables identified a risk of dementia in PPI users (HR, 1.44; 95% CI, 1.10-1.90; P = .008). However, notably, several other factors were associated with dementia, including presence of the *ApoE4* allele, depression, diabetes, and stroke (FIGURE 1[16]).[16] The results showed that the strongest predictors of dementia were depression (HR, 2.28; 95% CI, 1.80-2.88; P <.001) and stroke (HR, 1.92; 95% CI, 1.38-2.67; P <.001).[16] The presence of the *ApoE4* gene was also a strong predictor (HR, 1.87; 95 % CI, 1.52-2.31; P <.001).

In the conclusion, the authors cautioned that these results "can only show the statistical association between PPI use and risk of dementia … The underlying causal biological mechanisms are to be investigated in detail in further studies."[16]

Gomm 2016

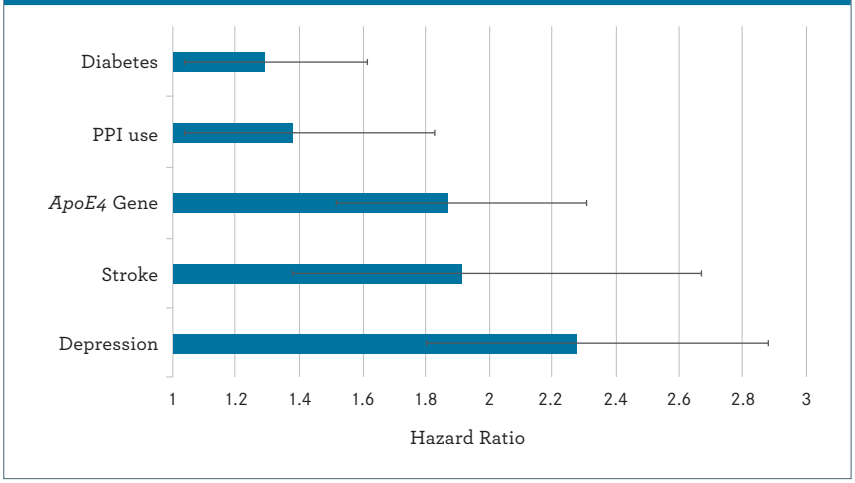
In another observational study, researchers Gomm et al analyzed data from a German health insurer (Allgemeine Ortskrankenkassen) from 2004 to 2011 to examine a possible association between incident cases of dementia and the use of PPIs. Data from 73,679 patients 75 years or older who did not have dementia at baseline

were analyzed for factors associated with incident diagnoses of dementia. By the end of the study, 40% (n = 29,510) of the patients studied had developed dementia.[19]

Adjusting for potential confounding factors, including age, sex, comorbidities, and polypharmacy, researchers identified a significantly increased risk of developing dementia in 2950 patients who used PPIs regularly versus 70,729 patients who did not receive PPIs (HR, 1.44; 95% CI, 1.36-1.52; *P* <.001).[19]

As in the Haenisch study, PPI use was associated with dementia (unadjusted HR, 1.66; 95% CI, 1.57-1.76; *P* <.001); other factors associated with dementia included depression (HR, 1.28; 95% CI, 1.24-1.32; *P* <.001), stroke (HR, 1.37; 95% CI, 1.29-1.46; *P* <.001), and each 1-year increase in age (HR, 1.083; 95% CI, 1.081-1.085; *P* <.001). Regarding the hypothesis-generating nature of this observational study, the authors wrote, "The present study can only provide a statistical association between PPI use and risk of dementia. The possible underlying causal biological mechanism has to be explored in future studies. To evaluate and establish direct cause-and-effect relationships between PPI use and incident dementia in the elderly, randomized, prospective clinical trials are needed."[19]

FIGURE 1. ESTIMATE OF UNADJUSTED HAZARD RATIO OF DEMENTIA IN PATIENTS 75 YEARS AND OLDER[16]



ApoE4 = apolipoprotein E4; PPI = proton pump inhibitor.
Adapted from reference 16.

