Review of Proton Pump Inhibitor Overuse in the US Veteran Population

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Abstract

Objective: A growing body of evidence provides proof that proton pump inhibitors (PPIs) are overused in the general population and that such use is associated with adverse risks and unnecessary costs. Our objective was to systematically evaluate PPI overuse in the veteran population. **Data Sources:** A literature search using MEDLINE and CINAHL databases (1946–December 2014) was performed using the search term *proton pump inhibitors* coupled with each of the following key words: *inappropriate use*, *misuse*, and *overuse*. Searches were limited to studies and reviews in English language and human subjects. Additional references were identified from a review of literature citations. **Study Selection and Data Extraction:** All articles that centrally addressed the issue of PPI overuse were evaluated, following the PRISMA guidelines for systematic reviews. Data were extracted into Microsoft Excel 2013. Articles that focused on the pediatric or non-US veteran populations were excluded. **Data Synthesis:** Among 30 articles included, 5 evaluated PPI overuse in veterans. The reported prevalence rate of PPI overuse in veterans ranged from 33% to 67%. Several cases reported PPI-associated *Clostridium difficile*–associated diarrhea and pneumonia. One Veterans Affairs center reported the total cost of PPI overuse to be more than \$200 000 based on over-the-counter costs and more than \$1.5 million based on average wholesale price cost. **Conclusions:** PPI overuse is common among veterans and exposes them to adverse risks and costs the system enormous dollars. Based on the findings of this review, we provide recommendations to curb PPI overuse among veterans and in the Veterans Affairs system.

Keywords

proton pump inhibitors, overuse, inappropriate use, veterans, Veterans Affairs

Introduction

Proton pump inhibitors (PPIs) are widely used by Americans, accounting for over 50% of prescriptions for all gastric acid–related disorders in the United States.¹ In 2009, PPIs accounted for more than 94 million prescriptions and over \$11 billion in sales.^{2,3} In addition, PPIs are available over-the-counter (OTC) in pharmacies, wholesale stores, convenience stores, and gas stations. Although PPIs may seem innocuous, a compilation of recent evidence provides proof that PPIs are overused in the general US population and that such use is associated with adverse risks^{4–6} and unnecessary costs.^{5–7}

Use of PPIs is expected to be highly prevalent in the US veteran population. One of the recent national health focuses for veterans returning from service in the Gulf War has been a high rate of functional gastrointestinal (GI) disorders. As a result, in 2011, the Department of Veterans Affairs (VA) implemented a new assessment rule for compensation, making it easier for veterans diagnosed with a functional GI disorder to gain disability benefits.⁸ In light of the associated risks and enormous costs related to PPI overuse in the general population, evaluation of PPI use in the veteran

population is warranted. We undertook a systematic review of the literature to gather information on the use of PPIs in the US veteran population. The findings of this review will be translated into recommendations to help guide efforts to ensure appropriate use of this important drug class in veterans in order to ultimately improve health care outcomes for veterans and decrease costs to the VA system.

Background

Appropriate Use of PPIs

A summary of the Food and Drug Administration (FDA)–approved indications for PPI use in the United States is provided in Table 1.^{9–14} For short-term use, the recommended

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Table 1. Approved Indications for Proton Pump Inhibitors in the United States.⁹⁻¹⁴

Indication	Proton Pump Inhibitor					
	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Duodenal ulcer treatment	4 weeks	—	4 weeks	—	—	≤4 weeks
Duodenal ulcer maintenance	—	—	No studies >12 months	—	—	—
<i>Helicobacter pylori</i> eradication	10 days ^a 14 days ^b	10 days ^a	10 or 14 days ^a 14 days ^b	—	—	7 days ^a
Gastric ulcer treatment	4-8 weeks	—	≤8 weeks	—	—	—
GERD (nonerosive)	4-8 weeks	4-8 weeks	≤8 weeks	4 weeks	—	4 weeks ^c
Erosive esophagitis treatment	—	—	≤8 weeks ^d	≤8 weeks	≤8 weeks ^d	4-8 weeks ^d
Erosive esophagitis maintenance	No studies >12 months	—	No studies >12 months	≤6 months	No studies >12 months	No studies >12 months
NSAID-associated gastric ulcer risk reduction	—	≤6 months	≤12 weeks	—	—	—
NSAID-associated gastric ulcer treatment	—	—	8 weeks	—	—	—
Pathologic hypersecretory conditions ^e	Long term	Long term	Long term	—	Long term	Long term

Abbreviations: GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

^aPart of a triple therapy regimen, which includes the PPI in combination with amoxicillin and clarithromycin.

^bPart of a dual therapy regimen, which includes the PPI in combination with clarithromycin (omeprazole) or amoxicillin (lansoprazole).

^cCan consider an additional 4 weeks if symptoms do not resolve.

^dCan consider an additional 8 weeks if incomplete healing.

