PHARMACIST'S LETTER

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PRESCRIBER'S LETTER

Proton Pump Inhibitors: Appropriate Use and Safety Concerns

Proton pump inhibitors make up more than half of the gastrointestinal drug market, and are estimated to cost Americans 11 billion dollars each year.[1] However, data suggest that only one-third of PPI use is appropriate.[2-4] This misuse can have both negative financial and health-related consequences. Studies have shown there are risks associated with chronic use, and occasionally even short-term use, of PPIs.[5-7] Treatment guidelines, such as those for gastroesophageal reflux disease, help tease out appropriate use of these drugs based on the latest evidence for their benefits and risks.[8] This chart discusses the appropriate use of PPIs along with the safety concerns associated with them.

Abbreviations: ADMA = asymmetric dimethylarginine; BMD = bone mineral density; COX-2 = cyclooxygenase-2; CKD = chronic kidney disease; CV = cardiovascular; GERD = gastroesophageal reflux disease; GI = gastrointestinal; ICU = intensive care unit; IM = intramuscular; INR = international normalized ratio; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; OTC = over-the-counter; PPI = proton pump inhibitor.

Clinical Question	Suggested Approach/Pertinent Information

Which conditions are appropriate for short-term PPI use?
 	
Continued…
	<u>GERD</u>
	• Recommend an initial eight-week course of therapy with a PPI.[8]
	• For patients that require more long-term therapy, recommend a trial of a lower dose, on-demand therapy, or intermittent therapy to minimize exposure.[8]
	<u>Gastric and duodenal ulcers</u>
	• Recommend FDA- and Health Canada-approved regimens for ulcer healing, these typically last four to eight weeks.[9,39,64]
	<u>*H. pylori*</u>
	• Recommend first-line PPI-containing regimens, in the U.S. and Canada.[10,49,50]
	• See our *PL Chart, H. Pylori Treatment Regimens for Adults*, for more information on specific regimens.
	<u>Stress ulcer prophylaxis</u>
	• Reserve stress ulcer prophylaxis with PPIs for ICU patients with at least one of the following:[11]
	  • Coagulopathy (platelet count <50,000 mm^3, INR >1.5, or aPTT >2 times control)
	  • Mechanical ventilation for >48 hours
	  • History of GI ulceration or bleeding within one year of admission
	  • Glasgow Coma score ≤10

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Clinical Question	Suggested Approach/Pertinent Information

Short-term PPI use, continued	• Thermal injury to >35% of body surface area
	• Partial hepatectomy
	• Multiple trauma
	• Transplantation perioperatively in the ICU
	• Spinal cord injury
	• Hepatic failure
	• Two or more of the following risk factors:
	  • Sepsis
	  • ICU stay of more than one week
	  • Occult bleeding lasting at least six days
	  • High-dose corticosteroids (>250 mg/day of hydrocortisone)
	• Recommend discontinuation at discharge, unless there is another indication for use.[11,15]

Which conditions may require long-term PPI therapy? *Continued…*	<u>Refractory GERD</u> • Consider GERD refractory in patients not responding to PPI therapy after two to three months.[8] • Suggest adding a bedtime dose of an H2-blocker, especially for nighttime symptoms.[52,53] • Consider switching to another PPI, doubling the dose, or adding metoclopramide for non-responders.[8] <u>Erosive esophagitis</u> • Consider maintenance PPI therapy with continued symptoms after an eight-week trial of PPI.[8] • The dose and length of therapy is determined by the severity of disease and the specific PPI being used.[9,39] • Recommend using the lowest effective dose, including on-demand or intermittent therapy during maintenance therapy.[8] <u>Zollinger-Ellison Syndrome</u> • Higher doses are often necessary initially; recommend reducing the dose as gastric output decreases.[12] • Suggest using symptom control (e.g., pain, diarrhea) to guide dosage titrations, when gastric output volumes are not an option.[12] • Recommend using the lowest effective dose.[12] <u>NSAID-induced ulcers</u> • Consider use in patients taking NSAIDs that have another risk factor for GI bleeding (e.g., older age; concomitant use of a corticosteroid, anticoagulant, or antiplatelet agent).[13] • In patients with a previous ulcer, PPI use with an NSAID reduces the incidence of recurrent bleeding by 4% to 6% over a six-month period.[14] • Recommend PPIs for patients with a history of an ulcer who also require an NSAID.[14]