In a commentary on the Gomm study, independent reviewers wrote, "Given the long duration required for individuals to develop dementia, the methodologic limitations of this study, and absence of high-grade evidence otherwise, it is much more likely that dementia and PPI use are 2 common co-occurring phenomena in individuals over the age of 75 than for there to be a direct link for PPIs to cause dementia over the relatively short period of a few years."[20]

Wijarnpreecha 2016

In a meta-analysis conducted by Wijarnpreecha et al, researchers evaluated conflicting evidence of concerns over a potentially elevated risk of dementia in observational studies. This meta-analysis was limited to 4 observational studies comparing PPI users with nonusers, including 2 cohort studies, 1 case-control study, and 1 cross-sectional study. Importantly, 2 studies were based on registry data, which, the authors wrote, "could raise a concern about coding inaccuracy and incompleteness."[21]

Across all 4 studies, the pooled relative risk of developing dementia was found to be statistically insignificant (RR, 1.08; 95% CI, 0.82-1.43). However, when only cohort studies were included in the analysis, researchers identified a statistically significant association between PPI use and dementia (RR, 1.44; 95% CI, 1.36-1.52). Regarding the meta-analysis, researchers wrote that these findings "could only demonstrate an association, but could not establish causality." Researchers continued, "Therefore, we cannot conclude that PPIs use does increase the risk of dementia, as this association could be a result of confounding."[21]

RECENT DATA: CHRONIC KIDNEY DISEASE

Recent data suggesting a link between PPI use and chronic kidney disease (CKD) include observational analyses by Xie et al (2016), Lazarus et al (2016), and Arora et al (2016).

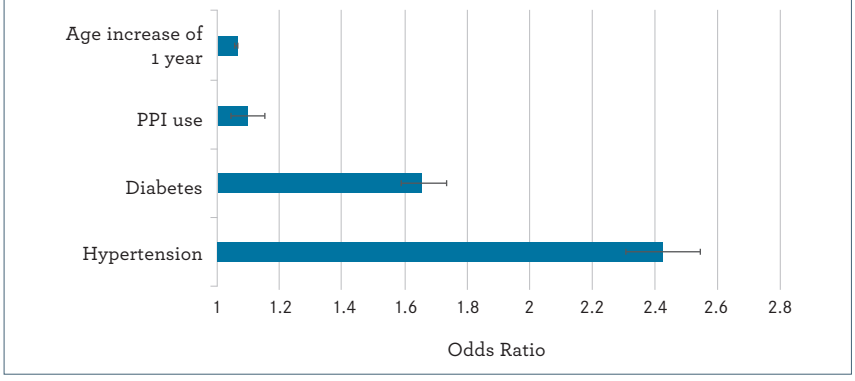
Xie 2016

In a study of the Department of Veterans Affairs national database, researchers studied renal outcomes over 5 years in a group of patients who had recently initiated PPI therapy (n = 173,321) and patients who had recently initiated treatment with histamine receptor-2 antagonists (n = 20,270). In their results, researchers identified a relationship between PPI use and CKD. Patients who had received a PPI were more likely to have a diagnosis of CKD (HR, 1.28; 95% CI, 1.23-1.34) and end-stage renal disease (HR, 1.96; 95% CI, 1.21-3.18). It is notable that the observational nature of this study could not establish causality.[22]

Lazarus 2016

Another study evaluating the potential risk of renal disease as related to PPI use was performed by Lazarus et al. Researchers evaluated the risk of renal dysfunction in patients without CKD at baseline (defined by an estimated glomerular filtration rate [eGFR] >60 mL/min/1.73 m^2) using 2 registries: 1) data from 10,482 patients enrolled in the Atherosclerosis Risk in Communities (ARIC) study and 2) an administrative claims

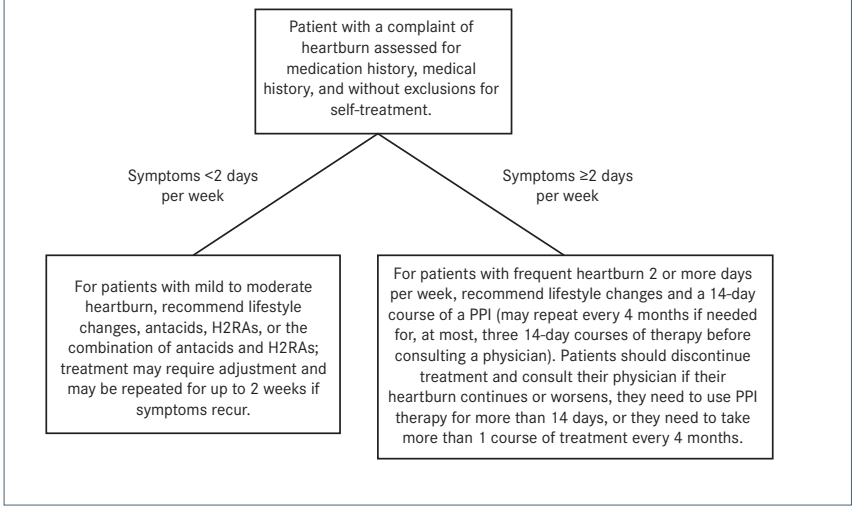
FIGURE 2. ESTIMATE OF ODDS RATIO IN CKD OUTCOMES[8]



CKD = chronic kidney disease; PPI = proton pump inhibitor.

