Drugs (2017) 77:547–561
DOI 10.1007/s40265-017-0712-6

REVIEW ARTICLE

The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus

David A. Johnson[1] · Philip O. Katz[2] · David Armstrong[3] · Henry Cohen[4] · Brendan C. Delaney[5] · Colin W. Howden[6] · Peter Katelaris[7] · Radu I. Tutuian[8] · Donald O. Castell[9]

Published online: 23 February 2017

Abstract The availability of over-the-counter (OTC) proton pump inhibitors (PPIs) for the short-term (2 weeks) management of frequent heartburn (≥2 days/week) has increased markedly, yet evidence-based recommendations have not been developed. A panel of nine international experts in gastroesophageal reflux disease developed consensus statements regarding the risks and benefits of OTC PPIs using a modified Delphi process. Consensus (based on ≥80% approval) was reached through multiple rounds of remote voting and a final round of live voting. To identify relevant data, the available literature was searched and summarized. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system terminology was used to rate the quality of evidence and strength of recommendations; consensus was based on ≥2/3 agreement. After 4 rounds of review, consensus was achieved for 18 statements. Notably, the available data did not directly reflect OTC use, but instead, prescription use; therefore, extrapolations to the OTC setting were often necessary. This limitation is regrettable, but it justifies performing this exercise to provide evidence-based expert opinion on a widely used class of drugs. The panel determined that using OTC PPIs according to label instructions is unlikely to mask the symptoms of esophageal or gastric cancer or adversely impact the natural history of related precursor conditions. OTC PPIs are not expected to substantially affect micronutrient absorption or bone mineral density or cause community-acquired pneumonia, *Clostridium difficile* infection, or cardiovascular adverse events. However, OTC PPI use may be associated with slightly increased risks for infectious diarrhea, certain idiosyncratic reactions, and cirrhosis-related spontaneous bacterial peritonitis. The available evidence does not suggest that OTC PPI use consistent with label instructions is associated with substantial health risks. To minimize

D. A. Johnson and P. O. Katz share first authorship of this manuscript.

Electronic supplementary material The online version of this article (doi:10.1007/s40265-017-0712-6) contains supplementary material, which is available to authorized users.

✉ David A. Johnson
dajevms@aol.com

✉ Philip O. Katz
philipokatz@gmail.com

[1] Department of Gastroenterology, Eastern Virginia Medical School, 885 Kempsville Rd, Suite 114, Norfolk, VA 23505, USA

[2] Division of Gastroenterology, Einstein Medical Center, 5401 Old York Rd, Suite 363 Klein Building, Philadelphia, PA 19141, USA

[3] Division of Gastroenterology, McMaster University, HSC-3V3, 1280 Main St W, Hamilton, ON L8S 4L8, Canada

[4] Department of Gastroenterology, National University of Uruguay, Av. Italia 2370, 11600 Montevideo, Uruguay

[5] Department of Surgery and Cancer, Imperial College, Kensington, London SW7 2AZ, UK

[6] Division of Gastroenterology, University of Tennessee Health Science Center, 956 Court Avenue, Suite H210, Memphis, TN 38163, USA

[7] Department of Gastroenterology, University of Sydney, Concord, Sydney 2139, Australia

[8] Department of Gastroenterology, University of Bern School of Medicine, Freiburgerstr 10, Bern, Switzerland

[9] Division of Gastroenterology and Hepatology, Medical University of South Carolina, 11 Harleston Place, Charleston, SC 29401, USA

potential risks, healthcare professionals and consumers must actively participate in decision making when managing reflux-related symptoms in the self-care setting.

Key Points

Based on the available data, the consensus panel determined that OTC PPIs are unlikely to mask the symptoms of esophageal or gastric cancer if used as directed.

OTC PPIs are not likely to affect micronutrient absorption or bone mineral density or cause community-acquired pneumonia, *Clostridium difficile* infection, or cardiovascular adverse events.

However, using an OTC PPI may increase the risks for infectious diarrhea, certain idiosyncratic reactions, and cirrhosis-related spontaneous bacterial peritonitis.

1 Introduction

Due to the high prevalence of acid reflux-related symptoms in the general population, the increasing availability of over-the-counter (OTC) proton pump inhibitors (PPIs), and the limited direct data that are available in this area, evidence-based treatment recommendations are needed to discuss the potential risks and benefits of treating gastroesophageal reflux symptoms in the OTC setting [1]. A recently published position paper describes the benefits and potential harms of using PPIs; however, it does not specifically discuss issues related to OTC PPI use. It focuses instead on use of PPIs that is more consistent with prescription indications [2]. The authors suggest that PPIs are essential for treating acid-related conditions, but that, as with any drug therapy, there are potential risks. These potential risks should not, however, outweigh the established benefits of PPIs when they are used as indicated, which means they should only be used when appropriate and for the shortest duration of time to achieve symptom response [2]. Many of the safety concerns related to the use of PPIs have been observed in studies conducted under conditions that are consistent with prescription use, which differs from OTC use in several key ways that are relevant for assessing safety [3]. Prescription PPIs are generally administered at higher doses, the durations of treatment are longer, and users of prescription PPIs often differ from OTC users in terms of their underlying conditions, which are frequently more severe [4, 5]. In contrast, OTC PPIs are used for shorter durations and generally represent the lower end of the dose range. Omeprazole was the first PPI to be approved for OTC use and is widely available in multiple international markets [6]. Omeprazole 20 mg is available OTC for treating frequent heartburn (defined as having symptoms $\geq$2 days/week) and is administered as a single daily dose for 2 weeks [5]. In contrast, omeprazole 20 mg once daily is used for 4–8 weeks for treating gastroesophageal reflux disease (GERD), and omeprazole 40 mg is used for 4–8 weeks for treating gastric ulcers [4]. By their nature, users of prescription PPIs are directly under a physician's care for their perceived acid-related disease, while users of OTC PPIs are not necessarily under a physician's care. As a result of these issues, interpreting the evidence to address concerns related to OTC PPI use requires reviewing the literature to identify relevant data and systematically extrapolating these findings to the OTC setting from studies that likely only indirectly address these issues. Therefore, specifically exploring these issues in the context of OTC use necessitates using evidence available from studies conducted with prescription PPIs, for which the safety profiles have been widely discussed. To achieve this end, an international group of experts was convened to develop evidence-based recommendations and provide accompanying literature reviews to inform global best practices among healthcare providers for the safe and appropriate use of OTC PPIs in the self-care setting.

2 Methods

A panel of nine international experts comprising eight gastroenterologists and one general practitioner convened to develop consensus, evidence-based recommendations for using OTC PPIs utilizing a modified, evidence-based Delphi process [7, 8]. The concept for this panel was conceived by the co-chairs (DAJ/POK) and discussed with the sponsor, who provided full latitude to select the international working group to represent the perspectives of general practitioners and gastroenterologists. Selection of the consensus panel was led by the panel co-chairs in August 2015. The members were primarily selected based on their expertise in the areas of gastroenterology and/or treating acid-related conditions. Additionally, their regional location was considered in order to provide international representation and to gain a global perspective on these topics. Because OTC PPIs may be more frequently recommended in a general practice versus a specialty care setting, a primary care physician was also included in the group. The panel co-chairs also developed a preliminary set of statements based on clinically important topics and assigned statement leads to review the available literature related to each topic based on their level of expertise in these areas.

To identify relevant evidence for each statement, the statement leads conducted literature reviews based upon their preferred search methodologies. These literature reviews included searches of the PubMed and Cochrane databases and were conducted beginning in September 2015 in preparation for a live meeting in November 2015. Searches were conducted utilizing terms that were based on relevant keywords for each statement (e.g. proton pump inhibitor <AND> esophageal cancer; Limits: humans). No limits were set on publication date, and the focus was on English-language publications. After literature searches were completed, the results were reviewed to identify the appropriate sources to be summarized. Because the topics that were analyzed were often based on indirect evidence, the criteria for determining the relevance of the available data differed for each statement. Additional relevant publications were identified by reviewing the bibliographies of the relevant articles. During the same time period that the literature searches were being conducted, consensus for each statement was reached through a series of three remote rounds of anonymous voting and feedback followed by a fourth round at the live meeting.

The level of agreement was rated using a 5-point scale: agree strongly (A+), agree with reservation (A), undecided (U), disagree (D), or disagree strongly (D+). Consensus was defined a priori as ≥80% of panelists strongly agreeing or agreeing with reservation (A+ or A). The quality of the evidence (high: ★★★★; moderate: ★★★; low: ★★; very low: ★) supporting each statement and strength of recommendation were categorized using GRADE (Grading of Recommendations Assessment, Development and Evaluation) terminology [9] and were developed by the statement leads and voted on by the panel using a consensus definition of at least two-thirds agreeing (yes/no) with the rating. A full summary of the voting through each round is provided in Figure 1 (Online Resource 1) and Table 1 (Online Resource 2), and questions about the integrity of the process and a description of withdrawn statements are provided in Online Resource 3.