^eAccording to prescribing information, the recommended duration of therapy for pathologic hypersecretory conditions, including Zollinger–Ellison syndrome, is “long term,” which is ill defined as being as long as clinically indicated.

duration of PPI therapy is 4 to 8 weeks for treatment of gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) and 7 to 14 days for eradication of *Helicobacter pylori* infection.⁹⁻¹⁴ If empiric therapy with a PPI, including a trial of dose escalation, does not control symptoms within the recommended short-term use time period, experts, including those of the American Gastroenterological Association, recommend performing further diagnostic workup (eg, endoscopy) to evaluate other potential causes of symptoms before or in lieu of continuing and/or escalating PPI therapy.¹⁵⁻¹⁸ According to FDA-approved indications, long-term use, defined as longer than 8 weeks of PPI therapy, is only recommended for complicated GERD (ie, incomplete healing or maintenance of healing of erosive esophagitis, Barrett’s esophagus), gastroprotection with chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), and pathologic hypersecretory conditions (eg, Zollinger–Ellison syndrome).⁹⁻¹⁴

Overuse of PPIs

Proton pump inhibitors are considered overused when prescribed without an appropriately documented FDA-approved indication (Table 1) or continued without appropriate reevaluation for persistent indication (eg, postdischarge after being

utilized only for hospital stress ulcer prophylaxis).⁴ Numerous studies, spanning over a decade, have consistently demonstrated that overutilization of PPIs in clinical practice is common in the United States, both in the outpatient and inpatient settings.¹⁹⁻³³ For example, studies of PPI use during transitions of care demonstrated that upwards of 75% of inpatients who were inappropriately prescribed a PPI during their hospital stay continued on this therapy following discharge, without an appropriately documented approved indication and often for a prolonged period of time (eg, ≥6 months).^{34,35} The concept of overutilization of PPIs in clinical practice has received significant attention in recent years, mainly because of the potential adverse risks and preventable costs associated with PPI use, especially long-term use.⁴

Several reviews have discussed the potential adverse risks associated with PPI use in depth, including their underlying etiologies.⁵ Although such a detailed discussion is beyond the scope of this review, the major risks are listed herein. These risks include enteric infections (bacterial gastroenteritis, *C difficile*-associated diarrhea), respiratory infections (community-acquired pneumonia, hospital-acquired pneumonia), vitamin and mineral deficiencies (hypomagnesemia, malabsorption of calcium, malabsorption of vitamin B₁₂), osteoporotic fractures, drug interactions, and other risks (acute interstitial nephritis).⁴⁻⁶

Figure 1. Literature search results.

Literature Search

To identify relevant literature on issues related to PPI overuse in veterans, a search of the MEDLINE and CINHAL databases (1946-December 2014) was performed using the search term *proton pump inhibitors* coupled with each of the following key words: *inappropriate use*, *misuse*, and *overuse*. Furthermore, a separate search was performed for each single PPI paired with the aforementioned key words as well as for the search term *proton pump inhibitors* paired with the key word *veterans*. Searches were limited to studies and reviews in English language and human subjects. Following the PRISMA guidelines for systematic reviews (www.prisma-statement.org), the data were then extracted into Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA), repeats were excluded, and then abstracts were critically evaluated by a single reviewer (ESM). Data extracted included type of article (eg, review) or study (eg, randomized controlled trial), population (ie, veteran or non-veteran), setting (ie, inpatient or outpatient), objective, intervention (if relevant), and outcome or finding.

All articles that centrally addressed the issue of PPI overutilization (as previously defined) were evaluated by 2 reviewers (ESM and KTB). Articles that focused on the pediatric or non-US veteran populations were excluded. The reference list of each remaining article was reviewed

to identify related articles that were not identified by the primary literature search.

Findings

Literature Summary

The literature search identified 460 articles, excluding duplicates. Of these, 431 were excluded. One article was identified by searching the reference list of each remaining article. Thus, 30 articles met the inclusion criteria. Among those included, 5 studies evaluated PPI overuse in the veteran population, including 3 in the outpatient setting and 2 in the inpatient setting (Figure 1).

PPI Overuse in the Veteran Population

Table 2 provides information on the studies of PPI overuse in the US veteran population.^{18,26,36-38} In summary, studies reveal that one third to two thirds of veterans may be prescribed a PPI without an appropriately documented FDA-approved indication. A more detailed review of these studies is provided below.

In a prospective, interventional study at the VA Pittsburgh Healthcare System,¹⁸ researchers reviewed the electronic medical records of 248 veterans with 2 consecutive months

Table 2. Summary of Studies of Proton Pump Inhibitor Overuse in the US Veteran Population.^{18,26,36-38}

Trial	Year	Study Design	Setting	Sample Size	Key Results
Gawron et al ³⁸	2013	Retrospective chart review	Outpatient	1621	<ul style="list-style-type: none"> • 23.3% high starting dose • 65.8% received ≥ 90-day prescription • 7.1% of high doses were stepped down
Hughes et al ³⁷	2011	Pretest posttest	Inpatient	234	<ul style="list-style-type: none"> • 23.9% inappropriate use in the pharmacist group vs 46.2% in the no pharmacist group
Heidelbaugh et al ²⁶	2010	Retrospective chart review	Outpatient	946	<ul style="list-style-type: none"> • 36.1% did not have an appropriate indication documented • \$233 994 to \$1 566 225/year
Dries et al ³⁶	2009	Retrospective chart review	Inpatient and outpatient >65 years old on NSAID	1491	<ul style="list-style-type: none"> • 28.3% did not have a documented indication • 11.2% of documented indications were inappropriate
Pohland et al ¹⁸	2003	Prospective intervention	Outpatient	248	<ul style="list-style-type: none"> • 65.7% did not have a documented indication • 49.1% of those lacked GI workup

Abbreviations: GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

of active prescriptions for high-dose (30 mg twice daily) lansoprazole therapy. Among these veterans, 65.7% ($n = 163$) did not have an appropriately documented indication, defined as an indication compliant with VA guidelines for appropriate use of high-dose PPI therapy. Indications not compliant with guidelines included uncomplicated GERD and NSAID-induced gastritis as well as no documented indication. Of the veterans who did not have an appropriately documented indication, only 50.9% ($n = 83$) had any documented GI workup.

