



ADVERSE EFFECTS ASSOCIATED WITH PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) have been used extensively since their initial release in 1989. Long-term use may be associated with several adverse effects including elevated risk of bone fractures, pneumonia, *Clostridium difficile* diarrhea, hypomagnesemia, vitamin B₁₂ deficiency, chronic kidney disease, and dementia. This issue of *CLIPs* reviews adverse effects associated with long-term PPI use. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at chipor@samford.edu.

Nehra AK, Alexander JA, Loftus CG, Nehra V. Proton pump inhibitors: review of emerging concerns. *Mayo Clin Proc.* 2018;93:240-246.

Introduction

- PPIs are one of the most commonly prescribed medications in the US and use in the hospital between 1999 and 2012 has resulted in more than \$11 billion annually.
- Well publicized studies have indicated a concern for adverse effects; however, the majority of the data comes from retrospective, observational studies.
- This reviews categories adverse drug reactions in which the association between PPI use and adverse effects are likely, unclear, or unlikely.

Table 1: Association of PPI-induced adverse events

Potential adverse effect	Association of the effect	Clinical considerations
Hypomagnesemia	Likely causative	Hypomagnesemia was initially described in 2006 after approximately 1 year of PPI therapy. Some guidelines indicate monitoring is necessary in some patients, especially those with malabsorption disorders.
Vitamin B ₁₂ deficiency		Vitamin B ₁₂ is released when appropriate amounts of gastric acid are available for absorption. In one study, use of 1 ½ or more PPI tablets per day was associated with vitamin B ₁₂ deficiency (OR, 1.95; 95 CI (1.77-2.15)).
Small intestine bacterial overgrowth		Decreases in gastric production can lead to an over production / growth of bacteria in the small intestine. Increases in bacteria in the small intestine were evaluated in PPI users and non-users and users had more bacterial growth than nonusers (OR, 2.28; 95% CI, 1.24-4.21). The clinical effect of this information is not known.

CONTINUED NEXT PAGE

Table 1: Association of PPI-induced adverse events (continued)

Bone fractures	Unclear	In 2010, the FDA released an alert on the risk of fracture with long-term use of PPIs. A meta-analysis revealed that PPI use was associated with a 33% increased risk for fracture at any site (RR, 1.33; 95%, (1.15-1.54)). Other data has been inconsistent.
<i>Clostridium difficile</i> infection (CDI)		FDA issued warning regarding the risk of CDI in patients receiving PPIs. A meta-analysis of 42 observational studies indicated an increased risk of incident and recurrent CDIs in patients taking PPIs (OR, 1.74; 95% CI, 1.47-2.85 and OR, 2.51; 95% CI, 1.16-5.44, respectively). H ₂ antagonists have also been shown to increase CDI. Another study found a 65% increase in CDI incidence in patients receiving PPIs. Other studies have had inconsistent results.
Acute and chronic kidney disease (CKD)		In one study, PPI users had a 50% greater risk of developing CKD compared to nonusers. Another study reported similar results – a 17% increase in CKD among PPI users; however, a significant increase in concomitant use of NSAIDs were observed in PPI users in this study. Although there appears to be an increased risk of CKD with long-term PPI use, no recommendations have been made regarding monitoring of kidney function in patients taking PPIs.
Dementia		Two prospective studies found an increase in PPI use and the risk of dementia. In one study, a 38% increase in dementia and a 44% increased risk of Alzheimer’s disease was observed. Another study reported a 44% increased risk of dementia in patients receiving PPIs. However, in a study of middle-aged patients, no association between PPI use and cognitive function was observed.
Community acquired pneumonia (CAP)		Unlikely

Summary

- PPI use has been associated with significant adverse events.
- Much of the evidence is from retrospective, observational studies.
- Even though there may be risks of adverse effects due to long-term PPI use, the absolute risk appears to be small.
- As a result, PPIs should be initiated at the lowest possible dose for the shortest duration of time.

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