3 Delphi Statements

1. When taken in accordance with label instructions, PPIs have not been shown to mask the symptoms of early esophageal cancer or meaningfully delay presentation. Available OTC PPIs would not be expected to differ.

A+: 78%; **A:** 22%
Recommendation: Strong
Evidence: ★

It is extremely difficult to prove that PPI treatment does not mask the symptoms of early esophageal cancer and, therefore, delay its diagnosis and management. Esophageal adenocarcinoma (EAC) is the only form of esophageal cancer that is considered to be GERD related, so the potential effects of PPI therapy were considered only in the context of EAC [10]. The most common presenting symptom of EAC is dysphagia [11], and since this is a feature of locally advanced disease, it is unlikely to be "masked" by short-term PPI use. No identified studies directly examined whether PPIs can mask the symptoms of early esophageal cancer. Rather, they focused on whether PPI use is a risk factor for cancer or has a chemopreventive role in Barrett's esophagus (BE) [12–16]. Although some reports demonstrated a higher than expected subsequent incidence of esophageal cancer, this was largely attributable to prevalent disease [17, 18]. Importantly, studies that have attempted to assess the risk of esophageal cancer with PPI use generally did not reflect OTC doses or treatment durations. Instead, they have focused on the long-term use of prescription—or even higher—PPI doses [17]. Therefore, individuals adhering to label instructions for OTC PPIs are extremely unlikely to have a delay in the diagnosis of EAC. Descriptions of an additional study conducted in this area and the role of BE in EAC are included in Data Summaries (Online Resource 4).

2. When taken in accordance with label instructions, it is unlikely that OTC PPIs produce achlorhydria.

A+: 89%; **A:** 11%
Recommendation: Strong
Evidence: ★★★★

Results from multiple comparative pH studies demonstrate that short-term use of PPIs at OTC doses does not suppress acid production enough to produce achlorhydria [19–22]. Although PPI therapy has the potential to increase *Helicobacter pylori* infection-related atrophic gastritis and metaplasia, an effect on gastric cancer incidence in this context has not been observed [23, 24]. Therefore, the short-term use of OTC PPIs is very unlikely to cause achlorhydria or gastric atrophy, even in the presence of *H. pylori* infection. These potential issues may be of greater concern in regions such as Asia and Latin America, where acid-related symptoms are more likely to be attributable to *H. pylori* infection, peptic ulcers, or an underlying malignancy [25], which should be considered when initiating any form of PPI therapy.

3. When taken in accordance with label instructions, PPIs have not been shown to meaningfully delay the presentation of early gastric cancer. Available OTC PPIs would not be expected to differ.

A+: 78%; **A:** 22%
Recommendation: Strong
Evidence: ★★

No randomized, controlled trials (RCTs) were identified that directly addressed this topic, but observational studies

analyzing the association between PPI use and gastric cancer incidence have been conducted. The various case reports that were identified describe patients and use patterns that are inconsistent with OTC PPIs in terms of the dose and duration of treatment [26–30]. In a population-based cohort study, a 2-fold greater risk of gastric cancer was observed in patients with ≥15 PPI prescriptions [31], yet no increased risk was observed with prolonged PPI exposure in a recent US Food and Drug Administration (FDA)-mandated follow-up study conducted with pantoprazole [32]. The identified studies did not focus specifically on early gastric cancer; furthermore, they were biased by the populations that were assessed, as well as types of analyses [12, 17, 18, 33, 34]. Most studies showed that any potential effects of PPIs tend to disappear with time and that the most likely explanation for the effects is confounding by indication rather than causality. Additionally, *H. pylori* infection status was not routinely determined in these studies. Importantly, early gastric cancer is likely to be asymptomatic, and any presenting symptoms would likely be inconsistent with acid reflux [35–37], so there is no indication that early gastric cancer causes symptoms that would prompt patients to seek PPI treatment. Additional details and results of studies conducted in this area are provided in Data Summaries (Online Resource 4).

4. When taken in accordance with label instructions, OTC PPIs may improve symptoms of peptic ulcer or GERD but are extremely unlikely to adversely affect the natural history of the conditions. Individuals with persistent (>1 month) or recurrent symptoms after use of an OTC PPI should consult a physician.

A+: 56%; **A:** 33%; **D:** 11%
Recommendation: Strong
Evidence: ★

No RCTs have evaluated the use of OTC PPIs in the treatment of peptic ulcer disease or severe GERD (i.e. erosive esophagitis). However, it is likely that patients with these conditions will not experience adequate symptom response to self-treatment with an OTC PPI or their symptoms will recur rapidly after a 2-week course of therapy [38, 39]. Individuals with frequent heartburn who receive treatment with an OTC PPI for 2 weeks are likely to respond adequately and not experience early symptom recurrences, but those who do should be referred to a physician for further evaluation [40, 41]. Additionally, frequent heartburn that is consistent with what is described in OTC PPI labelling is not generally associated with more serious conditions or significant endoscopy results [42]. A description of additional details related to this topic is provided in Data Summaries (Online Resource 4) [43, 44].

5. Patients with upper gastrointestinal alarm features should be referred for endoscopy.

A+: 100%
Recommendation: Strong
Evidence: ★★

Although esophageal and gastric cancers are a global concern, the risk is greater in developing countries [45, 46]. Some Asian countries with particularly high gastric cancer rates have implemented national screening programs [47]. Screening is not recommended in developed countries where individuals with typical reflux symptoms or dyspepsia have an extremely low probability of underlying malignancy [45, 47–51]. Screening may therefore not be directly relevant to OTC PPIs, which are used for individuals experiencing reflux symptoms. However, because there are concerns about the potential for use of OTC PPIs to delay seeking treatment for a more serious underlying condition, this statement was included to acknowledge the issue. The relevant issue is whether patients with upper gastrointestinal (GI) symptoms should be investigated or whether it is reasonable to offer OTC PPI therapy, at least in patients who are not experiencing alarm features. Those with alarm features—presumably indicating more advanced disease—may have poorer outcomes than those without alarm features [52]. However, while the presence of alarm features indicates a need for endoscopy, their absence does not preclude the presence of esophageal or gastric malignancy, particularly in high-risk populations [53, 54]. A description of the issues associated with low diagnostic yield and low sensitivity of alarm features is provided in Data Summaries (Online Resource 4).

6. Baseline or routine monitoring of iron, calcium, magnesium, and vitamin B_{12} levels in those taking OTC PPIs is not necessary.

A+: 100%
Recommendation: Strong
Evidence: ★★★

Data from nested case–control studies, case reports, and controlled trials suggesting that acid-suppressive therapy may reduce the absorption of iron, calcium, magnesium, and vitamin B_{12} [55–58] have raised concerns about micronutrient deficiencies in individuals taking PPIs. However, data from controlled trials suggest long-term prescription PPI use has little effect on the absorption of these nutrients [3, 55, 59–61]. Therefore, intermittent OTC PPI use would not be expected to have any deleterious effect on absorption of micronutrients. The FDA specifically warns clinicians about the potential for long-term prescription PPI use to lower serum magnesium levels, but they report that OTC PPI use consistent with the directions

in the labelling will have very little risk of causing hypomagnesemia [62]. As in other areas, patients with pre-existing conditions or those taking concomitant medications that can lead to the malabsorption of these elements should consult their healthcare provider. A summary of LOTUS (Long-Term Usage of Esomeprazole vs. Surgery for Treatment of Chronic GERD) and SOPRAN (Safety of Omeprazole in Peptic Reflux Esophagitis: A Nordic Open Study), studies that analyzed vitamin and mineral absorption with long-term acid-suppressive therapy, is provided in Data Summaries (Online Resource 4).

7. Patients requiring repeated courses of OTC PPIs do not need baseline bone density measurement or bone density monitoring unless other clinical risk factors are present.

A+: 100%
Recommendation: Strong
Evidence: ★★★

Because gastric acid plays an essential role in the intestinal absorption of dietary insoluble calcium salts, there is biological plausibility that PPI-induced hypochlorhydria may reduce fractional calcium absorption [56, 63–65]. Thus, PPIs may, theoretically, lead to decreased bone mineral density (BMD) and an increased fracture risk. However, these concerns related to PPI use are controversial in terms of causality and are often based on misinterpreted data resulting from a stratification bias associated with exposure risks. The totality of data from long-term studies conducted with prescription doses of PPIs indicates that there is a limited independent risk for BMD loss or fractures [65–72]. Additionally, any potential risk is likely related to higher doses and long-term treatment. Therefore, the occurrence of these bone complications with intermittent use of PPIs at OTC doses is expected to be inconsequential, which is consistent with a statement provided by the FDA on this topic [73]. A description of some key observational studies that analyzed the role of PPI use and BMD is included in Data Summaries (Online Resource 4).

