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EXPERT REVIEW

Patient Adherence in the Treatment of Gastroesophageal Reflux Disease: Proton Pump Inhibitors Versus Histamine-2 Receptor Antagonists

Cheryl A. Abel[1] and Kristine C. Willett[2]

[1]Assistant Professor of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences. [2]Associate Professor of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences.
Corresponding author email: cheryl.abel@mcphs.edu; kristine.willett@mcphs.edu

Abstract: Adherence to acid suppression therapy is essential in the management of gastroesophageal reflux disease (GERD). Current guidelines suggest that proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) are the mainstays of therapy. The likelihood of adherence to these medications and barriers that may affect adherence and persistence must be considered. A survey done by the Centers for Medicare and Medicaid Services suggests that barriers to adherence include complexity of therapeutic regimens, cost of therapy and lack of understanding of the purpose of treatment. Retrospective cohort studies have evaluated the rates of medication adherence and persistence to PPIs and have found overall rates to be low. When designing treatment regimens, clinicians often consider drug factors such as effectiveness, adverse effects and drug-drug interactions. However, barriers to adherence must also be considered by practitioners to ensure that maximum benefit of therapy can be achieved.

Keywords: GERD, medication adherence, PPIs

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Background

Adherence to medication is a crucial component of chronic disease management. In the absence of adherence, treatment failures will occur regardless of the strength of efficacy of that agent. Therefore, when choosing a medication regimen for a specific condition, the likelihood of adherence to the medication must be considered. Some known predictors of poor medication adherence include complexity of dosing regimen, undesirable adverse effects, uncertainty of the purpose of the medication and the cost of the medication.[1]

Gastroesophageal reflux disease (GERD) is a chronic condition that affects approximately 40% of Americans at least once a month and 10% of Americans weekly.[2] There are significant healthcare costs are incurred due to this disease with overall medical costs estimated to be 119% higher than those costs incurred by patients without GERD.[3] Of that increase in overall cost, 64.6% can be attributed to direct medical costs and 16.6% are related to increased prescription drug use.

Symptoms of GERD include heartburn (pyrosis), regurgitation or both, which is caused by the reflux of acidic gastric contents into the esophagus.[4] Patients may also experience belching, epigastric pain and or burning, postprandial fullness, early satiety, bloating and nausea.[2] Common recommended treatments include lifestyle modification, acid suppression therapy, endoscopic therapy and surgery. Lifestyle modifications consist of a reduction in fat intake, smoking cessation and avoidance of foods that decrease lower esophageal pressure, such as chocolate and alcohol. However, these methods have demonstrated little benefit in the control of GERD symptoms.[4] Acid suppression therapy is by far the most non-invasive and efficacious treatment modality. The mainstays of acid suppression therapy are proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RAs). Pharmacotherapeutic agents often produce resolution of symptoms that rapidly return upon discontinuation of therapy.[4]

Due to the high prevalence of this disease and potential for severe complications, long term, chronic management of GERD is essential. Long term exposure to acidic gastric contents may lead to erosion of the squamous epithelial cells of the esophagus potentially leading to esophageal strictures, Barrett's esophagus (BE) or esophageal adenocarcinoma. Adherence to maintenance therapy is a fundamental component in prevention of long term complications.

H2RAs, which include cimetidine, famotidine, nizatidine, and ranitidine, all competitively and reversibly bind to the histamine-2 receptor on gastric parietal cells.[5] Inhibition of the actions of histamine on parietal cells will lead to a reduction in acid production. The most common side effects experienced with this drug class include diarrhea, headache, drowsiness, fatigue, muscular pain and constipation.[6] The typical dosing frequency for the treatment of GERD is twice daily but can be up to four times per day depending on the agent.[7–10] All agents are available without a prescription. Major clinical differences between agents in this class relate to cost and drug-drug interactions, specifically with cimetidine.[6,11]

Unlike H2RAs, PPIs indirectly increase gastric pH by covalently binding to the cysteines of H,K-ATPase found within the parietal cells, thereby blocking the final step in gastric acid production.[12] Medications in this class include dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole. Current studies suggest that all PPIs are equally efficacious in the treatment of GERD symptoms.[13,14] Typical dosing frequency of PPIs for the treatment of GERD is once daily.[4] Common side effects among the class include abdominal pain, nausea, flatulence and diarrhea. Some of the agents may cause headache and or constipation.[15–18] While most PPIs are only available by prescription, omeprazole and lansoprazole may be purchased over the counter for self care. A complete listing of drug characteristics that may affect adherence to both H2RAs and PPIs can be found in Table 1.[6–10,14–20]

The objective of this review is to evaluate the difference in patient adherence to PPIs as compared to H2RAs and to assess factors that may affect patient adherence to these agents in the pharmacotherapeutic management of GERD.