Adapted from reference 8.

FIGURE 3. RECOMMENDATIONS FOR SELF-CARE[2,24]



H2RA = histamine2-receptor antagonist; PPI = proton pump inhibitor.

data set of 248,751 patients receiving care through Geisinger Health System.[23]

ARIC study data indicated an increased risk of CKD in users of PPIs in unadjusted (HR, 1.45; 95% CI, 1.11-1.90; $P = .006$) and adjusted analyses (HR, 1.50; 95% CI, 1.14-1.96; $P = .003$) for potential confounding factors, such as demographic and clinical characteristics. Similar findings were identified in an analysis of data from patients receiving care through Geisinger Health System (adjusted HR, 1.24; 95% CI, 1.20-1.28; $P < .001$). Notably, in this analysis, the use of high-dose PPIs (twice-daily dosing) was associated with a higher risk of developing CKD than low-dose PPIs (once-daily dosing) (adjusted HR, 1.15; 95% CI, 1.09-1.21; $P < .001$).[23]

Arora 2016

In a retrospective case-control study, researchers Arora et al used data from the Veterans Affairs Health Care Upstate New York network to examine a possible association between the use of PPIs and the development of CKD. The database analyzed for this observational study included records from 180,553 patients examined by primary care physicians from 2001 through 2008.[8]

Patients included in the analysis were required to have at least 1 outpatient eGFR, and patients were excluded from the study if their initial eGFR was less than 60 mL/min/1.73m^2 upon study entry, as these patients were assumed to have preexisting CKD. Patients who did not have CKD at baseline and later received a diagnosis of CKD, defined by an eGFR less than 60 mL/min/1.73 m^2, were compared with controls who did not develop CKD during the study period. A total of 76,462 patients were included in the analysis, including 22,734 PPI users.[8]

In an unadjusted analysis, researchers identified a roughly 10% increase in the risk of developing CKD in patients receiving PPIs (OR, 1.10; 95% CI, 1.05-1.16; $P < .0001$).[8] (See the TABLE[17,18] for more information on odds ratios.) Other factors associated with the development of CKD in this study included age (each 1-year increase in age increased the risk of developing CKD by 7%; $P < .0001$), sex (females had a 32% greater risk of developing CKD than males; $P < .0001$), and comorbidities (eg, presence of diabetes was associated with a 66% increase in the risk of developing CKD [$P < .0001$], and hypertension was associated with a 143% increase in the risk of developing CKD [$P < .0001$]) (FIGURE 2[8]).[8] Although many associations were observed, due to the observational design of this study, no causal link between PPI use and CKD was established.[8]

INTERPRETING AND UNDERSTANDING THE RELEVANCE OF OBSERVATIONAL EVIDENCE

Due to the observational nature of the studies published in 2015 and 2016 reviewed here that raised potential concerns about PPI safety, no causal relationship can be established between PPI use and dementia or CKD. Understanding the limitations of observational data is crucial to recognizing the relevance of these data.[8,14-16,19,21]

Unlike a randomized trial, in which patients are randomly assigned to receive treatment or no treatment, observational trials are drawn from existing pools of patients who chose to use medication or to not use medication. As a result, relationships identified in observational data cannot isolate the effect of an intervention by eliminating factors, such as the placebo effect, researcher bias, and patient bias, that may result from knowing the intervention used.[14,15]

Q&A with GARY W. FALK, MD, MS

***PT*®:** How have observational studies that suggest a potential link between PPI use and dementia or CKD affected your perception of the safety of PPIs?

Dr Falk: These studies bring up interesting questions. However, as all of these studies are observational, they do not prove cause and effect. The studies demonstrate that if there is a risk, it is quite small. While the mechanisms proposed for CKD are biologically plausible, the mechanisms proposed for dementia are less biologically plausible. At the end of the day, these and other such studies emphasize that PPIs are safe and should be used only in appropriate patients.