8. There are rare idiosyncratic drug reactions that may be associated with PPIs.

A+: 78%; **A:** 22%
Recommendation: Strong
Evidence: ★★

The level of evidence supporting the relationship between PPIs use and two important idiosyncratic drug reactions [i.e. acute interstitial nephritis (AIN) and subacute cutaneous lupus erythematosus (SCLE)], which is derived from case series and small nested case–control studies, is low [74–77]. Nevertheless, as for any other medication, clinicians should consider PPIs to be potential contributors and immediately discontinue use in patients who develop AIN or SCLE within weeks or months of initiating treatment. Subsequent reintroduction might be considered after the clinical course is carefully assessed. A description of some key studies that analyzed these idiosyncratic drug reactions and PPIs is provided in Data Summaries (Online Resource 4).

9. Patients who have ascites secondary to cirrhosis should be advised to consult a physician about the slightly increased risk for spontaneous bacterial peritonitis. Although this association has been reported for only prescribed PPIs, the relative risk with OTC PPI use has not been studied. A risk/benefit assessment for any PPI use in these patients, with close monitoring, is warranted.

A+: 56%; **A:** 44%
Recommendation: Strong
Evidence: ★

In cirrhotic patients, spontaneous bacterial peritonitis (SBP) occurs in 10%–30% of inpatients [78] and 3.5% of asymptomatic outpatients [79]. SBP is associated with substantial morbidity [80] and a 1-year mortality exceeding 60% [81]. Although prescription PPIs have been associated with an increased risk of SBP in cirrhotics with ascites [82–85], the relationship with OTC PPIs has not been specifically examined. It is unclear how PPIs might cause SBP, but translocation of small intestinal bacteria into the peritoneal cavity, facilitated by impaired immunity and increased small intestinal permeability in liver disease, may be exacerbated by bacterial overgrowth secondary to reduced gastric acidity [80]. It is recommended that patients with cirrhosis be evaluated by a gastroenterologist or hepatologist before initiating therapy with a PPI or histamine 2 receptor antagonist (H_2RA) to ensure such treatment is indicated. A more detailed description of some key studies that assessed the risk for SBP in PPI users is included in Data Summaries (Online Resource 4).

10. It is very unlikely that OTC PPI therapy leads to an increased risk of community-acquired pneumonia.

A+: 78%; **A:** 22%
Recommendation: Strong
Evidence: ★★

In the USA, 4.2 million ambulatory care cases of community-acquired pneumonia (CAP) were reported in 2006, with mortality rates of 3.8–8.5% for 2007–2008 [86]. The mechanisms underlying the relationship between acid suppression and respiratory infection have not been clearly

established. However, it has been postulated that acid suppression allows bacteria, viruses, fungi, and other organisms to proliferate in the proximal GI tract, whence they can reflux into the upper and then lower respiratory tract [87]. Importantly, however, GERD itself is associated with an increased risk of bronchitis and pneumonia [88]. The strongest association between PPI use and CAP is reported with short-duration therapy, suggesting protopathic bias consistent with GERD as a confounder rather than with PPI therapy as the cause of CAP [86, 87, 89–93]. This interpretation is supported by the finding that PPI use is not associated with an increased hospitalization for CAP in nonsteroidal anti-inflammatory drug users who do not have GERD [94]. Additional background information and more detailed descriptions of key studies of the risk for CAP in PPI users are provided in Data Summaries (Online Resource 4) [95].

11. Use of OTC PPIs may increase risk of infectious diarrhea.

A+: 67%; **A:** 33%
Recommendation: Strong
Evidence: ★★★

Infectious traveler's diarrhea is highly prevalent; attack rates range from 30 to 70% in higher-risk regions, such as the Middle East, Africa, Central and South America, and much of Asia [96]. There is biological plausibility that PPIs increase the risk of bacterial enteric infection by decreasing the gastric acid barrier to ingested organisms and potentially altering gut flora [97–102]. The impact of intermittent, short-term PPI treatment consistent with OTC labelling on the risk for bacterial enteric infections is unclear. The decision to continue using PPIs while travelling should be individualized based on the relative risks and benefits. Additional background information and more detailed descriptions of key studies that assessed the risk for infectious diarrhea with PPI use are provided in Data Summaries (Online Resource 4) [103–105].

12. The use of OTC PPIs is not strongly associated with increased risk of *Clostridium difficile* infection. There is insufficient evidence to determine an associated causal risk of relapsing *C. difficile* infection.

A+: 33%; **A:** 67%
Recommendation: Strong
Evidence: ★★★

In the USA, there are an estimated half-million cases of *C. difficile* infection per year, leading to 29,000 deaths within 30 days of diagnosis [106, 107]. Results of observational studies suggest that it is biologically plausible that PPIs may potentially increase the risk of *C. difficile* infection by decreasing the gastric acid barrier or negatively impacting the gut microbiome, allowing for survival and/or passage of vegetative forms of the bacteria [97, 102, 108–113]. Notably, however, the spore form, which is commonly the infective form of the organism, is not susceptible to gastric acid [111]. After an extensive review, the FDA concluded that PPI use could be associated with *C. difficile* infection, but the majority of reviewed studies only reported odds ratios (ORs) of <3, which are generally too low to establish causality [114]. Importantly, inappropriate PPI use is widespread, particularly in hospitals where higher doses are used [115, 116]. Given the risk for inappropriate use of PPIs, acid-suppressive therapy should be used cautiously in at-risk patients. It is unlikely that use of OTC PPIs by outpatients substantially increases the risk of *C. difficile*. In scenarios where there is a high risk of *C. difficile* infection, the need for PPIs should be reviewed, particularly in those with histories of *C. difficile* infection and/or a need for broad spectrum antibiotics [102]. Additional background information and more detailed descriptions of key studies that assessed the risk of *C. difficile* infection with PPI use are provided in Data Summaries (Online Resource 4) [117].

13. Patients taking medication, the absorption, metabolism, or effect of which may be affected significantly by PPI therapy, should be advised to consult with a healthcare professional before starting OTC PPI therapy.

A+: 100%
Recommendation: Strong
Evidence: ★

PPIs may interact with other medications by decreasing gastric acidity (leading to subsequent changes in solubility and absorption), by modifying metabolism [most commonly through the cytochrome P450 (CYP) enzyme system], or by inhibiting extragastric renal proton pumps (leading to altered drug excretion) [118, 119].

The solubility of atazanavir decreases at high pH in vitro, leading to an 87% reduction in exposure when administered in a buffered solution [120, 121]. Pharmacokinetic studies conducted in healthy volunteers have reported widely varying degrees of decreased exposure (10–94%) of atazanavir with concurrent use of an H_2RA or PPI based on the timing of administration [121]. The clinical relevance of this interaction is unclear because the effect of acid suppression is mitigated if atazanavir is taken approximately 16 hours after the PPI and because atazanavir treatment outcomes are affected by other factors, in particular, adherence to antiviral therapy [122]. The potential effect of increased pH on ledipasvir solubility

may also be mitigated by using acid suppressive therapies at different times of the day [123].

Citalopram and its *S*-enantiomer, escitalopram, are selective serotonin reuptake inhibitors that are metabolized primarily by CYP3A4 and CYP2C19, and at higher doses citalopram and escitalopram are associated with QT interval prolongation [124]. The FDA has recommended that the maximum dose of citalopram should be 20 mg daily in older adults [124]. Based on the analysis of a therapeutic drug monitoring database reporting markedly increased serum escitalopram concentrations in patients taking omeprazole and esomeprazole, the authors proposed a dose reduction of 50% for escitalopram if coprescribed with omeprazole or esomeprazole [125].

Renal proton pump inhibition is thought to be the mechanism whereby PPIs decrease methotrexate clearance; however, the clinical significance of this interaction is likely to be small [126]. PPI coadministration, therefore, is very unlikely to have any adverse impacts on patients taking low, immunomodulatory doses of methotrexate for inflammatory bowel disease, rheumatoid arthritis, or psoriasis.

Although the clinical relevance of these potential interactions is unclear, for patients with serious concomitant medical conditions requiring use of immunosuppressive, antiviral (e.g. for human immunodeficiency virus or hepatitis C virus infection), or selective serotonin reuptake inhibitor treatment or chemotherapy, use of an OTC PPI should first be discussed with a healthcare provider. A description of a systematic review of PPI drug interaction studies and some other potential interactions is provided in Data Summaries (Online Resource 4) [127–138].