Researchers at the Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, TX, retrospectively reviewed the electronic medical records of 1491 elderly (≥ 65 years) veterans concomitantly prescribed NSAIDs and PPIs to assess the therapeutic intent of PPI prescriptions.³⁶ An appropriate therapeutic intent was defined as NSAID gastroprotection, dyspepsia, symptomatic GERD or endoscopic esophagitis, Zollinger–Ellison syndrome, upper GI event, or *H pylori* infection. Of those veterans whose medical records were systematically abstracted, 28.3% ($n = 422$) had no documentation of therapeutic intent. Furthermore, of the 1069 veterans with documentation of therapeutic intent, 11.2% ($n = 120$) had been prescribed a PPI for an inappropriate indication. Three determinants were strongly associated with inappropriate PPI prescriptions: (1) patients who used the VA for medication refills only, (2) when the PPI was initiated by certain subspecialties (cardiology, endocrinology, and otolaryngology), and (3) patients who were prescribed a PPI while an inpatient. Regarding the latter, 45% of PPI prescriptions for inpatients were initiated for unknown or inappropriate reasons.

In a retrospective, medical record review conducted at the VA Ann Arbor Healthcare System,²⁶ researchers sought to determine the prevalence of inappropriate PPI use among veterans in an ambulatory care setting. Of 7877 veterans who received a prescription for a PPI during the 1-year study period, 31.4% ($n = 2474$) did not have an *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code indicating an upper GI tract diagnosis requiring PPI therapy. Among a random sample of 946 veterans selected from this population, an extensive review of the medical records confirmed that 36.1% ($n = 341$) did not have an appropriately documented indication, defined as an appropriate diagnosis for PPI therapy, empiric treatment based on upper GI tract symptoms without a documented GI diagnosis, or gastroprotection based on concomitant therapy with anticoagulants, corticosteroids, or NSAIDs. In addition, among these veterans, 100% ($n = 341$) received PPI therapy without documentation of reevaluation of symptomatic improvement or assessment of continued need for therapy, and the mean duration of PPI therapy was 823 days.

Researchers at the St Louis VA Medical Center in St Louis, MO, conducted a retrospective, medical record review to determine whether interventions made by clinical pharmacists (intervention group) compared with a nonpharmacist control group significantly decreased the rate of inappropriately prescribed acid-suppression therapy (AST) among veterans in a non-ICU geriatric unit.³⁷ The AST included PPIs as well as histamine-2 receptor antagonists and sucralfate. An appropriate indication was defined as an *ICD-9-CM* code on the medical diagnoses list for GERD; hiatal hernia; esophagitis; erosive esophagitis; gastritis;

dyspepsia; Barrett's esophagus; acid reflux; peptic, gastric, or duodenal ulcer; NSAID-induced ulcer; *H. pylori*; Zollinger–Ellison syndrome; or any GI bleed. Inappropriate use of AST was considered those patients on AST lacking one of these diagnoses. The primary outcome, the proportion of veterans receiving AST prior to discharge from the unit without an appropriate indication, occurred 46.2% ($n = 54/117$) versus 23.9% ($n = 28/117$) in the control and intervention groups ($P = .001$), respectively. It is worth noting that although the researchers observed a high rate of inappropriate AST use among this group of veterans, they did not distinguish the inappropriate use of PPIs from other AST. Furthermore, they did not analyze the length of AST prior to discharge or if the veteran received any AST in the subsequent period and, if so, for what duration; albeit, some veterans reportedly continued AST indefinitely.

In a retrospective, medical record review conducted at the Edward J Hines, Jr. VA Hospital in Hines, IL,³⁸ researchers aimed to determine how PPIs were initially prescribed in adult veterans (18–90 years of age) diagnosed with GERD (from 2003 to 2007), and to characterize subsequent PPI use over the 2 years following the initial prescription (through 2009 for veterans included from 2007). They used only outpatient data to identify the GERD diagnoses (*ICD-9-CM* code 530.81 or 530.11) due to potential confounding indications for inpatient PPI prescriptions. Veterans prescribed PPIs for an indication other than GERD and those concomitantly using high-dose NSAIDs (for a minimum of duration of 14 days) and/or a thienopyridine during the study period (≥ 30 days), were excluded. The initial PPI prescription was defined as the first outpatient PPI prescription within 30 days after the GERD diagnosis. Initial PPI prescriptions were categorized as “standard” total daily dose (ie, lowest available PPI dose given daily) or “high” total daily dose (ie, standard daily PPI dose given twice daily or double dose given once daily), and accuracy of these dosing categories was confirmed (showing excellent agreement of $>99\%$ for both categories) by manual chart review. Refill data and the medication possession ratio were calculated to evaluate PPI adherence, and changes in total daily dose in those veterans with at least one refilled prescription of the same PPI were evaluated to determine evidence of step-up and step-down therapy. Of the 1621 veterans included in the study, 76.7% ($n = 1243$) had standard total daily dose initial PPI prescriptions and 23.3% ($n = 378$) had high total daily dose initial prescriptions. The majority of veterans (65.8%) received a 90-day or greater initial PPI prescription, and a large majority (83.8%) had at least one refill over 2 years; the mean number of annual refills was 2.9. The overall medication possession ratio was 0.86. Over the 2 years following the initial PPI prescription, 13.0% of veterans with initial standard total daily dose prescriptions had evidence of step-up therapy, whereas only 7.1% with initial high total daily dose PPI prescriptions had evidence of step-down therapy. While

