

FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Is the long-term use of proton pump inhibitors safe?

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■ EVIDENCE-BASED ANSWER

Long-term use of proton pump inhibitors (PPIs) appears safe, resulting in no clinically relevant adverse effects (strength of recommendation: **B**, based on nonsystematic reviews, cohort studies, or low-quality randomized controlled trials). No evidence clearly links PPIs to gastric cancer or carcinoid, enteric infections, or significant nutrient malabsorption.

■ EVIDENCE SUMMARY

The long-term safety of PPIs is not completely known. There are 5 PPIs on the US market. Clinical experience with these medications ranges from 3 to 20 years. All of the identified studies addressing long-term use have follow-up of 10 years or less (**Table**). Studies of longer duration are warranted. We reviewed the possible adverse effects of these medications.

Gastric carcinoid. PPIs cause predictable and sustained hypergastrinemia in response to acid suppression. In rats, this causes enterochromaffin-like cell (ECL) hyperplasia and carcinoid tumors, raising a safety concern in humans. In a nonsystematic review of 11 studies of 1800 patients who used PPIs from 6 months to 8 years, there were no neoplastic ECL changes or carcinoid tumors.¹ Three other nonsystematic reviews support these findings.²⁻⁴ In a randomized controlled trial comparing efficacy and safety of rabeprazole with omeprazole for gastro-esophageal disease, 123 (51%) out of 243 patients completed 5 years of the study; no patients had neoplastic ECL changes.⁵

Atrophic gastritis and gastric cancer. Atrophic gastritis with intestinal metaplasia is associated with gastric adenocarcinoma. Because PPIs can theoretically cause atrophic gastritis, there is a concern that this could lead to gastric cancer. The evidence regarding atrophic gastritis is contradictory. A nonsystematic review

identified 1 cohort study and 1 randomized controlled trial of patients taking omeprazole from 1 to 4 years, which showed no association between PPI use and atrophic gastritis.¹ The same review reported that another cohort study of patients using omeprazole for 1 year showed an increase in atrophic gastritis. None of the studies reviewed showed an association between omeprazole use and intestinal metaplasia or its progression to gastric adenocarcinoma.¹ Three other nonsystematic reviews support these findings.^{2,3,5} The available evidence indicates that PPI use is not clearly associated with atrophic gastritis, or with progression from gastritis to metaplasia or cancer.

Enteric infections. Because hypochlorhydria is associated with bacterial enteric infections, bacterial enteritis is a theoretical risk of long-term PPI use. A large case-control study of 54,461 patients using omeprazole for 1 year showed no association with such infections.⁶

Mineral malabsorption. Dietary calcium, phosphorus, magnesium, zinc, and iron depend on gastric acid for absorption. Two separate non-systematic reviews showed no problems with malabsorption of these micronutrients.^{1,3}

B12 malabsorption. Two nonsystematic reviews showed a decrease in vitamin B12 absorption among patients on high-dose (up to 80 mg of omeprazole daily), long-term PPI therapy (eg, patients with Zollinger-Ellison syndrome).^{1,2} This has not been demonstrated for patients taking more typical doses of omeprazole. The clinical significance of this is unknown; however, the authors of these reviews suggested monitoring B12 levels of patients on long-term, high-dose PPI therapy.

Potential proton pump inhibitor safety concerns

Safety concern	PPI studied	Duration of studies	Evidence
Gastric carcinoids	Omeprazole, lansoprazole, pantoprazole, rabeprazole	1–8 years	No increased risk ¹⁻⁵
Gastric metaplasia/adenocarcinoma	Omeprazole	1–5 years	No increased risk ^{1-3,5}
Enteric infections	Omeprazole	1 year	No increased risk ⁶
Mineral malabsorption	Omeprazole	6 months–2 years	No increased risk ^{1,3}
B12 malabsorption	Omeprazole	10 years	Decreased B12 levels with high-dose therapy ^{1,2}

■ RECOMMENDATIONS FROM OTHERS

A Federal Drug Commission report indicates that labeling PPIs for cancer risk is not warranted.⁷ The American College of Gastroenterology and the University of Michigan Health System guidelines for treatment of gastroesophageal disease recommend long-term PPI therapy as an option without any warning against their use.^{8,9}

CLINICAL COMMENTARY

No evidence of long-term adverse health effects from PPIs, but cost still a problem

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Proton pump inhibitors work. They effectively treat the symptoms and reduce the complication involved with peptic ulcer disease. The lack of evidence suggesting any long-term adverse health effects, even if not definitive, is very encouraging, but the cost of these medicines remains a problem. Both patients and third-party payers continue to object to their cost, and for this reason, as well as longer safety track records, less expensive medicines such as H2 blockers and over-the-counter antacids should be tried for longer-term treatment.

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