14. The pharmacodynamic interaction of clopidogrel with omeprazole and esomeprazole has not been shown to have clinically meaningful adverse cardiovascular effects. Individuals being treated with clopidogrel may continue using OTC PPIs.

A+: 33%; **A:** 56%; **U:** 11%
Recommendation: Strong
Evidence: ★★★★

There is ample evidence showing that PPIs can be safely used in conjunction with clopidogrel to reduce the risk of GI bleeding in patients requiring anticoagulant therapy [139–142]. However, a recent systematic review of observational studies has suggested a potential negative effect on cardiovascular outcomes (ORs $\leq$1.4) in patients treated with a PPI and clopidogrel, which is unlikely to be clinically relevant [143]. Conversely, controlled trials conducted with PPIs and clopidogrel have not demonstrated any effects on cardiovascular outcomes [139, 144]. Although more rigorous data are needed to more clearly quantify the potential risks of using PPIs with clopidogrel, clinical experience suggests that the risk of negative cardiovascular effects is low. A description of background information and key studies that assessed the interaction between clopidogrel and PPIs is provided in Data Summaries (Online Resource 4) [145–148].

15. It is extremely unlikely that PPIs increase risk for myocardial infarction. OTC PPIs would not be expected to differ.

A+: 89%; **A:** 11%
Recommendation: Strong
Evidence: ★

One postulated mechanism by which PPIs might cause adverse cardiovascular events involves increasing asymmetric dimethyl arginine (ADMA), a known risk factor for cardiovascular events, which leads to decreased nitric oxide synthesis and endothelium-dependent vasodilation [149]. PPIs are thought to increase ADMA by binding to and inhibiting dimethylarginine dimethylaminohydrolase, which is responsible for metabolizing ADMA [150]. However, the available data suggest that the potential for PPIs to cause myocardial infarction is low, and that any observed association is likely attributable to other risk factors [151–153]. A detailed description of the studies that assessed the risk for adverse cardiovascular outcomes with PPI use is provided in Data Summaries (Online Resource 4).

16. There is no contraindication for the use of category B OTC PPIs for heartburn during pregnancy.

A+: 56%; **A:** 44%
Recommendation: Strong
Evidence: ★★★

Gastroesophageal reflux symptoms commonly occur during pregnancy [154, 155]. The FDA classifies omeprazole as category C based on potential embryotoxic and fetotoxic effects in animal studies and similar concerns from human case reports; all other PPIs are category B (no fetal teratogenicity or harm; limited human pregnancy data) [156, 157]. The American College of Gastroenterology treatment guidelines recommend using PPIs when clinically indicated during pregnancy [51], although a step-up treatment approach should be utilized, beginning with lifestyle changes, antacids/alginates, H_2RAs, then culminating with PPIs [156, 158]. During pregnancy, an obstetrician should always be consulted before any form of pharmacotherapy is initiated. A more detailed description of key studies conducted in pregnant women receiving PPI therapy is provided in Data Summaries (Online Resource 4) [159–161].

17. There is a rapid treatment response for heartburn with OTC PPIs, which begins on day 1 for many patients.

A+: 78%; **A:** 22%
Recommendation: Strong
Evidence: ★★★★

Although PPIs often require multiple doses to produce their full therapeutic effects [162, 163], a significant proportion of individuals will experience significant changes in gastric pH and associated reductions in symptom frequency and severity beginning on the first day of treatment with an OTC PPI [164–170]. Some patients report symptom relief on the first day of PPI therapy, but the proportion of patients who respond increases steadily during the 14-day treatment period. By day 14, the percentages of heartburn-free days among those treated with omeprazole 20 mg, lansoprazole 15 mg, and esomeprazole 20 mg were 45–70% [166, 167, 169, 171]. There are data demonstrating that certain PPIs have more rapid effects on intragastric pH [172]. However, whether these differences produce a clinically relevant effect on symptom response has not been established. A more detailed description of the results of these studies is provided in Data Summaries (Online Resource 4).

18. As there is a rapid treatment response for heartburn-related sleep impairment with PPIs, which begins on day 1 in many patients, OTC PPIs are likely to have the same effect.

A+: 67%; **A:** 33%
Recommendation: Strong
Evidence: ★★★

Nocturnal reflux symptoms and related sleep impairments are common and can have a significant negative effect on quality of life, general well-being, and functionality [173–175]. PPIs, including pantoprazole 20 mg, lansoprazole 15 and 30 mg, and rabeprazole 10 and 20 mg, have been shown to have a significant impact on nighttime heartburn beginning on the first day of treatment [168–170]. In two studies conducted with individuals not specifically experiencing nocturnal heartburn, 43–46% of those treated with esomeprazole 20 mg were heartburn free on the first night of treatment [171]. A more detailed description of these study results is provided in Data Summaries (Online Resource 4) [176, 177].

4 Discussion

Many of the recommendations of this consensus panel are based on indirect evidence, as potentially relevant studies were not generally conducted in the OTC setting. In the absence of direct evidence, results from studies in other clinical scenarios were reviewed and extrapolated to OTC use. The studies that were reviewed differed from the OTC setting in terms of using higher doses, longer durations of therapy, and enrollment of more severely ill patients, yet any effect would not be expected to differ meaningfully from what would be observed with OTC PPIs. Notably, where there was an established or expected relationship between the outcome and cumulative drug exposure, the effect may be even less pronounced with OTC PPIs. In such cases, consideration was made for the applicability to the OTC setting. If there was an absence of risk in this scenario, an assumption was made that lower doses taken for shorter durations in a generally healthier population would pose no greater risk than prescription PPIs. From a practical standpoint, the process of extrapolating findings from these studies may have been further complicated by the lack of consistency in labelling for different products in different regions. For example, in the USA, the labelling for OTC PPIs indicates that they should be taken for 14 days and that a physician should be consulted if more than one course of treatment every four months is necessary [163]. In the EU, the duration of treatment for nonprescription PPIs is up to 2 weeks, but the labelling specifically states that when complete symptom relief is experienced, treatment should be discontinued [178]. In addition, there is no limitation on the number of treatment courses that can be taken annually. Because these differences are relatively minor, the material impact of these variations is not known. For many statements, a qualifier was used (i.e. "when taken in accordance with label instructions") to account for variations in approved indications and usage instructions. Although these limitations are regrettable, they reflect the data that are available in the scientific literature, and in our opinion this lack of data provides additional support for our decision to convene this consensus panel. The Delphi process is utilized for areas of research where the data are limited and incomplete to allow for experts in the area to provide their opinion of available data. This is particularly pertinent for a class of drugs that is becoming more widely available without the need to consult a physician.

A potential issue associated with use of OTC PPIs involves allowing consumers direct access to these products without the need to consult a physician, which could lead to inappropriate use by some individuals. Although this is a potential concern, real-world-use data suggest that individuals using OTC PPIs self-select appropriately based on symptom presentation and are more likely to take the appropriate number of doses or fewer rather than take more than is recommended [179]. In addition, these data show that those who required more than the recommended doses

frequently consulted a physician. Other studies also suggest that individuals with frequent symptoms of gastroesophageal reflux will consult a physician when their symptoms become more severe or frequent, significantly impact their daily lives, or if alarm features appear [180, 181].

Consistent with the tenets of evidence-based medicine, results of RCTs were considered paramount. However, definitive data from these studies were not widely available and may never be conducted in many instances, particularly in relation to safety. As such, available epidemiological data from large administrative databases and observational studies were interpreted cautiously, due to the inherent limitation in their ability to inform clinical practice as they are not designed to determine causality, are subject to biases from potential confounding variables, and often evaluate multiple endpoints [182]. As a result, the risk for observing spurious effects is increased. It has, therefore, been suggested that outcomes with ORs <3–4 may be the result of these extrinsic factors rather than the treatment or other variable that is being evaluated [182, 183]. Thus, findings from observational studies that do not reach this threshold—even if statistically significant—may not have any actual clinical significance, particularly if the underlying mechanisms have not been established. Notably, subsequent to conducting the literature reviews used for this consensus panel, additional studies have been published that reported an increased risk for chronic kidney disease [184] and dementia [185] associated with PPI use. However, as is noted above and by the authors of these reports, there are significant limitations with these studies that preclude establishing a causal relationship between these events and PPI use. As a result, we did not feel the need to reconvene this panel to address these reports.

5 Conclusions

Consensus statements and accompanying evidence-based reviews were developed to provide guidance on the safe and appropriate use of OTC PPIs for treating frequent heartburn. Although direct evidence for many areas was limited, based on the available empirical evidence and clinical experience accumulated over nearly 30 years with prescription and OTC PPIs, the panel considers that OTC PPIs are generally safe and effective when used according to the label instructions. To minimize the risk of adverse outcomes associated with OTC PPIs, healthcare professionals should provide guidance to individuals taking them to help them make appropriate treatment decisions and to help identify specific risk factors.