***PT*®:** Given concerns raised by observational trials, how have patient attitudes toward PPIs changed in recent years, and what is the clinical effect of these concerns?

Dr Falk: Many patients are quite alarmed by these reports and have gotten their information from the media and "Dr Google" without appropriate context. Some patients have even requested surgery as an alternative. Surgery is an excellent option for a select subset of patients with GERD, but the complications of surgery are real and not theoretical as in the case of PPIs. Many of the patient fears are driven by incomplete understanding of the strengths and weaknesses of the observational studies that describe a potential link between PPIs and adverse events.

APPROPRIATE USE OF SHORT-TERM PPI THERAPY

In patients with frequent heartburn (occurring 2 or more days a week), short-term use of an OTC PPIs may be an appropriate treatment option (FIGURE 3[2,24]).[1,2] Short-term use of OTC PPIs is considered a 14-day regimen for up to 3 courses per year, but not more often than every 4 months. Patients should discontinue treatment and consult their physician if their heartburn continues or worsens, they need to use PPI therapy for more than 14 days, or they need to take more than 1 course of treatment every 4 months.[25-27]

Importantly, patients should seek medical care if they continue to experience heartburn symptoms after a 14-day course of PPI therapy.[25-27] Additionally, if, at any time, patients experience alarming symptoms, such as painful or difficult swallowing, gastrointestinal bleeding, laryngitis, unexplained weight loss, or chest pain suspected to be of cardiac origin, patients should be referred to a physician for treatment.[1] Older patients (>60 years) experiencing symptoms of acid reflux and patients 50 to 60 years of age with a family history of gastrointestinal cancers or other risk factors (eg, obesity or use of tobacco or alcohol) should also be encouraged to discuss their symptoms with a physician.[2,3]

Q&A with GARY W. FALK, MD, MS

***PT*®:** What are some of the most important points to reiterate in patients who are planning to use a PPI?

Dr Falk: If a PPI is needed, the lowest dose needed to control symptoms should be used. If a PPI is not needed, it should not be used.

***PT*®:** What are some considerations about the safety of PPIs?

Dr Falk: Short-term use of PPIs is associated with adverse events, including headaches and diarrhea. Long-term use of a drug that is not needed is to be avoided. PPIs should be prescribed in appropriate clinical settings at the lowest dose needed to control symptoms.

***PT*®:** How do you monitor for the potential adverse effects of PPIs?

Dr Falk: I will see patients at follow-up visits as needed and have them call me if there are issues or concerns. I do not require blood tests or perform imaging or other studies to monitor these patients for potential adverse events.

OTC PPI treatment should not be recommended for patients experiencing pain or difficulty when swallowing food, vomiting with blood, or bloody/black stools. Additionally, based on warnings listed on OTC monographs for PPIs, patients should consult with a physician before use if they have any of the following symptoms[25-27]:

- A history of heartburn symptoms lasting longer than 3 months, which may be a sign of a more serious condition
- Heartburn with lightheadedness, sweating, or dizziness
- Chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck, or shoulders; or lightheadedness
- Frequent chest pain
- Frequent wheezing, particularly with heartburn
- Unexplained weight loss
- Nausea or vomiting
- Stomach pain

PRACTICAL CONSIDERATIONS

Over the past 28 years, researchers have accrued thousands of

Q&A with GARY W. FALK, MD, MS

***PT*®:** What are some of the risks of withholding acid-reducing therapy in patients with frequent heartburn?

Dr Falk: The risks of withholding therapy include impairment of quality of life in patients with gastroesophageal reflux disease, loss of potential chemoprevention effect in those with Barrett's esophagus, and loss of benefit of ablative therapies for those with Barrett's esophagus and dysplasia or early adenocarcinoma.

patient-years of data on PPI use, and the safety profile of PPIs has been well established. Studies published in 2015 and 2016 that suggest a potential link between PPI use and dementia or CKD were observational in design; the results are not of the same quality as randomized-controlled trial data. Based on the quality of the evidence and chronic drug exposure in the studies, the results of these observational studies do not impact the short-term use of PPIs. Pharmacists should continue to take into account the concerns, needs, and concurrent health conditions of individual patients when counseling them and making recommendations regarding treatment for heartburn. If an OTC PPI is needed to control heartburn symptoms, patients should follow dosing instructions on the package or use as directed by their physician.

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