Methods

A literature search was conducted via MEDLINE (1948 to October week 2) and EMBASE (1980 to week 41) using the search terms proton pump inhibitors, histamine-2 receptor antagonists, and adherence. All clinical trials conducted in humans and published in English that evaluated patient adherence to acid

Table 1. Acid supression therapy and factors that may affect adherence.[6–10,14,15–20]

Class	Drug name	Brand name	Starting dose	Special considerations and other adverse effects	Rx cost in USD (OTC)*
H2RA				Adverse effects include constipation, dry mouth, diarrhea, nausea and abdominal discomfort. Can be taken without regard to meals.	
	Cimetidine	Tagamet	1600 mg/day in 2 to 4 divided doses	May cause several drug-drug interactions due to inhibition of CYP1A2 and CYP 2C19. May cause decrease in creatinine clearance. May cause transient two- to fourfold increase in aminotransferase levels. Adverse effects include bradycardia, hypotension, mental confusion, delirium and depression. May cause impotence.	$54.27 ($12.58)
	Famotidine	Pepcid	20 mg twice daily	Adverse effects include headache, anxiety, loss of equilibrium, paresthesis, depression, decreased libido, hallucinations, impotence at high doses. May cause impotence.	$9.00 ($7.76)
	Nizatidine	Axid	150 mg twice daily	Adverse effects include urticaria and anemia	$143.65 ($109.84)
	Ranitidine	Zantac	150 mg twice daily	May exacerbate migraines and severe headaches.	$91.97 ($12.58)
PPI				Should be used with caution in combination with antiplatelet medications. May interfere with the absorption of pH dependent medications.	
	Dexlansoprazole	Dexilant	60 mg once daily	Can be taken without regard to meals. Adverse effects include abdominal pain, diarrhea, flatulence, nausea, vomiting and upper respiratory tract infections.	$131.40
	Esomeprazole	Nexium	20 mg once daily	Should be taken prior to a meal. Adverse effects include diarrhea, abdominal pain and headache.	$161.27
	Lansoprazole	Prevacid	15 mg once daily	Should be taken prior to a meal. Adverse effects include diarrhea, abdominal pain, nausea and constipation.	$176.93 ($21.34)
	Omeprazole	Prilosec	20 mg once daily	Should be taken prior to a meal. Adverse effects include headache, abdominal pain, nausea, diarrhea, vomiting and flatulence.	$124.55 ($21.34)
	Pantoprazole	Protonix	40 mg once daily	Can be taken without regard to meals. Adverse effects include abdominal pain, nausea, vomting and headache.	$122.74
	Rabeprazole	Aciphex	20 mg once daily	Can be taken without regard to meals. Adverse effects include headache.	$215.62

Note: *Average wholesale price for a one month supply.
Abbreviations: H2RA, histmamine-2 receptor antagonist; PPI, proton pump inhibitor; OTC, over-the-counter.

suppression therapy in the treatment of gastroesophageal reflux disease were included for evaluation. A review of the bibliographies of the published literature was also conducted to retrieve additional publications.

Adherence to Acid Suppression Therapy

There is a lack of clinical studies which solely evaluate patient adherence to H2RAs for the management of GERD symptoms. However, there are several factors that have been validated as potential confounders to patient adherence. These include poor understanding of the disease and the prescribed treatment, complex drug regimens and high medication costs.[1] An analysis of a survey conducted by the Centers for Medicare and Medicaid Services (CMS) assessed medication adherence by evaluating the rate of unfilled prescriptions.[21] Participants were surveyed to determine if there were prescriptions in the previous year that were prescribed for them by their physician that they did not fill. The participants that answered "yes" were then asked to identify which medications they did not have filled and to select one or more of the prespecified reasons for not filling the medication. The most frequently reported unfilled prescription medications were central nervous system agents such as pain relievers and antidepressants (23.6% of reported prescriptions). Interestingly, it was found that 4.6% of all the prescriptions that were not filled by the beneficiaries were gastrointestinal agents with 4% being labeled as antacids/PPIs/H2RAs. When participants were asked why they did not fill the prescriptions, 55.5% of the respondents stated they "thought it would cost too much". Other common reasons for not filling the prescription were "medicine not covered by insurance" (20.2%), "didn't think medicine was necessary for the condition" (18%) and "was afraid of medicine reactions/contraindications" (11.8%). All of the information obtained for this study was self reported and relied on patients' recall and the sample of patients that answered "yes" was small. The information obtained, however, provides insight into potential reasons for medication non-adherence.