Acknowledgements The authors thank Tore Lind, MD, PhD, for his thoughtful input, guidance, and expertise in support of this manuscript.

Compliance with Ethical Standards

Financial support Pfizer Consumer Healthcare provided funding for the live consensus panel meeting and provided recommendations and background information on prospective members of the panel (with final decisions determined by the co-chairs). Literature search assistance and writing/editorial assistance for the publication were provided by Dennis Stancavish, MA, and Diane Sloan, PharmD, of Peloton Advantage and were funded by Pfizer.

Potential conflict of interest David A. Johnson, MD, is a paid consultant to Pfizer Consumer Healthcare and serves as an advisor for Pfizer. Philip O. Katz, MD, is a paid consultant to Pfizer Consumer Healthcare. David Armstrong, MA, MB BChir, has received an honorarium from Pfizer Consumer Healthcare and serves as an advisor for Pfizer. Henry Cohen, MD, has received an honorarium from Pfizer Consumer Healthcare. Brendan C. Delaney, MD, is a paid consultant to Pfizer Consumer Healthcare. Colin W. Howden, MD, has received an honorarium from Pfizer Consumer Healthcare. Peter Katelaris, MD, is a paid consultant to Pfizer Consumer Healthcare. Radu I. Tutuian, MD, PhD, has received an honorarium from Pfizer Consumer Healthcare. Donald O. Castell, MD, has no conflicts to disclose.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Boardman HF, Delaney BC, Haag S. Partnership in optimizing management of reflux symptoms: a treatment algorithm for over-the-counter proton-pump inhibitors. Curr Med Res Opin. 2015;31(7):1309–18.
2. Scarpignato C, Gatta L, Zullo A, Blandizzi C. Effective and safe proton pump inhibitor therapy in acid-related diseases—a position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016;14(1):179.
3. Ali T, Roberts DN, Tierney WM. Long-term safety concerns with proton pump inhibitors. Am J Med. 2009;122(10):896–903.
4. Prilosec [package insert]. Wilmington: AstraZeneca Pharmaceuticals; 2012.
5. Prilosec OTC [product monograph]. Cincinnati: Procter & Gamble; 2014.
6. Boardman HF, Heeley G. The role of the pharmacist in the selection and use of over-the-counter proton-pump inhibitors. Int J Clin Pharm. 2015;37(5):709–16.
7. de Villiers MR, de Villiers PJ, Kent AP. The Delphi technique in health sciences education research. Med Teach. 2005;27(7):639–43.
8. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials:

recommendations for the future based on a systematic review of existing studies. PLoS Med. 2011;8(1):e1000393.
9. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
10. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 2015;64(3):381–7.
11. Hippisley-Cox J, Coupland C. Identifying patients with suspected gastro-oesophageal cancer in primary care: derivation and validation of an algorithm. Br J Gen Pract. 2011;61(592):e707–14.
12. Lassen A, Hallas J, de Muckadell OB. The risk of missed gastroesophageal cancer diagnoses in users and nonusers of antisecretory medication. Gastroenterology. 2005;129(4):1179–86.
13. Milind R, Attwood SE. Natural history of Barrett's esophagus. World J Gastroenterol. 2012;18(27):3483–91.
14. Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 2014;63(8):1229–37.
15. Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut. 2012;61(7):970–6.
16. Abrams JA, Sharaiha RZ, Gonsalves L, Lightdale CJ, Neugut AI. Dating the rise of esophageal adenocarcinoma: analysis of Connecticut Tumor Registry data, 1940–2007. Cancer Epidemiol Biomark Prev. 2011;20(1):183–6.
17. Garcia Rodriguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. Gut. 2006;55(11):1538–44.
18. Bateman DN, Colin-Jones D, Hartz S, Langman M, Logan RF, Mant J, et al. Mortality study of 18 000 patients treated with omeprazole. Gut. 2003;52(7):942–6.
19. Katz P, Kahrilas P, Johnson D, Lind T, Rohss K, Traxler B, et al. Daytime intragastric acid control: post hoc analyses of esomeprazole 20 mg and over-the-counter proton-pump inhibitors. Ther Adv Gastroenterol. 2015;8(6):322–30.
20. Wilder-Smith C, Backlund A, Eckerwall G, Lind T, Fjellman M, Rohss K. Effect of increasing esomeprazole and pantoprazole doses on acid control in patients with symptoms of gastro-oesophageal reflux disease: a randomized, dose–response study. Clin Drug Investig. 2008;28(6):333–43.
21. Savarino V, Mela GS, Zentilin P, Bisso G, Pivari M, Vigneri S, et al. Comparison of 24-h control of gastric acidity by three different dosages of pantoprazole in patients with duodenal ulcer. Aliment Pharmacol Ther. 1998;12(12):1241–7.
22. Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. Aliment Pharmacol Ther. 2015;42(6):719–30.
23. Lundell L, Vieth M, Gibson F, Nagy P, Kahrilas PJ. Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. Aliment Pharmacol Ther. 2015;42(6):649–63.
24. Kuipers EJ. Proton pump inhibitors and gastric neoplasia. Gut. 2006;55(9):1217–21.
25. World Gastroenterology Organisation global guideline: *Helicobacter pylori* in developing countries. J Dig Dis. 2011;12(5):319–26.
26. Wong H, Yau T, Chan P, Ng IO, Chan G, Hui P, et al. PPI-delayed diagnosis of gastrinoma: oncologic victim of pharmacologic success. Pathol Oncol Res. 2010;16(1):87–91.
27. Wayman J, Hayes N, Griffin SM. The response of early gastric cancer to proton-pump inhibitors. N Engl J Med. 1998;338(26):1924–5.
28. Wayman J, Hayes N, Raimes SA, Griffin SM. Prescription of proton pump inhibitors before endoscopy. A potential cause of missed diagnosis of early gastric cancers. Arch Fam Med. 2000;9(4):385–8.
29. Tartaglia A, Vezzadini C, Bianchini S, Vezzadini P. Gastrinoma of the stomach: a case report. Int J Gastrointest Cancer. 2005;35(3):211–6.
30. Jianu CS, Fossmark R, Viset T, Qvigstad G, Sordal O, Marvik R, et al. Gastric carcinoids after long-term use of a proton pump inhibitor. Aliment Pharmacol Ther. 2012;36(7):644–9.
31. Poulsen AH, Christensen S, McLaughlin JK, Thomsen RW, Sorensen HT, Olsen JH, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer. 2009;100(9):1503–7.
32. Schneider JL, Kolitsopoulos F, Corley DA. Risk of gastric cancer, gastrointestinal cancers and other cancers: a comparison of treatment with pantoprazole and other proton pump inhibitors. Aliment Pharmacol Ther. 2016;43(1):73–82.
33. Ahn JS, Eom CS, Jeon CY, Park SM. Acid suppressive drugs and gastric cancer: a meta-analysis of observational studies. World J Gastroenterol. 2013;19(16):2560–8.
34. Tamim H, Duranceau A, Chen LQ, Lelorier J. Association between use of acid-suppressive drugs and risk of gastric cancer. A nested case–control study. Drug Saf. 2008;31(8):675–84.
35. Meyer C, Lozac'h P, Rohr S, Topar P, Youssef C. Gastric cancer: the French survey. Acta Gastroenterol Belg. 2002;65(3):161–5.
36. What you need to know about stomach cancer. Rockville: National Cancer Institute; 2009.
37. Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. Gastric Cancer. 2006;9(4):315–9.
38. Holtmann G, Bigard MA, Malfertheiner P, Pounder R. Guidance on the use of over-the-counter proton pump inhibitors for the treatment of GERD. Int J Clin Pharm. 2011;33(3):493–500.
39. Haag S, Andrews JM, Katelaris PH, Gapasin J, Galmiche JP, Hunt R, et al. Management of reflux symptoms with over-the-counter proton pump inhibitors: issues and proposed guidelines. Digestion. 2009;80(4):226–34.
40. Hunt R, Quigley E, Abbas Z, Eliakim A, Emmanuel A, Goh KL, et al. Coping with common gastrointestinal symptoms in the community: a global perspective on heartburn, constipation, bloating, and abdominal pain/discomfort May 2013. J Clin Gastroenterol. 2014;48(7):567–78.
41. Wu JC, Chan FK, Ching JY, Leung WK, Lee YT, Sung JJ. Empirical treatment based on "typical" reflux symptoms is inappropriate in a population with a high prevalence of *Helicobacter pylori* infection. Gastrointest Endosc. 2002;55(4):461–5.
42. Ho KY, Gwee KA, Khor CJ, Selamat DS, Wai CT, Yeoh KG. Empirical treatment for the management of patients presenting with uninvestigated reflux symptoms: a prospective study in an Asian primary care population. Aliment Pharmacol Ther. 2005;21(11):1313–20.
43. Malfertheiner P, Nocon M, Vieth M, Stolte M, Jaspersen D, Koelz HR, et al. Evolution of gastro-oesophageal reflux disease over 5 years under routine medical care—the ProGERD study. Aliment Pharmacol Ther. 2012;35(1):154–64.
44. Coping with common GI symptoms in the community: a global perspective on heartburn, constipation, bloating, and abdominal pain/discomfort. World Gastroenterology Organisation website. 2013. http://www.worldgastroenterology.org/assets/export/userfiles/2013_FINAL_Common%20GI%20Symptoms%20_long.pdf. Accessed 25 May 2016.

