Impact of Clinical Pharmacists’ Recommendations on a Proton Pump Inhibitor Taper Protocol in an Ambulatory Care Practice

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ABSTRACT

BACKGROUND: Previous studies have demonstrated an association between chronic proton pump inhibitor (PPI) utilization and adverse events such as fractures, infections, hypomagnesemia, and vitamin B12 deficiency. Because patients taking PPIs for an extended period of time are more susceptible to these adverse events, an approach to tapering patients off PPIs is clinically warranted.

OBJECTIVE: To evaluate the impact of clinical pharmacists’ recommendations to clinicians to decrease PPI use in patients when chronic therapy is not indicated.

METHODS: Clinical pharmacists electronically sent PPI taper recommendations for qualifying patients to primary care providers the day before each patient’s appointment. Using insurance claims data, an average pills per month (PPM) count was calculated for the 5-month period prior to initiating the PPI taper as well as for the 5-month period after the date of taper initiation. The PPM count was calculated by dividing the total number of pills a patient received by the total number of days in that period, multiplied by 30. The primary outcome for the study was the change in average PPM count from baseline (pretaper period) to follow-up (posttaper period) and was assessed using a paired t-test. Secondary outcomes included change in total annualized PPI costs to the organization, proportion of patients who began the taper protocol after primary care provider recommendation, and whether baseline characteristics were predictors of successful response. Change in annualized PPI costs to the organization was calculated by multiplying the average unit cost per pill (determined using a weighted average of the average wholesale price of the individual drugs) by the PPM change in PPI use. A logistic regression analysis was used to determine whether baseline variables including alcohol and tobacco use, diagnosis related to PPI use, PPI dose, dosing frequency, gender, and length of prior PPI use significantly impacted successful tapering.

RESULTS: Average PPM count decreased by 8.7 pills (95% CI: 6.4, 11.1), from 25.6 at baseline (95% CI: 23.1, 28.1) to 16.9 at follow-up (95% CI: 14.3, 19.5; P<0.001). For the 117 evaluable patients in the study, there was an annualized PPI cost reduction of $18,151. 37.6% (44/117) of pharmacists-recommended tapers were enacted upon by primary care providers at the patient visit. Baseline patient characteristics were not found to be predictors of a successful taper response.

CONCLUSION: Clinical pharmacist intervention may decrease overutilization of PPIs and associated costs in the primary care setting. While a decrease in PPI use was observed in this study, these findings do not imply improvement in clinically meaningful patient outcomes.

What is already known about this subject

• Gastroesophageal reflux disease (GERD) affects approximately 10%-20% of patients on a weekly basis. Proton pump inhibitors (PPIs) have become the first-line therapy for GERD; however, more cost-effective medications with fewer documented long-term side effects are available.
• Long-term PPI use may lead to adverse events including hip, wrist, and spine fractures; Clostridium difficile infections; pneumonia; hypomagnesemia; and vitamin B12 deficiency.
• It has been noted that PPIs are overutilized in the ambulatory care setting, often without documented indications and periodic re-evaluation of symptoms, which may lead to chronic use of PPIs when not indicated.
• Previous PPI taper studies have demonstrated successful tapering with various outcomes ranging from reduction of twice-daily dosing to once-daily dosing to full cessation of PPIs in asymptomatic patients.

What this study adds

• This study contributes to existing knowledge by showing that the inclusion of clinical pharmacists to identify eligible candidates and recommend a PPI taper yields a reduction in PPI use and medication cost savings in primary care.
• This study demonstrates a successful interdisciplinary model of care and taper method for reducing chronic PPI utilization and associated costs in an ambulatory care setting.

