Proposed Associations with PPI Use

	Summary Evidence
Renal Function Decline 1. Lazarus et al. JAMA Int Med Feb 2016 2. Antoniou et al. CMAJ Open April 2015	• NIH-funded cohort trial evaluating risk of new onset CKD in patients receiving PPIs relative to H2 blockers and no antisecretory therapy. Included>27,000 adults ages 45 - 64 and a baseline GFR >60 mg from two US databases.[1] • After adjusting for multiple factors including age, DM, HTN, diuretic and NSAID use, patients receiving PPIs were 20 - 50% more likely to develop CKD relative to patients receiving no antisecretory therapy. • The 10-year absolute risk difference of developing CKD on a PPI was estimated as 1.7% - 3.3%. (NNH: 30 - 58 patients treated for 10 years). • No significant increase in CKD was noted among patients receiving H2 blockers. • Consistent with previous literature, this trial showed an increased risk of AKI with PPI use.[2]
Dementia 3. Gomm et al. JAMA Neurology April 2016 4. Haenisch et al. Eur Arch Psych Clin Neurosci Aug 2015	• Review of German claims database. Included patients age ≥75 years with no prior diagnostic claims for dementia and regular prescription claims for a PPI during an 18 month period.[3] • After adjusting for age, gender, stroke, depression, and polypharmacy, frequent claims for a PPI was associated with a 44% increase risk of claims for dementia. While the use of claims data adds level of uncertainty, the results were consistent with the authors' previous findings.[4] • In a post-hoc analysis, claims for highly anticholinergic medications were associated with an 85% increased risk of dementia and no-adjustments were made for multiple other medication classes which could precipitate cognitive decline.
Hypomagnesemia 5. FDA Drug Safety Communication: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm	• FDA Drug Safety Communication, March 2011 based on cases reported to the organization as well as published reports.[5] • Time to onset ranged from 3 - 12 months, with most cases being reported after at least 1 year of use. There is an additive risk with concurrent use of thiazide or loop diuretics. • After discontinuation, median time to resolution is 7 days. Upon rechallenge, median time to recurrence is 2 weeks. • About 25% of cases are refractory to supplementation and require cessation of therapy. Case reports suggest effect is maintained despite substitution to another PPI.
Fractures 6. FDA Drug Safety Communication: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm 7. Khalili et al. BMJ Jan 2012	• FDA Drug Safety Communication May 2010 based on multiple observational trials.[6] • Risk appears to be dose and duration dependent, begins to emerge after at least 1 year of use, and is believed to be greater among patients with other risk factors including age >50 years and smoking. • One of the largest trials reported an absolute risk difference of 0.051% (NNH 1960 patients treated for 8 years).[7]
C. Diff 8. FDA Drug Safety Communication: http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm 9. Howell et al. Arch Int Med May 2010	• FDA Drug Safety Communication Feb 2012 based on multiple observational trials and meta-analyses.[8] • In trials, the magnitude of risk has varied (OR 1.4 - 2.75) and there is suggestion of higher risk with twice-daily therapy as well as additive risk among patients receiving antibiotics.[9]
Pneumonia 10. Eom et al. CMAJ Feb 2011 11. Filion et al. Gut April 2014	• Observational studies have yielded mixed results and interpretation is limited by the high potential for confounding. • One large meta-analysis found patients receiving PPIs or H2 blockers had a slight increase risk of pneumonia relative to those with no antisecretory therapy (OR 1.27 and 1.22, respectively).[10] • A second meta-analysis looking exclusively at PPIs for prophylaxis among new-start NSAID users found no association with PPIs or H2 blockers.[11]
B12 & Iron Malabsorption 12. Lam et al. JAMA Dec 2013	• PPIs have been shown to cause a slight reduction in B12 absorption and have been associated with an increased risk of deficiency. It is reasonable to consider PPIs as a potential cause of B12 deficiency in patient receiving long-term therapy[12] • The clinical relevance of reduced iron absorption is questionable and may be most applicable to patient receiving oral iron supplements.