45. Chen SL, Gwee KA, Lee JS, Miwa H, Suzuki H, Guo P, et al. Systematic review with meta-analysis: prompt endoscopy as the initial management strategy for uninvestigated dyspepsia in Asia. Aliment Pharmacol Ther. 2015;41(3):239–52.
46. Ferro A, Peleteiro B, Malvezzi M, Bosetti C, Bertuccio P, Levi F, et al. Worldwide trends in gastric cancer mortality (1980–2011), with predictions to 2015, and incidence by subtype. Eur J Cancer. 2014;50(7):1330–44.
47. Choi KS, Suh M. Screening for gastric cancer: the usefulness of endoscopy. Clin Endosc. 2014;47(6):490–6.
48. Shaukat A, Wang A, Acosta RD, Bruining DH, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in dyspepsia. Gastrointest Endosc. 2015;82(2):227–32.
49. Breslin NP, Thomson AB, Bailey RJ, Blustein PK, Meddings J, Lalor E, et al. Gastric cancer and other endoscopic diagnoses in patients with benign dyspepsia. Gut. 2000;46(1):93–7.
50. Vakil N, Talley N, van Zanten SV, Flook N, Persson T, Bjorck E, et al. Cost of detecting malignant lesions by endoscopy in 2741 primary care dyspeptic patients without alarm symptoms. Clin Gastroenterol Hepatol. 2009;7(7):756–61.
51. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–28.
52. Bowrey DJ, Griffin SM, Wayman J, Karat D, Hayes N, Raimes SA. Use of alarm symptoms to select dyspeptics for endoscopy causes patients with curable esophagogastric cancer to be overlooked. Surg Endosc. 2006;20(11):1725–8.
53. Fransen GA, Janssen MJ, Muris JW, Laheij RJ, Jansen JB. Meta-analysis: the diagnostic value of alarm symptoms for upper gastrointestinal malignancy. Aliment Pharmacol Ther. 2004;20(10):1045–52.
54. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology. 2006;131(2):390–401.
55. Termanini B, Gibril F, Sutliff VE, Yu F, Venzon DJ, Jensen RT. Effect of long-term gastric acid suppressive therapy on serum vitamin B12 levels in patients with Zollinger–Ellison syndrome. Am J Med. 1998;104(5):422–30.
56. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med. 2005;118(7):778–81.
57. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med. 2006;355(17):1834–6.
58. Koulouridis I, Alfayez M, Tighiouart H, Madias NE, Kent DM, Paulus JK, et al. Out-of-hospital use of proton pump inhibitors and hypomagnesemia at hospital admission: a nested case–control study. Am J Kidney Dis. 2013;62(4):730–7.
59. Attwood SE, Ell C, Galmiche JP, Fiocca R, Hatlebakk JG, Hasselgren B, et al. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. Aliment Pharmacol Ther. 2015;41(11):1162–74.
60. den Elzen WP, Groeneveld Y, de Ruijter W, Souverijn JH, Le CS, Assendelft WJ, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Aliment Pharmacol Ther. 2008;27(6):491–7.
61. Hirschowitz BI, Worthington J, Mohnen J. Vitamin B12 deficiency in hypersecretors during long-term acid suppression with proton pump inhibitors. Aliment Pharmacol Ther. 2008;27(11):1110–21.
62. FDA drug safety communication: low magnesium levels can be associated with long-term use of proton pump inhibitor drugs (PPIs). 2011. http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm. Accessed 24 Jan 2017.
63. Kopic S, Geibel JP. Gastric acid, calcium absorption, and their impact on bone health. Physiol Rev. 2013;93(1):189–268.
64. Mattsson JP, Vaananen K, Wallmark B, Lorentzon P. Omeprazole and bafilomycin, two proton pump inhibitors: differentiation of their effects on gastric, kidney and bone H(+)-translocating ATPases. Biochim Biophys Acta. 1991;1065(2):261–8.
65. Wright MJ, Sullivan RR, Gaffney-Stomberg E, Caseria DM, O'Brien KO, Proctor DD, et al. Inhibiting gastric acid production does not affect intestinal calcium absorption in young, healthy individuals: a randomized, crossover, controlled clinical trial. J Bone Miner Res. 2010;25(10):2205–11.
66. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296(24):2947–53.
67. Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. Gastroenterology. 2010;139(1):93–101.
68. Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. Arch Intern Med. 2010;170(9):765–71.
69. Targownik LE, Lix LM, Leung S, Leslie WD. Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss. Gastroenterology. 2010;138(3):896–904.
70. Targownik LE, Leslie WD, Davison KS, Goltzman D, Jamal SA, Kreiger N, et al. The relationship between proton pump inhibitor use and longitudinal change in bone mineral density: a population-based study [corrected] from the Canadian Multicentre Osteoporosis Study (CaMos). Am J Gastroenterol. 2012;107(9):1361–9.
71. Hansen KE, Jones AN, Lindstrom MJ, Davis LA, Ziegler TE, Penniston KL, et al. Do proton pump inhibitors decrease calcium absorption? J Bone Miner Res. 2010;25(12):2786–95.
72. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2011;106(7):1209–18 **(quiz 19)**.
73. FDA drug safety communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. Food and Drug Administration. 2011. http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm213206.htm. Accessed 24 Aug 2016.
74. Sierra F, Suarez M, Rey M, Vela MF. Systematic review: proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther. 2007;26(4):545–53.
75. Blank ML, Parkin L, Paul C, Herbison P. A nationwide nested case–control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. Kidney Int. 2014;86(4):837–44.
76. Dam C, Bygum A. Subacute cutaneous lupus erythematosus induced or exacerbated by proton pump inhibitors. Acta Derm Venereol. 2008;88(1):87–9.
77. Gronhagen CM, Fored CM, Linder M, Granath F, Nyberg F. Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case–control study of 234 patients in Sweden. Br J Dermatol. 2012;167(2):296–305.
78. Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol. 2000;32(1):142–53.