Gastroesophageal reflux disease (GERD) is a commonly encountered diagnosis in clinical practice, affecting about 10%-20% of people in Western countries on a weekly basis. While the main symptoms of GERD, such as heartburn, acid reflux, and esophagitis are effectively relieved with proton pump inhibitors (PPIs), in many instances, more cost-effective medications with better side effect profiles, such as histamine-2 receptor antagonists (H2RAs) and antigacids, may be sufficient for symptomatic relief. Patients taking PPIs for extended periods of time may be more susceptible to adverse events including hip, wrist, and spine fractures; Clostridium difficile infections; pneumonia; hypomagnesemia; and vitamin B12 deficiency. Previous literature has documented overutilization of PPIs and lack of symptom re-evaluation in the ambulatory care setting. Therefore, it is prudent to
Methods
The protocol for this prospective observational study was approved by the Massachusetts College of Pharmacy and Health Sciences Institutional Review Board. This study was conducted at Atrius Health, a nonprofit alliance of 5 multispecialty medical groups, consisting of Harvard Vanguard Medical Associates, South Shore Medical Center, Dedham Medical Associates, Granite Medical Group, and Southboro Medical Group, serving over 700,000 patients in Massachusetts across 24 sites.

Data Collection
Prescriptions for generic and brand-name PPIs (omeprazole [Prilosec], pantoprazole [Protonix], esomeprazole [Nexium], lansoprazole [Prevacid], dexlansoprazole [Dexilant], and rabeprazole [AcipHex]) were used as initial search terms in the Atrius Health electronic medical record (EMR) to identify eligible candidates. Patients classified as chronic PPI users were those provided with an electronic prescription order or prescription orders totaling 3 or more months of a PPI prescription written by their primary care providers in the 5 months prior to an upcoming appointment with their primary care providers. Patients were excluded from the study through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding, where applicable, along with prespecified search criteria. Those excluded had documentation of Zollinger-Ellison syndrome (251.5), Barrett’s esophagus (530.10, 530.85), esophageal stricture (530.3), eosinophilic esophagitis (530.13), Schatzki’s ring (530.3, 750.3), history of esophageal dilation (42.92), history of bariatric surgery (44.3), current gastrointestinal ulceration (530.2, 531, 532, 533), current H. pylori treatment (041.86), chronic oral steroid use (more than 1 refill in past 5 months), chronic nonsteroidal anti-inflammatory drug use (more than 2 refills in past year), a gastroenterologist office visit within the past 12 months or upcoming 3 months, or age less than 18 or greater than 70. Patients who recently saw a gastroenterologist or were planning on seeing one in the near future were excluded because these patients were believed to not be asymptomatic and were seeking a specialist consult for more severe or progressing symptoms. A summary of the selection of the sample size can be found in Figure 1.

Once patients were identified through the prespecified search terms noted previously, clinical pharmacists manually reviewed each patient for appropriate inclusion into the study and then electronically sent recommendations for PPI tapers to primary care providers the day before each patient’s appointment. At the appointment, the primary care provider may have initiated the PPI taper, by utilizing written instructions.
adapted from the PPI taper algorithm in Figure 2. Patients who began the PPI taper were not routinely followed for discussion of symptoms. The process for tapering and follow-up was ultimately at the discretion of the primary care provider. Using insurance claims data, both the average pills per month (PPM) count for the 5 months prior to the initiation of the PPI taper recommendation and the average PPM count for the 5 months after initiation of the taper were determined for each patient. The pretaper period began on the day 5 months prior to initiation of the PPI taper and ended on the day prior to the start of the PPI taper. The posttaper period began on the day of the initiation of the PPI taper and ended on the day 5 months after the initiation of the taper. PPM count was calculated for the pre- and posttaper period by dividing the total number of pills a patient received by the total number of days in that period, multiplied by 30.

The primary outcome for this study was the overall change in mean PPM count from baseline (pretaper period) to follow-up (posttaper period) for all patients. Secondary outcomes included change in total annualized PPI costs to the organization, proportion of patients who began the taper protocol after clinical pharmacist recommendations to primary care providers, and whether certain baseline characteristics were predictors of successful taper response.