the researchers could not completely determine appropriateness of PPI prescriptions, it is worth noting that although PPIs were prescribed for a variety of GERD-associated symptoms, a supplemental medical record review revealed that a substantial proportion of veterans (36.5%, $n = 89$) had no symptoms documented at time of the initial PPI prescription.

Discussion

Our review is the first of its kind to systematically evaluate PPI overuse in the US veteran population. Our findings demonstrate that PPIs are commonly prescribed within the VA system without appropriate documentation of the indication for use and without reevaluating the need for continued use. This is a major public health concern because PPI overuse is associated with adverse risks for veterans and substantial costs for the VA system as a whole and, hence, American citizens.

Potential Adverse Risks Associated With PPI Overuse in the Veteran Population

Cases from the studies included in our literature search suggest that overuse of PPIs in veterans is associated with certain adverse risks. Specifically, among the 5 studies meeting our inclusion criteria, 2 also reported deleterious effects. Heidelbaugh et al²⁶ reported 6 cases of *C. difficile*-associated diarrhea (CDAD) and 1 case of community-acquired pneumonia potentially related to PPI use in their cohort of veterans, but no cases of osteoporotic fractures, vitamin and mineral deficiencies, or other deleterious effects. Hughes et al³⁷ reported 10 cases (8.5%) of CDAD, 7 cases (6.0%) of pneumonia, and 1 case (0.9%) of potential GI bleeding in the control group and 7 cases (6.0%) of CDAD, 7 cases (6.0%) of pneumonia, and no cases (0.0%) of potential GI bleeding in the intervention group. Although these deleterious effects were not statistically different between groups ($P = ns$), the study was not adequately powered to detect a clinically meaningful difference. Nonetheless, despite the limitations of these studies, the results are consistent with other studies in veteran^{39–42} and nonveteran populations,^{5,6} showing that a correlation does exist between PPI use and certain deleterious effects, such as CDAD and pneumonia. Furthermore, based on reports from studies in nonveteran populations, is it reasonable to consider that use, especially long-term use, of PPIs in veterans is also associated with other adverse risks, such as those listed in the overuse section above.

Costs Associated With PPI Overuse in the Veteran Population

Adverse risks are not the only reason to curb PPI overuse in veterans; there are costs associated with PPI use in the

veteran population as well. From a financial perspective, there is the direct cost of the PPI therapy itself and the indirect cost of managing the deleterious effects associated with PPI use, which can significantly affect VA pharmacy and medical center budgets and impart a substantial financial burden on veterans. For example, in 2000, the cost of PPIs within the VA system was \$138 million, compared with \$11 million for the histamine-2 receptor antagonist drug class.¹⁸ While the direct cost of the PPI drug class has decreased since 2000, due to the introduction of generic prescription and OTC PPIs, the overall cost is not insignificant considering the considerable overuse of PPIs in the veteran population. In 2010, Heidelbaugh et al²⁶ reported the total cost of PPI overuse to be more than \$200 000 based on OTC PPI costs and more than \$1.5 million based on average wholesale price costs within a single VA medical center alone (VA Ann Arbor Healthcare System). In terms of direct cost for the consumer, a veteran typically incurs an \$8 or \$24 copay for a 30-day or 90-day supply of medication, respectively, dispensed by a VA pharmacy.³⁷ Thus, an individual veteran may pay nearly \$100 per year for PPI therapy that, in many cases, may be unjustified with regard to documentation of appropriateness of therapy.

Based on the available evidence, the indirect cost associated with PPI use in the veteran population cannot be estimated. A larger study focused on detecting and managing PPI-associated deleterious effects would be necessary to quantify such costs. Moreover, a larger study would be necessary to show an improvement in clinically significant deleterious effects resulting from the improvement in PPI use.³⁷ Though debate exists regarding the direct and indirect costs associated with PPI overuse, the widespread use of PPIs in the United States inevitably contributes to increased health care expenditures both for institutions and individuals and, thus, demands awareness.

Strategies for Reducing PPI Overuse in Veterans

Reducing PPI overuse has the potential to mitigate adverse risks and reduce costs,³⁷ which ultimately would improve veteran care and reduce expenditures to the VA system as a whole. However, given the magnitude of the problem and the challenges involved with influencing behavior change, it is likely that numerous, synchronized strategies are needed to reduce PPI overuse in the veteran population. Strategies that involve VA providers, pharmacists, and systems are listed in Box 1 and described in more detail below.