Clinical Question	**Suggested Approach/Pertinent Information**
Conditions requiring long-term PPI therapy, continued	• PPI use with COX-2 inhibitors decreases recurrent bleeds by almost 9% over one year, compared to COX-2 inhibitors alone.[14] • Recommend PPIs with a COX-2 inhibitor instead of a traditional NSAID, for patients with a GI bleed history.[14] <u>Chronic anticoagulation after a GI bleed</u> • Recommend PPIs for patients on anticoagulants after an upper GI bleed.[13] <u>Barrett's esophagus</u>[68] • Recommend once-daily treatment with a PPI. • Reserve twice-daily dosing for patients with poor control on once-daily PPI therapy.
Should H2-blockers and PPIs be taken together?	• Nighttime acid secretion is primarily mediated by histamine.[52] • Nighttime acid breakthrough occurs in over 70% of patients taking twice-daily PPI therapy.[51] • Consider adding a bedtime H2-blocker to PPI therapy, especially for nighttime control.[8,52,53] • Data is lacking on any benefit of administering PPIs and H2-blockers at the same time.

What are significant drug interactions associated with PPIs?	• PPIs inhibit CYP2C19 in varying degrees (e.g., esomeprazole and omeprazole are moderate inhibitors).
	• Consider H2-blockers as an alternative to avoid CYP2C19 interactions when acid suppression is needed.
	  • H2-blockers are not as effective in preventing GI bleeding.
	  • Avoid changing to cimetidine, as it also inhibits CYP2C19.[24,25]
	• PPIs can increase concentrations of some medications to toxic levels, by decreasing their metabolism. See our *PL Chart, Cytochrome P450 Drug Interactions*, for more information.
	• U.S. and Canadian product labeling recommend avoiding the use of clopidogrel with strong or moderate CYP2C19 inhibitors, such as omeprazole.[22,23]
	• GERD guidelines state there is not an increase of CV events in patients using clopidogrel with a PPI.[8]
	• For specifics, see *PL Detail-Document, Proton Pump Inhibitor and Plavix Interaction: An Update*.
	• PPIs can reduce effectiveness of medications requiring an acidic pH for absorption (e.g., atazanavir).[26]
	  • Recommend screening for interactions if starting a PPI in a patient taking critical or narrow therapeutic index medications.
	• Absorption of calcium, iron, and vitamin B12 may be reduced during PPI therapy. Most patients will not require additional replacement, especially if PPI use is short-term.[69]
	• If supplemental administration is needed:
	  • Recommend calcium citrate, as its absorption is less affected by GI pH.[16]
	  • Consider administering vitamin B12 by intranasal or IM routes.
	  • Consider administering iron intravenously.

Clinical Question	**Suggested Approach/Pertinent Information**

Is hypomagnesemia associated with PPI therapy?	• Magnesium absorption can also be reduced with PPI therapy, especially with long-term use.[28]
	  • Low magnesium levels can occur three months into PPI therapy, but risk is higher after a year.[27,28]
	  • Symptoms of low magnesium include muscle cramps, heart palpitations, dizziness, tremors, or seizures.[28]
	  • Normal serum magnesium levels vary by lab but are typically 1.8 to 2.3 mg/dL (1.5 to 1.9 mEq/L).[31]
	• Recognize concomitant medications that can lower magnesium levels (e.g., thiazides, loop diuretics).
	• Monitor with concomitant digoxin, as digoxin toxicity can occur with low magnesium levels.[48]
	• Consider checking levels during long-term therapy, especially those taking digoxin or on diuretics.[28]
	  • ICD-10 code (E43.82) may be required for reimbursement, as magnesium isn't included in standard electrolyte panels.[29]
	• Consider checking a baseline magnesium level for patients requiring long-term PPI therapy.[28]
	• Recommend OTC magnesium supplements (e.g., *Slow-Mag, MagOx*) to treat low levels.[30]
	  • Magnesium levels won't always improve in patients taking a PPI. Consider replacing PPI with an H2-blocker if magnesium levels don't improve with supplementation.[30]
	  • Recommend IV magnesium supplementation if magnesium is less than 1.2 mg/dL (1 mEq/L) or in symptomatic patients.[30]
	• For more information on the management of hypomagnesemia, see our *PL Detail-Document, Treating Magnesium Deficiency* and our *PL Chart, Comparison of Oral Magnesium Salts*.