**Sample Size Determination**
The number of participants required for this study was based on the projected percentage of patients who would be able to
step down to less frequent PPI dosing in their treatment of GERD. Previous research reported that 58% of patients were able to achieve full reduction of their PPI treatment as a result of step-down therapy. Therefore, we assumed that at least 70% of patients in this study would achieve a full (complete cessation) or partial (any reduction in dosing frequency) PPI dose reduction. The number of patients required to detect this percentage of full or partial reduction from baseline (0%) at the 5% level of significance with 80% power was determined to be 130. This value ensured that sufficient data were available for statistical analysis, in particular logistic regression. Additionally, based on estimations of unavailable claims data for some patients due to over-the-counter (OTC) PPI use and other discount drug programs (e.g., $4 generics drug discount), we assumed the clinical pharmacists needed to send 250 taper recommendations to achieve a study sample size of 130. Based on estimations of clinical pharmacist workload, a 2-month study period was believed to be long enough to accrue at least 250 taper recommendations.

### Statistical Analysis

Patient demographics and other health-related variables were summarized using descriptive statistics, including means and percentages. A paired t-test was used to assess the effect of step-down therapy on the overall mean number of pills taken per month at baseline versus follow-up for all patients. In addition, logistic regression analysis was used to determine whether baseline variables, including alcohol and tobacco use, diagnosis pertaining to PPI use (e.g., GERD, dyspepsia, gastritis, duodenitis, esophagitis), PPI dose, dosing frequency, gender, and length of prior PPI utilization significantly impacted successful step-down therapy. Results were considered statistically significant if the observed level of significance was \( P < 0.05 \).

To calculate a change in annualized PPI costs to the organization, the average unit cost per pill was determined using a weighted average of the average wholesale price (AWP) of the individual drugs, using AmerisourceBergen drug pricing data. The PPM change expressed as the primary outcome was multiplied by the average unit cost per pill and by the number of patients in the study and expressed over a full year. The decision to express the change in PPI costs as an annualized amount was based on the fact that the PPI taper protocol was an ongoing clinical program that began more than 1 year prior to this study. Therefore, the authors felt it reasonable to present cost data from this study as a snapshot of the current ongoing clinical program. All analyses were conducted using Number Cruncher Statistical System (NCSS) software.

### Results

A total of 302 taper recommendations were sent by clinical pharmacists to primary care providers between September 1, 2011, and October 31, 2011. As part of the Atrius Health payment structure, approximately 50% of patients are provided health care through capitated payments, which involve prepayments from insurance companies for medical care. Because of the availability of OTC PPIs, cash-paying customers, the use of generic and other drug discount programs, and pharmacy benefit managers providing claims data only for patients under the capitated payment structure, the primary outcome for 185 of 302 patients (approximately 61%) could not be assessed.

Data on the remaining 117 patients (approximately 39%) were available for analysis of the primary outcome and therefore were included in the study. The analysis of claims data for assessment of the primary outcome was planned for March 2012. Because of an unanticipated 2-month lag period in receiving insurance claims data, the study analysis scheduled to begin in March 2012 only included claims data up through January 31, 2012. Therefore, the posttaper period reflects a 3-month average of PPM count, rather than the intended 5-month PPM count average of the posttaper period. The decision to utilize a 3-month posttaper period was made prior to the collection of any data. The analysis of the pretaper period remained at 5 months, since all claims data for that period was obtainable.

The mean age (± standard deviation [SD]) of the 117 patients was 57.4±10.0 years. About 71% were female, 15% smoked tobacco; and 31% consumed alcohol. The most common diagnosis related to PPI use was GERD (65%), and about 25% of patients did not have a documented indication in their EMR for requirement of a PPI. The majority of patients (75%) were taking a PPI once daily upon study entry, and only 24% of the...
population had previously tried an H2RA for symptom relief. The mean length of prior PPI utilization (± SD) was 59.3 ± 36.1 months (Table 1).