Providers, especially primary care providers in the VA, are essential to veteran care. As a foundation, providers should only prescribe a PPI to a veteran for an appropriate clinical indication and document the indication in the medical record.⁶ Clinical practice guidelines, information obtained from diagnostic procedures or tests, and symptoms experienced by veterans may help guide decisions on

whether or not to begin, continue, or discontinue PPI therapy. As an example, the American College of Gastroenterology (ACG) clinical practice guideline⁴³ provides recommendations on PPI use for gastroprotection in patients using NSAID therapy, according to risk for NSAID-related ulcer complications. Patients with one of the following risk factors are considered at moderate risk: age >65 years, high-dose NSAID therapy, confirmed history of uncomplicated ulcer, or concurrent use of aspirin, corticosteroids, or anticoagulants. Patients with 2 or more of these risk factors or a confirmed history of complicated ulcers are considered at high risk. According to the ACG guideline,⁴³ patients at moderate or high risk for NSAID-related ulcer complications should use a PPI for gastroprotection while using NSAID therapy; conversely, patients at low risk (ie, with none of the aforementioned risk factors) should not use a PPI. As another example, the ACG along with the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) provide guidance on PPI use for gastroprotection in patients using antiplatelet therapy.^{44,45} According to the guidance,⁴⁴ gastroprotection should be used when one or more of the following risk factors are present: a confirmed history of GI bleed, dual antiplatelet therapy, or concomitant anticoagulant therapy. In the absence of these risk factors, gastroprotection with a PPI should only be used during antiplatelet therapy in the following patients: age >60 years, with concomitant corticosteroid use, or with dyspepsia or GERD symptoms.⁴⁴ As a principle, when prescribing a PPI to a veteran, providers should ensure that only the lowest effective dose is used and therapy is as brief as possible. For example, the healing dose of lansoprazole for treating an NSAID-associated gastric ulcer in patients who continue NSAID use is 30 mg once daily for up to 8 weeks; the maintenance dose for reducing the risk of NSAID-associated ulcers in patients with a prior documented gastric ulcer who require NSAID therapy is 15 mg once daily for up to 12 weeks.^{6,46} However, it is recognized that some patients may only partially respond to PPI therapy and thus may require use longer than 2 to 3 months and/or with higher PPI doses (eg, twice daily); still, other patients may require maintenance PPI therapy due to risk factors (as aforementioned) or underlying pathophysiology (eg, Barrett's esophagus, Zollinger-Ellison syndrome).⁴⁷⁻⁴⁹ Nonetheless, for patients that only partially respond to PPI therapy, providers should assess PPI adherence and PPI administration with regard to relation to meals and concomitant drug therapies because these factors may contribute to PPI response, or lack thereof.⁴⁷ Furthermore, long-term PPI therapy should be accompanied with routine monitoring for PPI-associated risks.^{48,49} As a behavior, providers should discontinue inappropriate or unnecessary PPI therapy in veterans. Although challenges exist to implement this strategy, a growing body of evidence indicates that a substantial proportion (25% to 75%) of patients using high total daily dose or standard total

Provider Strategies

- Only prescribe a PPI for an appropriate clinical indication and document the indication in the veteran's medical record.
 - FDA-approved indications for PPI therapy include, but are not necessarily limited to: duodenal ulcer, gastric ulcer, GERD, *Helicobacter pylori* (*H. pylori*) eradication, NSAID-induced ulcer healing or prophylaxis, and stress ulcer prophylaxis.
 - Not all PPIs are FDA approved for the same indications.
- When prescribing a PPI, only use the lowest effective dose for the shortest duration necessary.
 - For some PPIs and some indications, FDA-approved maintenance doses are half those of healing doses.
 - Healing with PPIs generally requires only 4 to 8 weeks of therapy, although the duration of therapy is determined by the severity of the condition and the specific PPI being used.
- Discontinue inappropriate or unnecessary PPI therapy.
 - Typically, long-term PPI use should be limited to erosive esophagitis or pathologic hypersecretory conditions.
- Educate veterans about PPI use.
 - For some veterans, avoidance of PPI therapy – even if temporarily and especially for non-urgent medical conditions – may be the safest approach.
 - In general, veterans should not self-medicate with a PPI for more than 14 days at a time and more than three courses of therapy per year.

Pharmacist Strategies

- Leverage the role of CPSs as an integral part of the PACT.
 - Coordinate care and medication management, namely PPI use, with primary care providers and specialists.
 - Speak with veterans about their PPI use (e.g., reason, duration, and frequency of use).
 - Educate veterans about appropriate PPI use and adverse effects to monitor while using a PPI.
- Utilize CPSs as non-physician providers with prescriptive authority.
 - Order laboratory tests to monitor for potential PPI-associated deleterious effects such as vitamin and mineral deficiencies.
 - Modify PPI therapy, which may include adjusting the PPI dose and/or duration, switching the PPI to a histamine-2 receptor antagonist, or discontinuing the PPI, if warranted.