Despite the lack of medication adherence studies with H2RAs specifically, there are several published cohort studies that evaluate adherence with PPI therapy. The first was a retrospective cohort study performed using the PHARMetrics Patient-Centric Database, a managed care plan database.[22] The purpose of the study was to determine the prescription patterns for PPIs and H2RAs in patients with or without BE. Investigators also sought to examine the determinants of adherence and persistence to PPI therapy. Medication profiles were evaluated in 59,124 patients with either BE or GERD. All patients were required to have at least 365 days in the database following the diagnosis of BE or GERD. Patients were excluded if they had a diagnosis of esophageal or stomach cancer between January 1, 2000 and one year following enrollment.

Adherence to PPIs was assessed using the medication ownership ratio (MOR). MOR was defined as the number of doses dispensed in relation to the dispensing period and was calculated as the percentage of patients on each treatment at each 3-month interval of follow-up. Medication persistence was defined as the duration of time from the initiation to the discontinuation of therapy and was measured by three methods, including length of therapy (LOT), fill-refill ratio, and discontinuation rate. LOT is the number of days between the enrollment and the date when the supply of the last prescribed PPI was depleted. The fill-refill ratio was calculated as the proportion of time on therapy between the first fill and the end of the last refill. Finally, discontinuation rate was calculated as the percentage of patients without a refill within 30 days after depletion of the last filled prescription.

Of the 59,124 patients assessed, 48,965 of those patients (82.8%) had a diagnosis of GERD. The mean age of those patients was 48 years old and 61.6% of them were women. Racial differences were not available. Approximately one-third of the patients with a diagnosis of GERD did not have prescription records for either a PPI or an H2RA. All patients were on acid suppression therapy for a short duration of time after endoscopy with a mean duration of therapy of 241 days for those patients on a PPI and 159 days for those patients taking an H2RA. Analysis of adherence using MOR in patients with GERD revealed that overall adherence to PPI therapy was low (32% at 60 days following diagnosis) and continued to decline with time (28.9% and 26% at 120 and 360 days after diagnosis, respectively).

Regarding persistence to PPI therapy, overall LOT was $\geq$0.8 in 43.1% of patients, indicating that 43.1% of PPI prescribed patients did not take their medication

as scheduled 20% of the time. The reported fill-refill ratio was 0.68 and rate of discontinuation occurred in 31.9% of patients. The low rates of adherence and persistence to PPI therapies is alarming in light of the long term effects of GERD. One component researchers were not able to assess, which may have affected the rate of adherence and persistence, is the potential for patient self use of over the counter PPI therapy. In 2003, omeprazole was made available over the counter. Use of an alternative insurance plan or payment was also not assessed which may have affected data due to uncaptured fills. As with other adherence studies, it is assumed that patients take medications as dispensed. Investigators did not utilize pill count or recall diaries. Although these limitations exist, this data suggests that general adherence to PPI therapy for the treatment of GERD is low.

The second retrospective cohort study assessed PPI usage patterns, focusing on persistence and adherence, in the general population.[23] Data was retrieved from the Integrated Primary Care Information (IPCI) database, a Dutch general practice database. Patients with at least one year of medical history in the database with recent start of a PPI were included in the study. Patients were excluded if they were using PPIs in the previous year, using a PPI for gastroprotection while taking NSAIDs or aspirin or using a PPI as needed. Patients who met the inclusion criteria were evaluated for adherence and persistence based on usage pattern for GERD, non-reflux dyspepsia or *H. pylori*-associated indications.

Adherence to proton pump inhibitors was calculated using the proportion of days covered (PDC) defined as the total number of PPI prescription days divided by the duration. Duration was calculated as the prescribed quantity divided by the prescribed units per day. Adherence was labeled as high (>80%), moderate (20%–80%) or low (<20%). Persistence was defined as the length of time the patient was on PPI therapy. Treatment was considered discontinued if there was not a prescription for a PPI within 6 months of the last fill.

A total of 386,002 patient profiles were reviewed of which 10,833 patients started a fixed dose PPI regimen during the study period and were not using PPIs for the prevention or treatment of NSAID- or aspirin-related complications. The study population was an even distribution of men and women with a mean age of 35.3 years. The average duration of patient follow up was 3.4 years. Notably, the most common indication was GERD (27%) with a total of 4330 patients. In this group the adherence to PPI therapy was labeled as "high" in only 55.1% of patients, while 43.9% had an overall adherence classified as "moderate". Investigators determined that factors such as advanced age and visit to a specialist were correlated to increased adherence with PPIs. Persistence calculations revealed that 38.7% of patients were still taking a PPI after 6 months and 24.4% after two years. The level of persistence to PPI therapy was significantly greater in patients with GERD compared with those with non-reflux dyspepsia and *H. pylori* infections. Interestingly, there were no available over the counter PPIs in the Netherlands at the time of this study. This decreases the possibility that adherence and persistence rates were affected by alternative methods to obtain PPI therapies. However the study is not able to account for over the counter use of alternative treatment options like nonprescription H2RAs or antacids.