For the primary outcome, there was a statistically significant decrease in mean PPM count of 8.7 pills (95% confidence interval [CI]: 6.4, 11.1) from 25.6 pills (95% CI: 23.1, 28.1) at baseline to 16.9 pills (95% CI: 14.3, 19.5) at follow-up (P < 0.001). Logistic regression revealed that none of the baseline variables (alcohol and tobacco use, diagnosis, dose, dosing frequency, gender, and length of prior PPI use) significantly impacted successful step-down therapy (P > 0.05).

Using a weighted average, the cost per PPI unit dose was determined to be $2.02 per pill. The cost per unit dose was calculated by utilizing the AWP per pill from AmerisourceBergen pricing data,33 the primary wholesaler used for on-site pharmacies (Table 2). Each of the 117 study participants had an average monthly reduction of 8.7 pills (95% CI: 6.4, 11.1). We chose to represent the yearly PPI cost reduction as a conservative estimate using the lower limit of the 95% CI. Therefore, a PPI reduction of 6.4 pills would yield an estimated yearly PPI cost savings of $18,151. Although only 37.6% of patients began the PPI taper protocol as advised by their primary care providers, every pharmacist taper recommendation made to the primary care provider in this study, $155 was saved per year. This cost specifically represents a change in PPI costs and does not factor in the additional costs of H2RAs and antacids as alternate prescription therapies at follow-up.

After the conclusion of the taper protocol, patient EMRs were thoroughly reviewed in March 2012 for assessment of assigned medication to treat symptoms of GERD as well as for documentation regarding the PPI taper initiation on the date that the patient/primary care provider intervention took place. Based on EMR documentation, 37.6% (44/117) of patient encounters had documented PPI taper recommendations by their primary care providers. Of these 44 documented taper recommendations, 13 encounters contained documentation of a visit summary with written instructions on the proper taper method encouraged for the study, illustrated in Figure 2. Visit encounters from the other 31 taper recommendations did not specify the taper approach.

Thirty-one percent of patients in this study were able to fully taper off their PPI at the conclusion of the study. Twenty-six percent of the patients in the study were able to fully taper off their PPI and only required intermittent H2RA or antacid therapy to control symptoms. Five percent of patients were able to fully taper off of their PPI, but still required a once- or twice-daily scheduled H2RA therapy to control symptoms. A majority of the patients in the study (59%) were still on the same PPI dose and frequency at follow-up, but this number may represent the inclusion of intermittent and on-demand users, all of whom would have been accounted for by utilizing the PPM count with insurance claims data. Three percent of patients increased their PPI dose or frequency because of worsening symptoms. The remaining 7% of patients decreased their PPI dose or frequency and represent the portion of partial tapers in the study (Figure 3).

**Discussion**

The purpose of this study was to evaluate whether the inclusion of clinical pharmacists to identify eligible candidates and recommend a PPI taper yields a reduction in PPI usage and medication costs in primary care. This study demonstrated the significant impact clinical pharmacists can have in reducing chronic PPI use as part of a medical team in an ambulatory care setting, as well as their impact on reducing medication costs to an organization. While this study demonstrated a statistically significant reduction in PPI utilization in primary care, whether this PPI taper protocol reduces the incidence of clinical outcomes associated with long-term PPI use such as bone fractures, *Clostridium difficile* infections, pneumonia, hypomagnesemia, and vitamin B12 deficiency is unknown.