System Strategies

- Leverage VA technology for identification of PPI overuse in veterans.
 - Develop an electronic query algorithm within the VA medical record systems (CPRS and VistA) to identify veterans using PPI therapy without an appropriate indication and/or veterans on long-term PPI therapy who may be candidates for dose reduction or discontinuation.
- Develop and implement clinician-targeted intervention(s) to improve PPI prescribing practice within the VA system.
 - Utilize flags within the pharmacy package system to alert prescribers of the appropriate indications for PPI therapy at the point of prescribing.
 - Employ dashboards within the VA platform to allow clinicians to identify PPI overuse candidates with upcoming clinic visits.
 - Utilize the clinical reminders system within CPRS to prompt clinicians to take action during the clinic visit (i.e., encounter).

Box 1. Strategies to potentially reduce proton pump inhibitor overuse in veterans.

Abbreviations: CPRS, computerized patient record system; CPSs, clinical pharmacy specialists; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PACT, patient aligned care team; PPI, proton pump inhibitor; VA, veterans affairs; VistA, veterans health information systems and technology architecture.

daily dose PPI therapy can be “stepped down” to standard dose therapy, “on-demand” therapy, or histamine-2 receptor antagonist therapy without symptom recurrence and with significant cost savings.^{18,36,50-54} For example, at the VA Pittsburgh Healthcare System, 46% of pharmacist interventions for PPI step-down therapy were accepted by providers, resulting in a [projected] cost savings of \$85 000 per year.¹⁸ Last, as a routine, considering the high potential for veterans to self-medicate with PPIs, because these medications are heavily advertised and some are available OTC, providers should educate veterans on the safe and appropriate use of PPIs. For example, providers might educate veterans who are receiving antibiotics, especially broad-spectrum antibiotics, or traveling to a country where the risk of enteric infection is high to avoid, at least temporarily, using a PPI.⁶ Providers should inform veterans who self-medicate with a

PPI not to use the medication for more than 14 days at a time and not to use more than 3 courses of therapy per year.

Pharmacists are a great resource to help identify and curb PPI overuse in veterans. The positive impact of pharmacists on veteran outcomes and cost savings within the VA has been well documented in the medical literature.^{55,56} In particular, the expansion of pharmacists into clinical pharmacy specialists (CPSs) may alleviate some strains on a primary care provider work force struggling to meet the increasing demands of a burgeoning veteran population⁵⁶ and may specifically aid providers in curbing PPI overuse. At VA medical centers throughout the United States, CPSs are integrated into the primary care medical home team, which the Veterans Health Administration (VHA) has named the Patient Aligned Care Team (PACT).⁵⁶ The PACT CPSs function as nonphysician providers and provide

medication therapy management (MTM) services under an advanced scope of practice that includes prescriptive authority.⁵⁶ Most veterans are directly referred to a CPS by their primary care provider.⁵⁶ The referred veteran is managed by a CPS in conjunction with usual primary care follow-up.⁵⁶ This increased follow-up frequency provides the opportunity for CPSs to assist in coordination of care with primary care providers and also with referrals to specialists for veterans who may need additional workup so that overuse of PPIs can be avoided. Additionally, the referred veteran is managed by a CPS through direct patient care encounters.⁵⁶ The direct patient care encounters provide the opportunity for CPSs to ask veterans questions about their PPI use (eg, reason, duration, and frequency of use) and educate them about appropriate PPI use and adverse effects to monitor while using a PPI. One common overuse scenario, and educational opportunity for CPSs, is a veteran taking both prescription and OTC versions of a PPI. Educating the veteran about this therapy duplication could prevent PPI overuse, particularly overuse that may go otherwise unnoticed by the primary care provider. Last, the direct patient encounters also provide the opportunity for CPSs to order laboratory tests to monitor for potential PPI-associated deleterious effects (eg, vitamin and mineral deficiencies) and to modify PPI therapy, which may include adjusting the PPI dose and/or duration, switching the PPI to a histamine-2 receptor antagonist, or discontinuing the PPI. Within the VA³⁷ and in non-VA settings,⁵⁷⁻⁵⁹ pharmacist-provided MTM services and recommendations have been shown to reduce PPI overuse and associated costs.

The VA system is the largest integrated health care system in the United States. Thus, it is a ripe environment for implementing strategies to curb medication overuse and modify prescribing practices. This could include clinical decision support in the electronic medical record via automatic alerts, using existing flag and clinical reminder technology within the VA computerized patient record system, and the need for documented justification when VA providers attempt to prescribe PPIs for veterans.³⁸ Automatically generated reports and/or letters could be sent to primary care providers regarding PPI use for veterans under their care. Additionally, the quantity and day supply of PPI prescriptions could be limited to specific durations (eg, 30 days) and refills (eg, 1 refill) in order to encourage VA providers to reevaluate the ongoing need for PPI therapy.³⁸ Although there are other strategies with the potential to change national VA prescribing practices and PPI use within the VA system,³⁷ these are some relatively low-cost strategies.

Limitations

Unfortunately, the evidence for PPI overuse in the US veteran population is largely limited to observational studies of medical records. It is possible that a number of providers

were prescribing PPIs appropriately without properly documenting the indications in the medical records of the VA system resulting in overestimations of PPI overuse.^{36,37} However, by most definitions in the literature, overuse not only includes continued use without appropriate reevaluation but also use without an appropriately *documented* indication. Notwithstanding the shortcomings of such methodologies, these studies have routinely shown that substantial proportions (33% to 67%) of veterans are using PPIs for unclear or inappropriate indications, which is worthy of further study.