The third prospective cohort study assessed factors linked to adherence in the long term use of PPIs.[24] Data was collected via a validated questionnaire sent to 175 patients that were identified as receiving a prescription for a PPI for more than one year. Questions assessed awareness of treatment, side-effects, forgetfulness, the desire to control treatment, the presence or severity of symptoms, treatment effectiveness, and the influence of prescription charges.

Of the 158 patients that completed the survey, 70.9% reported taking their PPI on a daily basis, 15.8% reported taking them "most days" and 13.3% reported taking them "sometimes". The most common factors influencing compliance were the presence or absence of symptoms, the severity of symptoms and a personal preference about when to take the medication. Other factors noted were fear of side effects, addiction, or lack of knowledge about why the treatment was needed and how it worked. While the study relied on patient recall to assess adherence and the overall sample was small but the information retrieved provides insight into adherence with PPI treatment.

The final study was a prospective cohort study that assessed patient and prescriber treatment satisfaction among patients with GERD.[25] Medication adherence was one component of patient satisfaction that was assessed in this study. Primary care physicians were chosen from an independent database. Patients 18 years of age and older were enrolled in the study if

they presented to the physician with reflux symptoms, had been taking prescribed PPIs for at least a month. Those patients who were unable to complete the questionnaire or were not treated with a PPI continuously were excluded from the trial.

Overall, determination of patient treatment satisfaction was the primary purpose of this study. Results showed that the majority of the patients (72%) rated their satisfaction with their PPI treatment for GERD as either "excellent" or "good". Interestingly, 72% of physicians also rated their patients' level of satisfaction as "excellent" (27.3%) or "good" (44.7%). In addition to assessment of patient satisfaction, adherence to PPI therapy was assessed in the questionnaire. Of all the patients, 92.2%stated that they took their PPI as prescribed. While the investigators attempted to assess adherence, this was done through a simple response to a question. For that reason, it may be difficult to assess the accuracy of these results especially given that the questionnaire was not validated.

Discussion

Studies that evaluated adherence to PPIs in the chronic management of GERD have overall low adherence rates, consistent with other published findings on adherence. Generally, there is a no consensus on sufficient level of adherence. However, several studies suggest that a rate of greater than 80%–95% can be considered adequate. Investigators suggest that possible factors for low adherence include cost of therapies, patient use of over the counter agents for symptom management, provider apathy or lack of knowledge, severity of symptoms.

There have been several studies that have evaluated patient adherence to gastroprotection agents (GPA) when used in combination with nonsteroidal anti-inflammatory drugs (NSAID).[23,26–28] Results show that overall adherence to GPAs range from 50 to 80% with rate of adherence further decreasing when more than one NSAID and one GPA is used. The primary reason for low adherence reported from these studies include multidrug regimens, in which more than one agent used resulted in even lower adherence rates. Use of combination drug products may improve these rates. Other possible reasons include cost of therapies and lack of understanding of the importance of medications.

Adherence to medications remains one of the primary factors for therapeutic success in almost every chronic medical condition. Several studies assessing patient adherence have been conducted in patients with a variety of other chronic illness, including human immunodeficiency virus (HIV), hepatitis C and coronary artery disease (CAD).[29–31] Again, these studies have concluded that optimal ways to overcome low adherence rates include simplification of regimens to once daily dosing, if possible and education of patients about the value and effectiveness of therapies and how then impact the management of their conditions.

Conclusion

Medication adherence and persistence for treatment of chronic diseases plays an important role in the short and long term outcomes of the disease. While the efficacy and safety of approved agents is confirmed, adherence to these medications ultimately determines the extent to which they can exert their effectiveness. Acid suppression therapy is the mainstay for long term management of GERD. As clinicians, we cannot predict a patient's level of adherence. However, an understanding of barriers to adherence may help overcome the challenges. Low adherence rates has consistently been correlated to increased disease related morbidity and mortality, such as BE and esophageal adenocarcinoma in the case of GERD. In order to improve patient care through pharmacotherapy, an in-depth analysis of common barriers must exist. Commonly reported barriers to patient adherence include cost of therapy, lack of understanding of the value to therapy, potential or perceived side effects of therapy and complicated treatment regimens. Although studies have not directly compared adherence of PPIs versus H2RAs, there are differences among these classes that may affect adherence rates, such as dosing frequency, side effects and cost. Results from retrospective cohort studies evaluating adherence to PPI therapy demonstrate that rate of adherence and persistence need improvement. Consideration of common barriers to adherence is essential when educating patients about the value of their prescribed regimens, as well as potential side effects, preferred dosing frequency and medication cost. Identifying and minimizing barriers to adherence is invaluable to the successful treatment of chronic medical conditions, such as GERD.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal

and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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