Do PPIs cause rebound hypersecretion?	• Rebound hypersecretion can occur in a significant number of patients taking PPIs for at least two months.
	• Degree of rebound hypersecretion is directly related to gastrin levels and duration of PPI use.[47]
	• Symptoms of rebound hypersecretion may last three months or more, and can lead to inappropriate continued use of PPIs.[72]
	• Consider tapering PPIs to successfully discontinue and limit hypersecretion.[46]
	  • Recommend reducing the dose, if not at the minimum dose per day.
	  • Extend the dosing interval to every other day and possibly every third day for a week or longer.
	• Recommend antacids or H2-blockers as needed for breakthrough symptoms after PPI discontinuation.[17,46]

What do you do with PPI therapy at transitions of care?	• PPIs are often used inappropriately in the hospitalized patient.[55,56] • Recommend reevaluating PPI indications at transitions of care as an opportunity to eliminate unnecessary therapy.[14,54]

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Clinical Question	Suggested Approach/Pertinent Information
Is there an association between PPI use and asthma?	• Asthma and gastroesophageal reflux disease often co-exist.[19] • Patients with asthma may be prone to asymptomatic reflux disease.[19] • PPIs have been shown to provide no benefit compared to placebo in managing asthma symptoms.[18] • Avoid PPIs in patients with asthma, unless they have an appropriate indication.[19]

Is there an association between PPI use and pneumonia?	• Even short-term use (under one week) may increase the incidence of infections.[32]
	• Ensure PPIs have a clear indication in hospitalized patients, especially those at risk for pneumonia (e.g., elderly, chronic lung disease, patients taking immunosuppressants).[32]
	  ◦ Hospitalized patients on mechanical ventilators while taking a PPI are at greatest risk of developing hospital-acquired gram-negative pneumonia.[32]
	  ◦ One additional case of hospital-acquired pneumonia was seen for every 111 non-ICU patients treated with a PPI for at least three days.[33]
	• The evidence is not as strong linking PPIs with community-acquired pneumonia.[58]
	  ◦ One extra case of community-acquired pneumonia for every 226 patients treated with a PPI for five months.[34]
	  ◦ Meta-analysis found that PPIs do not increase the risk of hospitalization for community-acquired pneumonia.[44]
	  ◦ Analysis of pooled patient data from 24 randomized controlled trials concluded that there was no causal association between treatment with esomeprazole and a higher risk of community-acquired pneumonia over 180 days.[45]

Is there an association between PPI use and *Clostridium difficile* infections?	• PPI use may also lead to an increase in *C. difficile* infections and diarrhea.[11] • For every 533 patients receiving a daily PPI in the hospital, at least one will develop *C. difficile*.[35] • Patients being treated for *C. difficile* while taking a PPI are at a 42% increased risk of having a recurrent infection within 90 days.[11,36] • Per Health Canada, though a firm cause and effect relationship between PPIs and *C. difficile* has not been confirmed, the possibility is still there.[67] • Ensure PPIs have a clear indication to limit risk of *C. difficile*.[11] • Use PPIs cautiously in patients at risk for *C. difficile* infection, (e.g., patients taking antibiotics).[8] • Consider H2-blockers as alternative to PPIs, as they increase the risk of *C. difficile* to a lesser extent.[37]
Is there an association between PPI use and fractures? *Continued…*	• PPI use has been associated with a 25% increase in overall fractures and a 47% increase in spinal fractures in postmenopausal women [Evidence level B; epidemiologic study].[5]

Clinical Question	Suggested Approach/Pertinent Information
PPIs and fractures, continued	• Approximately 2000 Canadian females would need to be treated with a PPI for one year to cause one additional fracture.[65] • Taking high doses and/or long-term therapy have been reported to increase the incidence of hip, wrist, or spine fractures.[5,43] • PPIs probably don't increase fracture risk when used short-term in low doses.[20] • Data suggest that PPIs do not increase the risk of osteoporosis and that the risk of hip fracture is only increased in patients with at least one other risk factor for hip fracture.[8] • PPIs have not been shown to have a conclusive relationship with BMD.[6] • Recommend PPIs for approved indications without concern for impact on BMD or risk for fractures, unless patients have other risk factors for hip fracture.[8] • Encourage calcium citrate and vitamin D supplementation in PPI patients at risk for osteoporosis.[20] • Per the FDA and Health Canada, use the lowest effective dose, for the shortest time period to minimize fracture risk.[20,66]
Is there an association between PPI use and gastric or colon cancer?	• Evidence does not support an increased incidence of cancer in patients on PPIs.[21]