Although inclusion criteria required patients to have 3 months’ worth of prescriptions for any PPI to be classified as a chronic user, individuals in this study on average had taken a PPI for almost 5 years (59.3 months) prior to study entry. In this study, 36.8% (43/117) of patients were on high-dose PPI therapy, defined as a total daily dose greater than the lowest
available prescription dose. Previous studies have suggested that the relationship between bone fractures and PPIs is most significant with extended duration of PPI use\textsuperscript{4,5} as well as in patients taking higher PPI doses.\textsuperscript{4,6} Therefore, baseline PPI use in this study was comparable to baseline PPI use in studies that suggested an increased risk for hip, wrist, and spine fractures.\textsuperscript{1,8}

Data from a previous study suggested that for every additional 12 months of prior PPI use, patients were 34% less likely to step down from twice-daily to once-daily PPI therapy\textsuperscript{24} and may highlight an important rate-limiting step toward tapering off the PPI in the highest risk patients. Since the patients in this study were previously on their PPIs longer (59.3 months) than other PPI protocol studies (21.3 months and 48 months),\textsuperscript{23,26} this may contribute to reasons why this study resulted in fewer PPI cessations.

It is unknown from this study to what degree clinicians routinely evaluate patients for step-down therapy. Many of the patients in this study also see or have seen other providers and specialists, including otolaryngologists and gastroenterologists, who may have initiated the PPI. Of note, patients who have seen a gastroenterologist in the past year or were scheduled to see one within the upcoming 3 months from the date of taper recommendation were not included in this study, as these patients were assumed to have worsening conditions requiring specialist intervention. Additionally, patients may have been prescribed a PPI upon hospital discharge and may not have been evaluated soon after for clinical need of the medication. Furthermore, primary care providers may not routinely monitor a patient for efficacy and safety of these drugs if they were not the prescriber. In this study, 25% of patients did not have a documented indication for taking a PPI in their EMRs, which is consistent with previous literature,\textsuperscript{20} and questions arise as to whether the PPIs were being utilized appropriately in these patients.

Because this approach to tapering involved no direct patient contact by clinical pharmacists and no routine follow-up by primary care providers, this may be one reason why only 31% of patients were able to fully taper off of their PPIs. Previous studies showed that up to 58% of patients were able to fully taper off using proactive pharmacist follow-up for 1 year.\textsuperscript{23} However, in the study noting that 58% of patients successfully tapered, it was suggested that advancing age is a predictive factor for successful taper response.\textsuperscript{23} The patients in our study were on average 7 years younger. Since this study did not find any correlation between baseline characteristics and taper response rates, it is unknown why 62% of patients either remained on the same PPI dose (59%) or increased their dose or frequency (3%). Additionally, understanding why only 38% of patients were able to taper off or decrease their PPI dose or frequency would be a valuable aim for future studies.

Based on EMR documentation, the majority of the patients in the study (76.1%) did not have documented instruction to try an H2RA prior to PPI initiation. This number may be an overestimate due to the availability of OTC medications and inconsistent chart documentation, but it still highlights that patients could receive a trial of a scheduled H2RA before stepping up to a PPI.

In the 2-month data collection period, a total of 302 taper recommendations were sent by clinical pharmacists; however, only 117 (38.7%) of those recommendations could be assessed for the primary outcome because insurance claims data were lacking due to OTC PPI use, cash-paying customers, discount drug programs, and the capitated payment structure at Atrius Health. We estimated our annualized cost savings for 117 patients to be $18,151. Clinical pharmacists in the normal
workload of this same study period actually sent 302 taper recommendations. Our annualized cost savings estimate, which represents less than half of the taper recommendations, may well be a conservative estimate of the actual annual costs savings accrued. Additionally, since the posttaper period assessed an average PPM count over a 3-month period that included the actual taper process, we believe that if a 3-month PPM count was averaged over a period beginning several months after the date of taper initiation, this might represent a larger overall decline in PPM from the pretaper to posttaper period than the decline seen in this study.

The annualized cost savings of $18,151 is representative of the 2-month study period; therefore, if the taper process was continued for 1 full year, the annualized cost savings would likely be much higher. We reasoned that since this study sampled a 2-month period of a clinical pharmacy program that had been ongoing for a year prior to the start of the study and continues, data collected over the course of a full year (6 study periods) may yield an annualized PPI cost savings of $108,906. However, this is merely an extrapolation and cannot necessarily be implied based on the study results.

