Appendix 4: Evidence reviews and related references

Summary of Systematic Review Findings

Our systematic review of deprescribing to on-demand or abrupt discontinuation of PPIs found six studies [1–6]. The 2004 Cochrane review that involved dose-lowering and step-down to H2RAs (eligible deprescribing methods)[7] included nine eligible studies [8–16]. We updated the literature search from the Cochrane review to April 2014 but found no additional studies meeting our eligibility criteria. We considered five studies of on-demand use, one study of abrupt discontinuation and nine studies of dose-lowering or H2RA for grading and recommendations.

Five studies investigating on-demand PPI use (in which the PPI was abruptly stopped and the on-demand regimen offered) measured risk of symptom relapse (lack of symptom control: return of symptom(s) of at least moderate severity/symptoms incompatible with well-being) [1–3,5,6]. In these studies, on-demand PPI use increased the risk of symptom relapse compared to continuous PPI use (relative risk (RR) 1.71, 95% confidence interval (CI) 1.31 to 2.21; number needed to harm (NNH) 14). Three on-demand studies measured weekly pill burden (number of pills taken per week) [1,5,6]. In these studies, on-demand PPI use reduced weekly pill burden by 3.8 pills compared to continuous PPI use (95% CI -4.73 to -2.84). Patient satisfaction was measured in five studies comparing on-demand PPI use to continuous PPI use (satisfaction reported as inadequate relief or unwillingness to continue) [1–3,5,6]. In these studies, patients using PPIs on-demand had an increased risk of being dissatisfied with therapy compared to those using PPIs continuously (RR 1.82, 95% CI 1.26 to 2.65; NNH 14); however, there was indirectness of evidence as poor methods of satisfaction were used (see Appendix 2). The quality of evidence for on-demand PPI use graded as low due to concerns surrounding risk of bias (attrition,

performance, detection and selective reporting) as well as imprecision and indirectness. Only one study with a small number of participants (n=105) and events examined abrupt discontinuation (without use of on-demand PPI therapy) [4]. Significantly increased risk of symptom relapse (RR 3.02, 95% CI 1.74 to 5.24; NNH 2) and endoscopic relapse (RR 3.41, 95% CI 1.91 to 6.09; NNH 2) was found in this study. The quality of evidence for this study was very low due to concerns regarding imprecision, blinding and attrition bias.

Symptom relapse (return of symptoms enough to interfere with normal activity for 3-7 consecutive days) was measured in five studies of patients receiving low (maintenance) dose PPI[17] compared to continuous PPI use (healing/standard dose) [10–14,16]. In these studies, there was no difference in risk of symptom relapse for patients using low dose PPI (RR 1.16, 95% CI 0.93 to 1.44). Six studies measured risk of esophagitis relapse (endoscopic findings) with low dose PPI use [10–16]. In these studies, low dose PPI increased risk of esophagitis relapse compared to continuous dose PPI (RR 1.54, 95% CI 1. 25 to 1.89; NNH 13). The quality of evidence was low for symptom relapse due to inconsistency; there was also statistically significant heterogeneity that was unexplained (I^2 = 48%). The quality of evidence for esophagitis relapse was moderate.

Step-down to H2RAs was compared to continuous PPI use (healing dose PPI) in three trials [8–10]. Use of H2RAs as maintenance therapy increased risk of symptom relapse (RR 1.92, 95% CI 1.44 to 2.58; NNH 5) and esophagitis relapse (RR 3.52, 95% CI 1.80 to 6.87; NNH 3) compared to continuous PPI use. The quality of evidence was rated as moderate due to concerns surrounding risk of bias.

GRADE evidence tables with further details are presented in Appendix 2.

Harms of continued PPI use

PPIs are generally safe and well-tolerated. Commonly reported side effects include diarrhea and headache and although their incidence is comparable to placebo, the risk for diarrhea may be increased in older persons [18]. PPI use has also been associated with vitamin B12 deficiency and hypomagnesemia [19–21]. If unrecognized as potential PPI adverse effects, these symptoms may lead to a prescribing cascade whereby another drug is used to treat these iatrogenic effects.

Epidemiological data has emerged demonstrating that there are other potential harms associated with PPI use. A review of reviews of PPI harms was therefore completed; a librarian conducted an English only literature search in Pubmed, EMBASE via OVID, International Pharmaceutical Abstracts database, Scopus and the Cochrane Library (strategy available upon request). Our search returned 84 studies. Two research assistants independently reviewed the studies using the following inclusion criteria to identify relevant literature: systematic reviews of RCTs or observational studies, and outcomes resulting in harms. The research assistants met with one investigator to reconcile the resulting list of studies. A total of 36 studies were eligible. We conducted a narrative synthesis and summary of these systematic reviews and compiled their results (including harm outcomes, study designs, and outcome variables) – full results are available upon request. The range of estimates (OR, RR, or HR) and citations for eligible reviews are outlined in Appendix 3.