Is there an association between PPI use and cardiovascular events?	• In 2007, the FDA concluded that there was no relationship between PPIs and adverse cardiac events.[38]
	• In 2015, a data mining study found there MAY be an association of PPI exposure with risk for MI in the general population.[41]
	  ◦ A proposed mechanism is that PPIs might lead to increased plasma levels of ADMA and decreased levels of nitrous oxide.[40]
	  ◦ Elevated ADMA is associated with an increased risk of CV disease.[40]
	• Randomized clinical trials do NOT show an increased risk for MI with PPI use.[42]
	• A causal relationship between PPIs and cardiovascular events has not been firmly established.[42]
	• Recommend ensuring PPIs have a clear indication and using the lowest effective dose.

Is there an association between PPI use and dementia?	• PPI use may be associated with an increased risk of dementia [Evidence level B, clinical cohort study].[59] • Additional studies are needed to evaluate this association, assess if there is a causal relationship, and identify the mechanism.[60] ◦ Possible mechanisms proposed for this association include effects on amyloid and neurologic damage secondary to vitamin B12 deficiency, since PPIs may reduce vitamin B12 absorption.[59,60] • Recommend H2-blockers, if these effectively control patient symptoms. • If PPIs are required, recommend ensuring they have a clear indication and using the lowest effective dose.

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Clinical Question	Suggested Approach/Pertinent Information
Is there an association between PPIs and CKD?	• PPI use may be associated with a slight increased risk of CKD.[57] • Additional studies are needed to evaluate this association, assess if PPIs have a causal relationship, and identify the mechanism.[57] • H2-blockers have not been shown to have an association with CKD.[57] • Recommend H2-blockers, if these effectively control patient symptoms. • If PPIs are required, recommend ensuring they have a clear indication and using the lowest effective dose.
Is there evidence to support on-demand dosing with PPIs?	• On-demand dosing involves starting therapy when symptoms begin and stopping therapy when symptoms resolve. • PPIs are not approved for on-demand dosing, but patients still use them this way with good results.[62] • Patient satisfaction is sometimes improved with on-demand dosing compared to daily regimens.[61] • Consider on-demand dosing for non-erosive GERD and mild erosive esophagitis.[61-63]

How should self-medication with OTC PPIs be addressed?	• PPIs are heavily advertised and readily available OTC.
	• Encourage the following non-pharmacologic/lifestyle management first-line for GERD symptoms:
	  • Elevating head of the bed six inches[8]
	  • Avoiding meals two to three hours before bedtime[8]
	  • Weight loss, if appropriate[8]
	  • Smoking cessation[8]
	  • Psychological stress reduction, if necessary[70]
	  • Ensure adequate sleep (limited data exists)[71]
	• Recommend limiting duration of self-medication to 14 days per treatment, and no more than three treatments per year.[20]
	• Encourage patients to contact their prescriber if longer therapy is necessary.[20]
	• Provide our *PL Patient Education Handout, What You Should Know About Proton Pump Inhibitors*, to teach patients how to take their PPIs correctly.

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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References

1. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol* 2012;5:219-32.
2. Katz MH. Failing the acid test: benefits of proton pump inhibitors may not justify the risks for many users. *Arch Intern Med* 2010;170:747-8.
3. Hamzat H, Sun H, Ford JC, et al. Inappropriate prescribing of proton pump inhibitors in older patients: effects of an educational strategy. *Drugs Aging* 2012;29:681-90.
4. 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:e228-34.
5. Gray SL, LaCroix AZ, Larson J, 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;170:765-71.
6. 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;138:896-904.
7. Abrahamsen B, Eiken P, Eastell R. Proton pump inhibitor use and the antifracture efficacy of alendronate. *Arch Intern Med* 2011;171:998-1004.
8. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308-28.
9. *PL Detail-Document*, Comparison of Proton Pump Inhibitors (U.S.). *Pharmacist's Letter/Prescriber's Letter*. June 2013.
10. *PL Detail-Document*, *H. pylori* Treatment Regimens for Adults. *Pharmacist's Letter/Prescriber's Letter.* February 2012.
11. *PL Detail-Document*, Overuse of Acid Suppressing Drugs in the Hospital. *Pharmacist's Letter/Prescriber's Letter*. July 2009.
12. Ito T, Igarashi H, Urehara H, Jensen RT. Pharmacotherapy of Zollinger-Ellison syndrome. *Expert Opin Pharmacother* 2013;14:307-21.
13. 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: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010;14:2619-33.
14. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010;152:101-13.
15. Yachimski 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;170:779-83.
16. *PL Detail-Document*, Proton Pump Inhibitors and Risk of Hip Fracture. *Pharmacist's Letter/Prescriber's Letter*. February 2007.
17. *PL Detail-Document*, Proton Pump Inhibitors and Rebound Acid Hypersecretion. *Pharmacist's Letter/Prescriber's Letter*. September 2009.
18. The American Lung Association Asthma Clinical Research Centers. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med* 2009;360:1487-99.
19. *PL Detail-Document*, Do Proton Pump Inhibitors (PPIs) Improve Asthma? *Pharmacist's Letter/Prescriber's Letter*. June 2009.
20. FDA. FDA drug safety communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. May 25, 2010 (updated March 23, 2011). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm. (Accessed March 3, 2016).
21. Brunner G, Athmann C, Schneider A. Long-term, open-label trial: safety and efficacy of continuous maintenance treatment with pantoprazole for up to 15 years in severe acid-peptic disease. *Aliment Pharmacol Ther* 2012:36:37-47.
22. Product information for *Plavix*. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Bridgewater, NJ 08807. July 2015.

More. . .

23. Product monograph for *Plavix*. Sanofi-Aventis. Laval, QC H7V 0A3. May 2015.
24. *PL Detail-Document*, Proton Pump Inhibitor and *Plavix* Interaction: an Update. *Pharmacist's Letter/Prescriber's Letter.* June 2013.
25. Liu TJ, Jackevicius CA. Drug interaction between clopidogrel and proton pump inhibitors. *Pharmacotherapy* 2010;30:275-89.
26. Product information for *Reyataz*. Bristol-Myers Squibb Company. Princeton, NJ 08543. September 2015.
27. Florentin M, Elisaf MS. Proton pump inhibitor-induced hypomagnesemia: a new challenge. *World J Nephrol* 2012;1:151-4.
28. FDA. FDA drug safety communication: low magnesium levels can be associated with long-term use of proton pump inhibitor drugs (PPIs). March 2, 2011. http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm. (Accessed March 3, 2016).
29. CDC. International classification of diseases, tenth revision, clinical modification (ICD-10). October 1, 2015. http://www.cdc.gov/nchs/icd/icd10cm.htm. (Accessed March 3, 2016).
30. Martin KJ, Gonzalez EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol* 2009;20:2291-5.
31. Yu AS. Disorders of magnesium and phosphorus. In: Goldman L, Ausiello D, eds. Cecil Medicine. 23rd ed. Philadelphia, PA: Saunders Elsevier, 2008:859.
32. Vakil N. Acid inhibition and infections outside the gastrointestinal tract. *Am J Gastroenterol* 2009;104(Suppl 2):S17-20.
33. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009;301:2120-8.
34. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955-60.
35. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med* 2010;170:784-90.
36. Linsky A, Gupta K, Lawler EV, et al. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Intern Med* 2010;170:772-8.
37. Kwok CS, Arthur AK, Anibueze CI, et al. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012;107:1011-9.
38. FDA. FDA's safety reviews of *Prilosec* and *Nexium* find no evidence of increased rates of cardiac events. December 10, 2007. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109037.htm. (Accessed March 3, 2016).
39. *PL Detail-Document*, Comparison of Proton Pump Inhibitors (Canada). *Pharmacist's Letter/Prescriber's Letter*. October 2010.
40. Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. *Circulation* 2013;128:845-53.
41. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS One* 2015;10. Doi:10.1371/journal.pone.0124653.
42. Attwood SE, Ell C, Galmiche JP, 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;11:1162-74.
43. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947-53.
44. Filion KB, Chateau D, Targownik LE, et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. *Gut* 2014;63:552-8.
45. Estborn L, Joelson S. Frequency and time to onset of community-acquired respiratory tract infections in patients receiving esomeprazole: a retrospective analysis of patient-level data in placebo-controlled studies. *Aliment Pharmacol Ther* 2015;42:607-13.
46. Haastrup P, Paulsen MS, Begtrup LM, et al. Strategies for discontinuation of proton pump inhibitors: a systematic review. Family Practice 2014;31:625-30.
47. Qvigstad G, Waldum H. Rebound hypersecretion after inhibition of gastric acid secretion. *Basic Clin Pharmacol Toxicol 2004;94:202-8.*
48. Young IS, Goh EM, McKillop UH, et al. Magnesium status and digoxin toxicity. *Br J Clin Pharmacol* 1991;32:717-21.
49. Hunt R, Fallone C, Veldhuyzan van Zanten S, et al. Canadian Helicobacter Study Group consensus conference: update on the management of *Helicobacter pylori*--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for *H. pylori* infection. *Can J Gastroenterol* 2004;18:547-54.
50. Chey WD, Wong BC, Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007;102:1808-25.
51. Thompson CA. First federal comparative effectiveness review examines GI disorder. *Am J Health Syst Pharm* 2006;63:302.
52. Pan T, Wang YP, Liu FC, Yang JL. Additional bedtime H2-receptor antagonist for the control of nocturnal gastric acid breakthrough: a Cochrane systematic review. *Chin J Dig Dis* 2006;7:141-8.
53. Ang TL, Fock KM. Nocturnal acid breakthrough: clinical significance and management. *J Gastroenterol Hepatol* 2006;21:S125-8.
54. Barnes MN. Overuse of proton pump inhibitors in the hospitalized patient. *US Pharmacist*. 2015;40:HS22-6.