Another limitation of the evidence base lies in the dearth of information about the long-term risks associated with PPI use in the US veteran population. Although there have been several case reports of PPI-associated CDAD and pneumonia, there have been no cases of osteoporotic fractures or vitamin and mineral deficiencies among veterans in the studies identified in this review. It is unclear whether this observation represents underdetecting and underreporting or is better explained by other factors, yet to be determined. Nevertheless, in clinical practice, the risks associated with PPI use need to be considered and carefully weighed with their benefits.

Finally, as with any focused review, the results should be interpreted cautiously. Our findings and our recommended strategies to reduce PPI overuse must be considered in the context of the population studied. While there is a plethora of data showing that PPI overuse applies to the US population as a whole, we purposefully limited the scope of our review to the US veteran population. Therefore, we cannot generalize our findings and our strategies to the US population as a whole or to the non-US veteran population.

Conclusion

Our findings provide insight into how PPIs are used in the VA system, demonstrating that a significant proportion of veterans and the system as a whole are unnecessarily exposed to the adverse risks and costs associated with PPI therapy. We also offered recommendations to curb PPI overuse among veterans. Future work should involve identification of provider- and veteran-specific factors associated with PPI overuse. Collectively, these findings and recommendations could be used to guide specific strategies to decrease PPI overuse and modify prescribing practices within the VA system.

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References

1. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. *Gastroenterology*. 2009;136:376-386.
2. Drug Topics. 2009 Top 200 branded and generic drugs by retail dollars. <http://www.drugtopics.com>. Accessed January 24, 2011.
3. Drug Topics. 2009 Top 200 branded and generic drugs by total prescriptions. <http://www.drugtopics.com>. Accessed January 24, 2011.
4. Heidelbaugh JJ, Metz DC, Yang YX. Proton pump inhibitors: are they overutilised in clinical practice and do they pose significant risk? *Int J Clin Pract*. 2012;66:582-591.
5. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Adverse risks associated with proton pump inhibitors: a systematic review. *Gastroenterol Hepatol*. 2009;5:725-734.
6. Yang YX, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology*. 2010;139:1115-1127.
7. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. *Am J Gastroenterol*. 2009;104(suppl 2):S27-S32.
8. US Department of Veterans Affairs. Gulf War Veterans' medically unexplained illnesses. <http://www.publichealth.va.gov/exposures/gulfwar/medically-unexplained-illness.asp>. Accessed February 17, 2015.
9. AstraZeneca Pharmaceuticals LP. Prilosec (omeprazole) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.
10. AstraZeneca Pharmaceuticals LP. Nexium (esomeprazole) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.
11. Takeda Pharmaceuticals America, Inc. Prevacid (lansoprazole) [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2012.
12. Takeda Pharmaceuticals America, Inc. Dexilant (deslansoprazole) [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2013.
13. Wyeth Pharmaceuticals. Protonix (pantoprazole) [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals; 2013.
14. Eisai Inc. Aciphex (rabeprazole) [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2013.
15. AGA medical position statement: evaluation of dyspepsia. *Gastroenterology*. 1998;114:579-581.
16. Kahrilas P. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med*. 2008;359:1700-1707.
17. Pandolfino JE, Vela MF. Esophageal-reflux monitoring. *Gastrointest Endosc*. 2009;69:917-930.
18. Pohland CJ, Scavnick SA, Lasky SS, Good CB. Lansoprazole overutilization: methods for step-down therapy. *Am J Manag Care*. 2003;9:353-358.
19. Afif W, Alsulaiman R, Martel M, Barkun AN. Predictors of inappropriate utilization of intravenous proton pump inhibitors. *Aliment Pharmacol Ther*. 2007;25:609-615.
20. Gingold AR, Narasimhan G, Augello S, Clain DJ. The prevalence of proton pump inhibitor use in hospitalized patients. *Practical Gastroenterol*. 2006;29:24-34.
21. Mat Saad AZ, Collins N, Lobo MM, O'Connor HJ. Proton pump inhibitors: a survey of prescribing in an Irish general hospital. *Int J Clin Pract*. 2005;59:31-34.
22. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. *J Clin Pharm Ther*. 2000;25:333-340.
23. Pillans PI, Kubler PA, Radford JM, Overland V. Concordance between use of proton pump inhibitors and prescribing guidelines. *Med J Aust*. 2000;172:16-18.
24. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. *Am J Gastroenterol*. 2009;104(suppl 2):S27-S32.
25. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. *J Clin Pharm Ther*. 2000;25:333-340.
26. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. *Am J Manag Care*. 2010;16:e228-e234.
27. Choudhry MN, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with *Clostridium difficile*-associated disease. *QJM*. 2008;101:445-448.
28. Glew CM, Rentler RJ. Use of proton pump inhibitors and other acid suppressive medications in newly admitted nursing facility patients. *J Am Med Dir Assoc*. 2007;8:607-609.
29. Sebastian SS, Kernan N, Qasim A, O'Morain CA, Buckley M. Appropriateness of gastric antisecretory therapy in hospital practice. *Ir J Med Sci*. 2003;172:115-117.
30. Brandhagen DJ, Pheley AM, Onstad GR, Freeman ML, Lurie N. Omeprazole use at an urban county teaching hospital. *J Gen Intern Med*. 1995;10:513-515.
31. Zink DA, Pohlman M, Barnes M, Cannon ME. Long-term use of acid suppression started inappropriately during hospitalization. *Aliment Pharmacol Ther*. 2005;21:1203-1209.
32. Yachinski PS, Farrell EA, Hunt DP, Reid AE. Proton pump inhibitors for prophylaxis of nosocomial upper gastrointestinal tract bleeding: effect of standardized guidelines on prescribing practice. *Arch Intern Med*. 2010;170:779-783.
33. Herzig SJ, Vaughn BP, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for nosocomial gastrointestinal tract bleeding. *Arch Intern Med*. 2011;171:991-997.
34. Pham CQ, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. *Ann Pharmacother*. 2006;40:1261-1266.
35. Grant K, Al-Adhami N, Tordoff J, Livesey J, Barbezat G, Reith D. Continuation of proton pump inhibitors from hospital to community. *Pharm World Sci*. 2006;28:189-193.