The eligible systematic reviews reported an increased risk of the following outcomes in PPI users versus those not using PPIs: fractures (overall fractures risk, spine fractures, hip fractures), *Clostridium difficile* infections, *Clostridium difficile*-related diarrhea, community-acquired pneumonia, hospitalisations for community-acquired pneumonia, gastric cancer, gastric atrophy, intestinal metaplasia, simple ECL hyperplasia, focal ECL hyperplasia, colorectal cancer, increased risk of vascular events among patients taking clopidogrel, bacterial peritonitis, small intestine bacterial overgrowth, vitamin B12 deficiency, and hypomagnesemia. When interpreting the impact of the aforementioned risks, consideration should be given to the prevalence of PPI use, the baseline risk of such harms, and the magnitude of increased risk for harms. It should also be noted that overall effect sizes were small, and that residual confounding that cannot be fully adjusted for is always a concern in epidemiological studies. As such, the quality of evidence for harms is of low to very low quality.

Values and patient preferences related to PPIs

Semi structured patient interviews consistently report that patients believe PPIs are the most effective treatment for controlling their GI symptoms [22,23]. A high percentage of patients also believe taking a PPI has improved their quality of life [22,24]. Patients with GERD symptoms generally do not take their prescriptions continuously as prescribed, instead taking their medication on an "as needed" basis [25]. Documentation of this behaviour has been attributed to the development of on-demand treatment strategies.

Patient's perceived satisfaction with continuous compared to on-demand treatment demonstrated a statistically significant difference in favor of continuous treatment in two open label trials. The

clinical significance of these results however is unlikely to be meaningful as the absolute differences between groups were quite small [1,3]. In contrast, a third study comparing continuous to on-demand treatment found that patient's willingness to continue taking their assigned PPI regimen was greater with on–demand treatment [26]. A blinded study comparing maintenance treatment with continuous (daily) PPI and placebo rescue versus daily placebo and PPI rescue demonstrated that quality of life was independent of the daily PPI intake, despite a 30% decrease in medication use in the daily placebo arm [2]. The results of these studies suggest that patient's level of acceptance for maintenance GERD treatment compared with taking an on-demand PPI is likely similar, if not superior, to taking the same medication every day.

Some patients may be reluctant to reduce or taper PPI therapy for fear that their GI symptoms will return [22–24]. The clinical considerations section of the guideline provides information regarding how to manage mild (e.g. LA Grade A/B) symptom recurrence.

Resource implications and cost-effectiveness

In 2012, anti-ulcer therapy accounted for 26 billion U.S dollars in sales globally [27]. In Canada, PPIs accounted for $247 million Canadian dollars spent by public drug programs (except Quebec, Newfoundland and Labrador, and the Territories) in 2012 [28]. The proportion of seniors taking a PPI amongst low, moderate and high medication users was 8.3%, 27.1% and 60.8%, respectively [29]. Studies consistently show inappropriate PPI use in approximately 40-65% of patients depending on the setting (i.e., ambulatory or inpatient) [20,30,31]. A retrospective review of ambulatory patients estimated the drug cost associated with inappropriate PPI use to be over 1

million dollars for just 341 patients who had accumulated 768 patient-years of treatment with no indication [32].

Interventions to reduce PPI use have proven successful. These interventions can be resource intense, however, involving extensive chart reviews to determine eligible patients, audit and feedback processes, and development or implementation of specialty GI clinics [33–35].

Step-down, intermittent and on-demand PPI use have all been shown to reduce direct medical costs compared to continuous PPI maintenance treatment for patients with GERD [36–38]. Preliminary evidence from a modeling study suggests that intermittent PPI treatment is more cost effective than continuous treatment when factoring in costs related to diagnosis, procedures and unsuccessful pharmacological treatment [37]. An open label, randomized study comparing on demand treatment to intermittent treatment found the former resulted in less direct and indirect medical costs [39]. Unfortunately, there is no evidence that directly compares these strategies or captures long-term costs (e.g. increase in medical visits). As well, the differing patient populations, definitions of the treatments, included costs and duration of study/ modeling make it difficult to support a single strategy as cost effective for all patients. For patients with severe GERD (LA Grade C/D) symptoms, the projected cost of continuous PPI treatment per quality adjusted life year (QALY) demonstrates its cost effectiveness in this subset of patients [40].