More. . .

55. Jain G, Jabeen SA, Vallurupalli S. Efforts to reduce stress ulcer prophylaxis use in non-critically ill hospitalized patients by internal medicine residents: a single-institution experience. *J Clin Outcomes Manage* 2013;20:13-9.
56. Barletta JF, Sclar DA. Use of proton pump inhibitors for the provision of stress ulcer prophylaxis: clinical and economic consequences. *Pharmaco Economics* 2014;32:5-13.
57. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016;176:238-46.
58. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. *JAMA Intern Med* 2016;176:172-4.
59. Gomm W, Holt KV, Thome F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol*. Published online February 15, 2016. doi:10.1001/jamaneurol.2015.4791.
60. Kuller LH. Do proton pump inhibitors increase risk of dementia. *JAMA Neurol*. Published online February 15, 2016. doi:10.1001/jamaneurol.2015.4931
61. Labenz J, Malfertheiner P. Treatment of uncomplicated reflux disease. *World J Gastroenterol* 2005;11:4291-9.
62. Metz DC, Inadomi JM, Howden CW, et al. On demand therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 2007;102:642-53.
63. Goh KL. "On-demand" therapy for gastroesophageal reflux disease: are current proton pump inhibitors good candidates? *J Gastroenterol Hepatol* 2006;21:S115-8.
64. Vakil N, Fennerty MB. Direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease. *Aliment Pharmacol Ther* 2003;18:559-68.
65. Moayyedi P, Yuan Y, Leontiadis G. Canadian Association of Gastroenterology position statement: hip fracture and proton pump inhibitor therapy – a 2013 update. *Can J Gastroenterol* 2013;10:593-5.
66. Health Canada. Proton pump inhibitors: risk of bone fracture. April 4, 2013. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/26523a-eng.php. (Accessed March 16, 2016).
67. Health Canada. Proton pump inhibitors (antacids): possible risk of *Clostridium difficile*-associated diarrhea. February 16, 2012. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/13651a-eng.php. (Accessed March 16, 2016).
68. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol* 2016;111:30-50.
69. Sheen E, Triadafilopoulos, G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci* 2011;56:931-50.
70. Talley NJ, Ford AC. Functional dyspepsia. *N Engl J Med* 2015;373:1853-63.
71. Schey R, Dickman R, Parthasarathy S, et al. Sleep deprivation is hyperalgesic in patients with gastroesophageal reflux disease. *Gastroenterology* 2007;133:1787-95.
72. Jensen RT. Consequences of long-term proton pump blockade: insights from studies of patients with gastrinomas. *Basic Clin Pharmacol Toxicol* 2006;98:4-19.

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