36. Dries AM, Richardson P, Cavazos J, Abraham NS. Therapeutic intent of proton pump inhibitor prescription among elderly nonsteroidal anti-inflammatory drug users. *Aliment Pharmacol Ther*. 2009;30:652-661.
37. Hughes GJ, Belgeri MT, Perry HM. The impact of pharmacist interventions on the inappropriate use of acid-suppression therapy. *Consult Pharm*. 2011;26:485-490.
38. Gawron AJ, Pandolfino JE, Miskevics S, Lavela SL. Proton pump inhibitor prescriptions and subsequent use in US veterans diagnosed with gastroesophageal reflux disease. *J Gen Intern Med*. 2013;28:930-937.
39. Bajaj JS, Ratliff SM, Heuman DM, Lapane KL. Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis. *Aliment Pharmacol Ther*. 2012;36:866-874.
40. Hermos JA, Young MM, Fonda JR, Gagnon DR, Fiore LD, Lawler EV. Risk of community-acquired pneumonia in veteran patients to whom proton pump inhibitors were dispensed. *Clin Infect Dis*. 2012;54:33-42.
41. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Intern Med*. 2010;170:772-778.
42. Cadle RM, Mansouri MD, Logan N, Kudva DR, Musher DM. Association of proton-pump inhibitors with outcomes in *Clostridium difficile* colitis. *Am J Health Syst Pharm*. 2007;64:2359-2363.
43. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104:728-738.
44. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Am J Gastroenterol*. 2008;103:2890-2907.
45. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Am J Gastroenterol*. 2010;105:2533-2549.
46. US Food and Drug Administration. FDA drug safety communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. Silver Spring, MD: Center for Drug Evaluation and Research. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm>. Published May 25, 2010. Accessed March 23, 2011.
47. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108:308-328.
48. Wang KK, Sampliner RE; Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol*. 2008;103:788-797.
49. Nieto JM, Pisegna JR. The role of proton pump inhibitors in the treatment of Zollinger-Ellison syndrome. *Expert Opin Pharmacother*. 2006;7:169-175.
50. Inadomi JM, McIntyre L, Bernard L, Fendrick AM. Step-down from multiple- to single-dose proton pump inhibitors (PPIs): a prospective study of patients with heartburn or acid regurgitation completely relieved with PPIs. *Am J Gastroenterol*. 2003;98:1940-1944.
51. Gadzhanova SV, Roughead EE, Mackson JM. Initiation and duration of proton pump inhibitors in the Australian veteran population. *Intern Med J*. 2012;42:e68-e73.
52. Lind T, Havelund T, Lundell L, et al. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis—a placebo-controlled randomized trial. *Aliment Pharmacol Ther*. 1999;13:907-914.
53. Pace F, Tonini M, Pallotta S, Molteni P, Porro G. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken "on-demand". *Aliment Pharmacol Ther*. 2007;26:195-204.
54. Inadomi JM, Jamal R, Murata GH, et al. Step-down management of gastroesophageal reflux disease. *Gastroenterology*. 2001;121:1095-1100.
55. Lee AJ, Boro MS, Knapp KK, Meier JL, Korman NE. Clinical and economic outcomes of pharmacist recommendations in a Veterans Affairs medical center. *Am J Health Syst Pharm*. 2002;59:2070-2077.
56. Hough A, Vartan CM, Groppi JA, Reyes S, Beckey NP. Evaluation of clinical pharmacy interventions in a Veterans Affairs medical center primary care clinic. *Am J Health Syst Pharm*. 2013;70:1168-1172.
57. Bunde AW, Zaiken K. Impact of clinical pharmacists' recommendations on a proton pump inhibitor taper protocol in an ambulatory care practice. *J Manag Care Pharm*. 2013;19:325-333.
58. Tasaka CL, Burg C, VanOsdol SJ, et al. An interprofessional approach to reducing the overutilization of stress ulcer prophylaxis in adult medical and surgical intensive care units. *Ann Pharmacother*. 2014;48:462-469.
59. Mousavi M, Dashti-Khavidaki S, Khalili H, Farshchi A, Gattmiri M. Impact of clinical pharmacy services on stress ulcer prophylaxis prescribing and related cost in patients with renal insufficiency. *Int J Pharm Pract*. 2013;21:263-269.