References :

1. Bour B, Staub J-L, Chousterman M, Labayle D, Nalet B, Nouel O, et al. Long-term treatment of gastro-oesophageal reflux disease patients with frequent symptomatic relapses using rabeprazole: on-demand treatment compared with continuous treatment. Aliment Pharmacol Ther. 2005 Apr;21(7):805–12.
2. van der Velden AW, de Wit NJ, Quartero AO, Grobbee DE, Numans ME. Pharmacological dependency in chronic treatment of gastroesophageal reflux disease: a

randomized controlled clinical trial. Digestion. 2010;81:43–52.
3. Morgan DG, O'Mahony MFJ, O'Mahony WF, Roy J, Camacho F, Dinniwell J, et al. Maintenance treatment of gastroesophageal reflux disease: an evaluation of continuous and on-demand therapy with rabeprazole 20 mg. Can J Gastroenterol. 2007 Dec;21(12):820–6.
4. Pilotto A, Ndro GLEA, Anceschi MFR, Alf BEH, The OF, Eing AG, et al. Short- and long-term therapy for reflux oesophagitis in the elderly : a multi-centre , placebo-controlled study with pantoprazole. 2003;1399–406.
5. Janssen W, Meier E, Gatz G, Pfaffenberger B, Pfivate I. Effects of Pantoprazole 20 mg in Mild Gastroesophageal Reflux Disease : Once-Daily Treatment in the Acute Phase , and Comparison of On-Demand Versus Continuous Treatment in the Long Term. 2005;66(4):345–63.
6. Bayerdörffer E, Bigard M-A, Weiss W, Mearin F, Rodrigo L, Dominguez Muñoz JE, et al. Randomized, multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease. BMC Gastroenterol [Internet]. 2016 Dec 14;16(1):48. Available from: http://bmcgastroenterol.biomedcentral.com/articles/10.1186/s12876-016-0448-x
7. Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane database Syst Rev. 2004 Jan;(2):CD003245.
8. Annibale B, Franceschi M, Fusillo M, Beni M, Cesana B DFG. Omeprazole in patients with mild or moderate reflux esophagitis induces lower relapse rates than ranitidine during maintenance treatment. Hepatogastroenterology. 1998;45:742–51.
9. Dent J, Yeomans ND, Mackinnon M, Reed W, Narielvala FM, Hetzel DJ, et al. Omeprazole v ranitidine for prevention of relapse in reflux oesophagitis. A controlled double blind trial of their efficacy and safety. Gut [Internet]. 1994 May 1;35(5):590–8. Available from: http://gut.bmj.com/cgi/doi/10.1136/gut.35.5.590
10. Gough a L, Long RG, Cooper BT, Fosters CS, Garrett a D, Langworthy CH. Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. Aliment Pharmacol Ther. 1996 Aug;10(4):529–39.
11. Robinson M, Lanza F, Avner D, Haber M. Effective Maintenance Treatment of Reflux Esophagitis with. Ann Intern Med. 1996;124(10):859–67.
12. Escourrou J, Deprez P, Saggioro a, Geldof H, Fischer R, Maier C. Maintenance therapy with pantoprazole 20 mg prevents relapse of reflux oesophagitis. Aliment Pharmacol Ther. 1999 Nov;13(11):1481–91.
13. Plein K, Hotz J, Wurzer H, Fumagalli I, Luhmann R SA. Pantoprazole 20 mg is an effective maintenance therapy for patients with gastro-oesophageal reflux disease. Eur J Clin Pharmacol. 2000;12:425–32.
14. Baldi F, Bardhan K, Borman B, Brullet E, Dent J, Galmiche J, et al. Lansoprazole maintains healing in patients with reflux esophagitis. Gastroenterology. 1996;(110):A55.
15. Poynard T, Staub J, Lemerez M, Deltenre M, Rekacevicz C, Sallerin V. Efficacy and safety of lansoprazole 15 mg oad or 30mg oad as one year maintenance treatment for erosive reflux esophagitis. A randomized trial. Gastroenterology [Internet]. 1995 Apr;108(4):A195. Available from: http://linkinghub.elsevier.com/retrieve/pii/0016508595234411
16. Hatlebakk JG, Berstad A. Lansoprazole 15 and 30 mg daily in maintaining healing and