**Limitations**

One limitation of the study is that the follow-up (posttaper) period was shortened from 5 months to 3 months due to a significant lag period in the collection of claims data. It is unknown whether the 3-month follow-up period was an adequate amount of time to taper for a majority of the patients. Many previous studies utilized a follow-up period of 6-12 months.²³,²⁴,²⁶,²⁷ Due to the fact that the follow-up period was shortened by 2 months, a greater portion of this period represented the actual taper process; thus, we postulated that the PPM count at follow-up may have been higher than what would have resulted if the follow-up period remained 5 months. Patients on the highest dose of a twice-daily PPI may have required upwards of 3 months before being transitioned to a H2RA. Therefore, the majority of the 3-month posttaper period would include the taper process, and the PPM count average for that period would be slightly higher. On the other hand, because of the short follow-up posttaper period, patients may have tried to taper off their PPI, been successful initially, but because of recurrent symptoms, resumed their original PPI prescription. These patients may have caused a slight decrease in the PPM count at follow-up, but were ultimately not able to step down their therapy. While it is unknown what effect, if any, shortening the posttaper period had on the final results, we believe that shortening the posttaper period from 5 months to 3 months for analysis likely caused the PPM count to be slightly higher at follow-up, since a larger portion of the period consisted of the actual tapering process. This would result in a slightly smaller decline in the PPM count from baseline to follow-up. We also believe that the comprehensive chart review performed 6 months after the start of the taper period in March 2012 to assess for posttaper PPI, H2RA, or antacid use accounted for the long-term efficacy of the taper protocol and identified potential re-initiations of PPIs (Figure 3).

While a chart review suggested that only 37.6% of all pharmacist-recommended tapers were enacted upon by clinicians at the patient visit, this may represent an underestimate of the true incidence of PPI tapering. The reasons why primary care providers did not act upon the majority of clinical pharmacist taper recommendations may include not enough time at the visit; the patient declined; the provider determined the taper not appropriate at the time of recommendation; the provider did not read the electronic message prior to the appointment; or the provider did not appropriately document the taper recommendation. It would be valuable for future studies to evaluate some of the rate-limiting steps involved with the clinical pharmacist and primary care provider taper collaboration process.

When calculating the PPM count, it was necessary to assume that all pills picked up by patients at the pharmacy were taken as prescribed until finished. Baseline data showed 75% of patients were taking a PPI once daily, and 25% of patients were taking a PPI twice daily; therefore, we expected the baseline PPM count to be approximately 37.5; instead it was 25.6. This suggests that some patients were not necessarily taking their PPIs as prescribed and were often utilizing their PPI on-demand or intermittently. This is consistent with previous reports, which indicate that up to 29% of patients may decrease the frequency of PPI use without instruction by their providers.³⁵,³⁶ The PPM count method used in this study to analyze PPI prescription utilization before and after the taper protocol was able to objectively incorporate these on-demand and intermittent PPI users into the assessment of the taper protocol. The degree to which these patients were able to completely cease using their PPIs at the conclusion of the study is unknown. Conversely, it is also unknown how many of the 59% of patients who remained on the same PPI dose at the conclusion of the taper protocol actually consisted of on-demand or intermittent PPI users.

**Conclusion**

Clinical pharmacists decreased PPI utilization and PPI costs in an ambulatory care setting by a statistically significant proportion. Through collaboration with primary care providers, clinical pharmacists demonstrated their value to the health care team. The clinical importance of identifying patients as chronic PPI users and evaluating these patients for potential step-down therapy may be understated in the practice of medicine. This study adds another potential model for PPI taper protocols to the current literature and provides information about a potential model of patient care involving a clinical pharmacist. With increasing data surrounding long-term adverse events with chronic PPI use, evaluation of a successful PPI taper protocol on clinical outcomes would be beneficial to the medical literature.
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