79. Evans LT, Kim WR, Poterucha JJ, Kamath PS. Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites. Hepatology. 2003;37(4):897–901.
80. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. Gut. 2012;61(2):297–310.
81. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010;139(4):1246–56, 56.
82. Deshpande A, Pasupuleti V, Thota P, Pant C, Mapara S, Hassan S, et al. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. J Gastroenterol Hepatol. 2013;28(2):235–42.
83. Ratelle M, Perreault S, Villeneuve JP, Tremblay L. Association between proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhotic patients with ascites. Can J Gastroenterol Hepatol. 2014;28(6):330–4.
84. Chang SS, Lai CC, Lee MT, Lee YC, Tsai YW, Hsu WT, et al. Risk of spontaneous bacterial peritonitis associated with gastric acid suppression. Medicine (Baltimore). 2015;94(22):e944.
85. Min YW, Lim KS, Min BH, Gwak GY, Paik YH, Choi MS, et al. Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites: a propensity score matched cohort study. Aliment Pharmacol Ther. 2014;40(6):695–704.
86. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One. 2015;10(6):e0128004.
87. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ. 2011;183(3):310–9.
88. Gaude GS. Pulmonary manifestations of gastroesophageal reflux disease. Ann Thorac Med. 2009;4(3):115–23.
89. Sultan N, Nazareno J, Gregor J. Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. Can J Gastroenterol. 2008;22(9):761–6.
90. Garcia Rodriguez LA, Ruigomez A, Wallander MA, Johansson S. Acid-suppressive drugs and community-acquired pneumonia. Epidemiology. 2009;20(6):800–6.
91. Laheij RJ, Van Ijzendoorn MC, Janssen MJ, Jansen JB. Gastric acid-suppressive therapy and community-acquired respiratory infections. Aliment Pharmacol Ther. 2003;18(8):847–51.
92. Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. Aliment Pharmacol Ther. 2010;31(11):1165–77.
93. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004;292(16):1955–60.
94. Filion KB, Chateau D, Targownik LE, Gershon A, Durand M, Tamim H, et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut. 2014;63(4):552–8.
95. Jena AB, Sun E, Goldman DP. Confounding in the association of proton pump inhibitor use with risk of community-acquired pneumonia. J Gen Intern Med. 2013;28(2):223–30.
96. Connor BA. The pre-travel consultation self-treatable conditions: traveler's diarrhea. 2016 Yellow Book. 2016. http://www.nc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/travelers-diarrhea. Accessed 9 June 2016.
97. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol. 2007;102(9):2047–56.
98. Doorduyn Y, Van Den Brandhof WE, Van Duynhoven YT, Wannet WJ, Van PW. Risk factors for *Salmonella* Enteritidis and Typhimurium (DT104 and non-DT104) infections in The Netherlands: predominant roles for raw eggs in Enteritidis and sandboxes in Typhimurium infections. Epidemiol Infect. 2006;134(3):617–26.
99. Freeman R, Dabrera G, Lane C, Adams N, Browning L, Fowler T, et al. Association between use of proton pump inhibitors and non-typhoidal salmonellosis identified following investigation into an outbreak of *Salmonella mikawasima* in the UK. Epidemiol Infect. 2013;2015:1–8.
100. Doorduyn Y, Van Den Brandhof WE, Van Duynhoven YT, Breukink BJ, Wagenaar JA, Van PW. Risk factors for indigenous *Campylobacter jejuni* and *Campylobacter coli* infections in The Netherlands: a case–control study. Epidemiol Infect. 2010;138(10):1391–404.
101. DuPont HL, Formal SB, Hornick RB, Snyder MJ, Libonati JP, Sheahan DG, et al. Pathogenesis of *Escherichia coli* diarrhea. N Engl J Med. 1971;285(1):1–9.
102. Bavishi C, DuPont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther. 2011;34(11–12):1269–81.
103. Diemert DJ. Prevention and self-treatment of traveler's diarrhea. Clin Microbiol Rev. 2006;19(3):583–94.
104. Juckett G. Prevention and treatment of traveler's diarrhea. Am Fam Physician. 1999;60(1):119–24.
105. Schwille-Kiuntke J, Mazurak N, Enck P. Systematic review with meta-analysis: post-infectious irritable bowel syndrome after travellers' diarrhoea. Aliment Pharmacol Ther. 2015;41(11):1029–37.
106. Nearly half a million Americans suffered from *Clostridium difficile* infections in a single year [press release]. 2015. http://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html. Accessed 24 Aug 2016.
107. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372(9):825–34.
108. Dalton BR, Lye-Maccannell T, Henderson EA, Maccannell DR, Louie TJ. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low-endemicity, non-outbreak hospital setting. Aliment Pharmacol Ther. 2009;29(6):626–34.
109. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. *Clostridium difficile*-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012;107(7):1001–10.
110. Zacharioudakis IM, Zervou FN, Pliakos EE, Ziakas PD, Mylonakis E. Colonization with toxinogenic *C. difficile* upon hospital admission, and risk of infection: a systematic review and meta-analysis. Am J Gastroenterol. 2015;110(3):381–90.
111. Seto CT, Jeraldo P, Orenstein R, Chia N, DiBaise JK. Prolonged use of a proton pump inhibitor reduces microbial diversity: implications for *Clostridium difficile* susceptibility. Microbiome. 2014;2:42.
112. Jump RL, Pultz MJ, Donskey CJ. Vegetative *Clostridium difficile* survives in room air on moist surfaces and in gastric contents with reduced acidity: a potential mechanism to explain the association between proton pump inhibitors and *C. difficile*-associated diarrhea? Antimicrob Agents Chemother. 2007;51(8):2883–7.
113. Freedberg DE, Toussaint NC, Chen SP, Ratner AJ, Whittier S, Wang TC, et al. Proton pump inhibitors alter specific taxa in the human gastrointestinal microbiome: a crossover trial. Gastroenterology. 2015;149(4):883–5.
114. FDA drug safety communication: *Clostridium difficile*-associated diarrhea can be associated with stomach acid drugs known

as proton pump inhibitors (PPIs). 2013. http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm. Accessed 24 Aug 2016.
115. Choudhry MN, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with *Clostridium difficile*-associated disease. QJM. 2008;101(6):445–8.
116. 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(9):e228–34.
117. Parente F, Cucino C, Gallus S, Bargiggia S, Greco S, Pastore L, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. Aliment Pharmacol Ther. 2003;17(12):1503–6.
118. Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. Drug Saf. 2014;37(4):201–11.
119. Bezabeh S, Mackey AC, Kluetz P, Jappar D, Korvick J. Accumulating evidence for a drug–drug interaction between methotrexate and proton pump inhibitors. Oncologist. 2012;17(4):550–4.
120. Luber AD, Brower R, Kim D, Silverman R, Peloquin CA, Frank I. Steady-state pharmacokinetics of once-daily fosamprenavir/ritonavir and atazanavir/ritonavir alone and in combination with 20 mg omeprazole in healthy volunteers. HIV Med. 2007;8(7):457–64.
121. Beique L, Giguere P, la Porte C, Angel J. Interactions between protease inhibitors and acid-reducing agents: a systematic review. HIV Med. 2007;8(6):335–45.
122. Sahloff EG, Duggan JM. Clinical outcomes associated with concomitant use of atazanavir and proton pump inhibitors. Ann Pharmacother. 2006;40(10):1731–6.
123. Harvoni [summary of product characteristics]. London: Gilead Sciences; 2015.
124. Marcum ZA, Vande Griend JP, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. Am J Geriatr Pharmacother. 2012;10(4):264–71.
125. Gjestad C, Westin AA, Skogvoll E, Spigset O. Effect of proton pump inhibitors on the serum concentrations of the selective serotonin reuptake inhibitors citalopram, escitalopram, and sertraline. Ther Drug Monit. 2015;37(1):90–7.
126. Reeves DJ, Moore ES, Bascom D, Rensing B. Retrospective evaluation of methotrexate elimination when co-administered with proton pump inhibitors. Br J Clin Pharmacol. 2014;78(3):565–71.
127. Lahner E, Annibale B, Delle FG. Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy. Aliment Pharmacol Ther. 2009;29(12):1219–29.
128. Kofler S, Shvets N, Bigdeli AK, Konig MA, Kaczmarek P, Deutsch MA, et al. Proton pump inhibitors reduce mycophenolate exposure in heart transplant recipients-a prospective case–controlled study. Am J Transplant. 2009;9(7):1650–6.
129. Kofler S, Deutsch MA, Bigdeli AK, Shvets N, Vogeser M, Mueller TH, et al. Proton pump inhibitor co-medication reduces mycophenolate acid drug exposure in heart transplant recipients. J Heart Lung Transplant. 2009;28(6):605–11.
130. Rupprecht K, Schmidt C, Raspe A, Schweda F, Shipkova M, Fischer W, et al. Bioavailability of mycophenolate mofetil and enteric-coated mycophenolate sodium is differentially affected by pantoprazole in healthy volunteers. J Clin Pharmacol. 2009;49(10):1196–201.
131. Schaier M, Scholl C, Scharpf D, Hug F, Bonisch-Schmidt S, Dikow R, et al. Proton pump inhibitors interfere with the immunosuppressive potency of mycophenolate mofetil. Rheumatology (Oxford). 2010;49(11):2061–7.
132. Takahashi K, Motohashi H, Yonezawa A, Okuda M, Ito N, Yamamoto S, et al. Lansoprazole-tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. Ann Pharmacother. 2004;38(5):791–4.
133. Itagaki F, Homma M, Yuzawa K, Nishimura M, Naito S, Ueda N, et al. Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. J Pharm Pharmacol. 2004;56(8):1055–9.
134. Itagaki F, Homma M, Yuzawa K, Fukao K, Kohda Y. Drug interaction of tacrolimus and proton pump inhibitors in renal transplant recipients with CYP2C19 gene mutation. Transplant Proc. 2002;34(7):2777–8.
135. Kim S, Lee H, Park CH, Shim CN, Lee HJ, Park JC, et al. Clinical predictors associated with proton pump inhibitor-induced hypomagnesemia. Am J Ther. 2015;22(1):14–21.
136. Suzuki K, Doki K, Homma M, Tamaki H, Hori S, Ohtani H, et al. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. Br J Clin Pharmacol. 2009;67(1):44–9.
137. Methotrexate safety information. Food and Drug Administration. 2011. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm284421.htm. Accessed 24 Aug 2016.
138. Chan AJ, Rajakumar I. High-dose methotrexate in adult oncology patients: a case–control study assessing the risk association between drug interactions and methotrexate toxicity. J Oncol Pharm Pract. 2014;20(2):93–9.
139. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010;363(20):1909–17.
140. Cardoso RN, Benjo AM, DiNicolantonio JJ, Garcia DC, Macedo FY, El-Hayek G, et al. Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis. Open Heart. 2015;2(1):e000248.
141. Schjerning Olsen AM, Lindhardsen J, Gislason GH, McGettigan P, Hlatky MA, Fosbol E, et al. Impact of proton pump inhibitor treatment on gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use among post-myocardial infarction patients taking antithrombotics: nationwide study. BMJ. 2015;351:h5096.
142. Wang ZY, Chen M, Zhu LL, Yu LS, Zeng S, Xiang MX, et al. Pharmacokinetic drug interactions with clopidogrel: updated review and risk management in combination therapy. Ther Clin Risk Manag. 2015;11:449–67.
143. Sherwood MW, Melloni C, Jones WS, Washam JB, Hasselblad V, Dolor RJ. Individual proton pump inhibitors and outcomes in patients with coronary artery disease on dual antiplatelet therapy: a systematic review. J Am Heart Assoc. 2015;4(11):e002245.
144. Hsu PI, Lai KH, Liu CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. Gastroenterology. 2011;140(3):791–8.
145. Hulot JS, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood. 2006;108(7):2244–7.
146. Li XQ, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos. 2004;32(8):821–7.
147. Frelinger AL III, Lee RD, Mulford DJ, Wu J, Nudurupati S, Nigam A, et al. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state

pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. J Am Coll Cardiol. 2012;59(14):1304–11.
148. Arbel Y, Birati EY, Finkelstein A, Halkin A, Kletzel H, Abramowitz Y, et al. Platelet inhibitory effect of clopidogrel in patients treated with omeprazole, pantoprazole, and famotidine: a prospective, randomized, crossover study. Clin Cardiol. 2013;36(6):342–6.
149. Ghebremariam YT, LePendu P, Lee JC, Erlanson DA, Slaviero A, Shah NH, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation. 2013;128(8):845–53.
150. Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. PLoS One. 2015;10(6):e0124653.
151. Charlot M, Ahlehoff O, Norgaard ML, Jorgensen CH, Sorensen R, Abildstrom SZ, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. Ann Intern Med. 2010;153(6):378–86.
152. Shih CJ, Chen YT, Ou SM, Li SY, Chen TJ, Wang SJ. Proton pump inhibitor use represents an independent risk factor for myocardial infarction. Int J Cardiol. 2014;177(1):292–7.
153. Turkiewicz A, Vicente RP, Ohlsson H, Tyden P, Merlo J. Revising the link between proton-pump inhibitors and risk of acute myocardial infarction—a case-crossover analysis. Eur J Clin Pharmacol. 2015;71(1):125–9.
154. Rey E, Rodriguez-Artalejo F, Herraiz MA, Sanchez P, Alvarez-Sanchez A, Escudero M, et al. Gastroesophageal reflux symptoms during and after pregnancy: a longitudinal study. Am J Gastroenterol. 2007;102(11):2395–400.
155. Malfertheiner SF, Malfertheiner MV, Kropf S, Costa SD, Malfertheiner P. A prospective longitudinal cohort study: evolution of GERD symptoms during the course of pregnancy. BMC Gastroenterol. 2012;12:131.
156. Richter JE. Review article: the management of heartburn in pregnancy. Aliment Pharmacol Ther. 2005;22(9):749–57.
157. Dexilant [package insert]. Deerfield: Takeda Pharmaceuticals America, Inc.; 2015.
158. Majithia R, Johnson DA. Are proton pump inhibitors safe during pregnancy and lactation? Evidence to date. Drugs. 2012;72(2):171–9.
159. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med. 2010;363(22):2114–23.
160. Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. Am J Gastroenterol. 2009;104(6):1541–5.
161. Marshall JK, Thompson AB, Armstrong D. Omeprazole for refractory gastroesophageal reflux disease during pregnancy and lactation. Can J Gastroenterol. 1998;12(3):225–7.
162. Prevacid 24HR [drug facts label]. Parsippany: Novartis Consumer Health Inc; 2014.
163. Nexium 24HR [product labeling]. Madison: Pfizer Consumer Healthcare; 2014.
164. Miner PB Jr, Allgood LD, Grender JM. Comparison of gastric pH with omeprazole magnesium 20.6 mg (Prilosec OTC) o.m. famotidine 10 mg (Pepcid AC) b.d. and famotidine 20 mg b.d. over 14 days of treatment. Aliment Pharmacol Ther. 2007;25(1):103–9.
165. Hata S, Arai M, Maruoka D, Tanaka T, Matsumura T, Suzuki T, et al. Intragastric acidity during the first day following administration of low-dose proton pump inhibitors: a randomized crossover study. Clin Res Hepatol Gastroenterol. 2013;37(3):296–301.
166. Allgood LD, Grender JM, Shaw MJ, Peura DA. Comparison of Prilosec OTC (omeprazole magnesium 20.6 mg) to placebo for 14 days in the treatment of frequent heartburn. J Clin Pharm Ther. 2005;30(2):105–12.
167. Kushner PR, Snoddy AM, Gilderman L, Peura DA. Lansoprazole 15 mg once daily for 14 days is effective for treatment of frequent heartburn: results of 2 randomized, placebo-controlled, double-blind studies. Postgrad Med. 2009;121(4):67–75.
168. Haag S, Holtmann G. Onset of relief of symptoms of gastroesophageal reflux disease: post hoc analysis of two previously published studies comparing pantoprazole 20 mg once daily with nizatidine or ranitidine 150 mg twice daily. Clin Ther. 2010;32(4):678–90.
169. Peura DA, Riff DS, Snoddy AM, Fennerty MB. Clinical trial: lansoprazole 15 or 30 mg once daily vs. placebo for treatment of frequent nighttime heartburn in self-treating subjects. Aliment Pharmacol Ther. 2009;30(5):459–68.
170. Miner P Jr, Orr W, Filippone J, Jokubaitis L, Sloan S. Rabeprazole in nonerosive gastroesophageal reflux disease: a randomized placebo-controlled trial. Am J Gastroenterol. 2002;97(6):1332–9.
171. Peura DA, Traxler B, Kocun C, Lind T. Esomeprazole treatment of frequent heartburn: two randomized, double-blind, placebo-controlled trials. Postgrad Med. 2014;126(4):33–41.
172. Pantoflickova D, Dorta G, Ravic M, Jornod P, Blum AL. Acid inhibition on the first day of dosing: comparison of four proton pump inhibitors. Aliment Pharmacol Ther. 2003;17(12):1507–14.
173. Tack J, Becher A, Mulligan C, Johnson DA. Systematic review: the burden of disruptive gastro-oesophageal reflux disease on health-related quality of life. Aliment Pharmacol Ther. 2012;35(11):1257–66.
174. Farup C, Kleinman L, Sloan S, Ganoczy D, Chee E, Lee C, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. Arch Intern Med. 2001;161(1):45–52.
175. Mathias SD, Colwell HH, Miller DP, Pasta DJ, Henning JM, Ofman JJ. Health-Related quality-of-life and quality-days incrementally gained in symptomatic nonerosive GERD patients treated with lansoprazole or ranitidine. Dig Dis Sci. 2001;46(11):2416–23.
176. Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J, et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease—an analysis based on the ProGERD initiative. Aliment Pharmacol Ther. 2003;18(8):767–76.
177. Johnson DA, Le Moigne A, Hugo V, Nagy P. Rapid resolution of sleep disturbances related to frequent reflux: effect of esomeprazole 20 mg in 2 randomized, double-blind, controlled trials. Curr Med Res Opin. 2015;31(2):243–50.
178. Nexium Control (esomeprazole) [summary of product characteristics]. Kent: Pfizer Consumer Healthcare Ltd.; 2014.
179. Fendrick AM, Shaw M, Schachtel B, Allgood L, Allgood G, Grender J, et al. Self-selection and use patterns of over-the-counter omeprazole for frequent heartburn. Clin Gastroenterol Hepatol. 2004;2(1):17–21.
180. Bretagne JF, Honnorat C, Richard-Molard B, Caekaert A, Barthelemy P. Comparative study of characteristics and disease management between subjects with frequent and occasional gastro-oesophageal reflux symptoms. Aliment Pharmacol Ther. 2006;23(5):607–16.
181. Rey E, Moreno-Elola-Olaso C, Rodriguez-Artalejo F, Diaz-Rubio M. Medical consultation for gastro-oesophageal reflux symptoms: reasons and associated factors. Digestion. 2004;70(3):173–7.

182. Grimes DA, Schulz KF. False alarms and pseudo-epidemics: the limitations of observational epidemiology. Obstet Gynecol. 2012;120(4):920–7.
183. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
184. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Int Med. 2016;176(2):238–46.
185. Gomm W, von Holt K, Thome F, Broich K, Maier W, Fink A, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol. 2016;73(4):410–6.