symptom relief in patients with reflux oesophagitis. Aliment Pharmacol Ther [Internet]. 1997 Apr;11(2):365–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9146777
17. CADTH. Evidence for PPI Use in Gastroesophageal Reflux Disease, Dyspepsia and Peptic Ulcer Disease: Scientific Report. 2007;1(2).
18. Pilotto A, Franceschi M, Vitale D, Zaninelli A, Di Mario F, Seripa D, et al. The prevalence of diarrhea and its association with drug use in elderly outpatients: a multicenter study. Am J Gastroenterol. 2008 Nov;103(11):2816–23.
19. Lam JR, Schneider JL, Zhao W, Corley D a. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 2013 Dec;310(22):2435–42.
20. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. J Clin Pharm Ther. 2008 Jul;25(5):333–40.
21. Pillans PI, Kubler PA, Radford JM, Overland V. Concordance between use of proton pump inhibitors and prescribing guidelines. Med J Aust. 2000 Jan;172(1):16–8.
22. Boath EH, Blenkinsopp A. The rise and rise of proton pump inhibitor drugs: Patients' perspectives. Soc Sci Med. 1997 Nov;45(10):1571–9.
23. Grime J, Pollock K, Blenkinsopp A. Proton pump inhibitors: perspectives of patients and their GPs. Br J Gen Pract. 2001 Sep;51(470):703–11.
24. Spijker-Huiges A, Winters JC, Meyboom-De Jong B. Patients' views on dyspepsia and acid suppressant drug therapy in general practice. Eur J Gen Pract. 2006 Jan;12(1):10–4.
25. Hungin AP, Rubin G, O'Flanagan H. Factors influencing compliance in long-term proton pump inhibitor therapy in general practice. Br J Gen Pract. 1999;49:463–4.
26. Pace F, Tonini M, Pallotta S, Molteni P, Porro GB. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken "on-demand". Aliment Pharmacol Ther. 2007 Jul;26(2):195–204.
27. IMS Health, IMS Health Incorporated and its affiliates. Top 20 Therapeutic Classes 2012. 2012.
28. Canadian Institute for Health Information (CIHI). Drug use among seniors on public drug programs in Canada, 2012. Ottawa, ON; 2014.
29. Canadian Institute for Health Information. Drug Use Among Seniors on Public Drug Programs in Canada. 2010;
30. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol. 2012 Jul;5(4):219–32.
31. Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. Am J Gastroenterol. 2000 Nov;95(11):3118–22.
32. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. Am J Manag Care [Internet]. 2010 Sep;16(9):e228-34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21250399
33. Bundeff AW, Zaiken K. Impact of clinical pharmacists' recommendations on a proton pump inhibitor taper protocol in an ambulatory care practice. J Manag Care Pharm. 2013 May;19(4):325–33.
34. Lucas LM, Gerrity MS, Anderson T. A practice-based approach for converting from proton pump inhibitors to less costly therapy. Eff Clin Pract. Jan;4(6):263–70.
35. Murie J, Allen J, Simmonds R, de Wet C. Glad you brought it up: a patient-centred programme to reduce proton-pump inhibitor prescribing in general medical practice. Qual Prim Care. 2012;20:141–8.

36. Inadomi JM, Jamal R, Murata GH, Hoffman RM, Lavezo LA, Vigil JM, et al. Step-down management of gastroesophageal reflux disease. Gastroenterology. 2001 Nov;121(5):1095–100.
37. Gerson LB, Robbins AS, Garber A, Hornberger J, Triadafilopoulos G. A cost-effectiveness analysis of prescribing strategies in the management of gastroesophageal reflux disease. Am J Gastroenterol. 2000 Feb;95(2):395–407.
38. Wahlqvist P, Junghard O, Higgins A, Green J. Cost effectiveness of proton pump inhibitors in gastro-oesophageal reflux disease without oesophagitis: comparison of on-demand esomeprazole with conventional omeprazole strategies. Pharmacoeconomics. 2002 Jan;20(4):267–77.
39. Meineche-Schmidt V, Hauschildt, Juhl H, Ostergaard JE, Luckow A and H. Costs and efficacy of three different esomeprazole treatment strategies for long-term management of gastro-oesophageal reflux symptoms in primary care. Ailm Pharmacol There. 2004;19:907–15.
40. Moayyedi P, Armstrong D, Hunt RH, Lei Y, Bukoski M, White RJ. The gain in quality-adjusted life months by switching to esomeprazole in those with continued reflux symptoms in primary care: EncomPASS--a cluster-randomized trial. Am J Gastroenterol. 2010;105:2341–6.