Published in final edited form as:

Gastroenterol Clin North Am. 2010 September ; 39(3): 529–542. doi:10.1016/j.gtc.2010.08.009.

The Safety of Drugs Used in Acid-related Disorders and Functional Gastrointestinal Disorders

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Abstract

Acid-related disorders and functional gastrointestinal disorders (FGIDs) are associated with morbidity and impairment of quality of life. However, with the exception of complicated peptic ulcer disease, these disorders do not have appreciable mortality. Treatments for these disorders have consequently been held to a high standard of safety and tolerability by regulatory authorities. Some agents for FGIDs have been withdrawn or restricted based on assessments and perceptions of unfavorable risk/benefit profiles. For most of the agents discussed in this article, the risk of serious toxicity is low. However, even low risks must be weighed against potential benefit. There is no justification for continuing any treatment that is not having an appreciable positive effect on a patient's symptoms; in the absence of discernable benefit, any risk is unacceptable.

Keywords

Acid-related disorders; Functional gastrointestinal disorders; Proton pump inhibitors; H₂-receptor antagonists; Prokinetic agents; Serotonergic agents

PROTON PUMP INHIBITORS

These drugs have been successful both clinically and commercially for the treatment of various acid-related disorders; mainly gastroesophageal reflux disease (GERD). Other indicated uses of proton pump inhibitors (PPIs) include the treatment and prevention of upper gastrointestinal (GI) tract ulcers from nonsteroidal antiinflammatory drugs (NSAIDs), as part of therapeutic regimens for eradication of *Helicobacter pylori* infection, and in the management of patients with bleeding peptic ulcer. These applications are considered elsewhere in this issue. PPIs have also been used in the management of functional dyspepsia (one of the FGIDs), albeit with limited success. Although generally safe, some possible adverse consequences of long-term PPI use deserve further consideration.

Drug-drug Interactions

After systemic absorption and initial wide distribution within the body, the liver rapidly metabolizes PPIs via the cytochrome P450 enzyme system.¹⁻⁶ The principal isoenzymes

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Financial disclosure information: Dr Neehar Parikh has no relationships to disclose. Dr Colin W. Howden has, at various times, been a paid consultant for Takeda Pharmaceuticals North America, Takeda Global Research and Development, Santarus Inc, Novartis Consumer Health, Novartis Oncology, Tercica, Procter & Gamble, Merck/Schering-Plough Healthcare, Xenoport, KV Pharmaceuticals, and Otsuka. In the past 3 years, Dr Howden has received speaking honoraria from Takeda Pharmaceuticals North America, Santarus, AstraZeneca, and Otsuka. Dr Howden has received research support from AstraZeneca for an investigator-initiated project.

involved are 2C19 and, to a lesser extent, 3A4. The potential for individual PPIs to influence P450 enzyme activity has raised concerns about possible drug-drug interactions (DDIs). However, there is little, if any, clinical significance to PPI interactions with other medicines; those commonly included in package inserts with PPIs as having the potential for P450-related interactions include warfarin, diazepam, tacrolimus, cyclosporine, and theophylline.¹⁻⁶ However, dose adjustments are not routinely required in patients taking PPIs and other medications metabolized by the cytochrome P450 system.

Most medicines with which at least some PPIs have been proposed to interact have wide therapeutic indices. That is, their steady-state plasma concentrations associated with toxicity are much higher than those associated with the desired therapeutic effect. A perfect example is diazepam. Although omeprazole interacts with diazepam to slow its metabolism and raise its steady-state plasma concentration, this is not associated with any measurable pharmacodynamic effect. Some drugs (notably warfarin, phenytoin, and theophylline) have much narrower therapeutic indices, so plasma concentrations associated with toxicity are close to those normally associated with their desired therapeutic effects. Theoretically, slowing of the hepatic metabolism of any of these drugs by the concomitant use of a P450 inhibitor (such as a PPI) might increase steady-state plasma concentrations to toxic levels. However, DDIs reported to the United States Food and Drug Administration (FDA) with omeprazole, lansoprazole, and pantoprazole included estimated frequencies of less than 1 per million prescriptions, with no discernable differences among them.⁷ The American Gastroenterological Association Institute published a technical review on GERD in 2008, which included an overview of various potential safety concerns with the PPIs, including possible DDIs.⁸ They endorsed the view that clinically significant DDIs occurred with a frequency of less than 1 per million prescriptions.

There are a few DDIs common to all the PPIs with respect to their inhibition of gastric acid secretion. All PPIs may reduce the absorption of the antiretroviral agent atazanavir. This reduction may potentially lead to subtherapeutic blood levels of that agent, with risks of treatment failure against human immunodeficiency virus (HIV) infection or the emergence of resistant strains of HIV. All PPIs may increase the bioavailability of digoxin by around 10%, which is unlikely to be clinically relevant.

PPIs and Clopidogrel

Clopidogrel is a prodrug that must be activated in the liver to exert its desired antiplatelet effect. This effect is accomplished in a multistep process that includes cytochrome P450 2C19, the isoenzyme most closely connected with PPI metabolism. Some in vitro studies suggested that omeprazole, and perhaps other PPIs, reduces the rate of conversion of clopidogrel to its active metabolite when used concomitantly.⁹ Clopidogrel is generally administered with aspirin, and this combination puts some patients at risk of upper GI hemorrhage. PPI cotherapy is advised for patients with identifiable risk factors such as advanced age, a past history of ulcer or bleeding, or concomitant NSAID or anticoagulant use.¹⁰ Some retrospective studies reported worse cardiovascular outcomes among patients on clopidogrel and a PPI compared with those on clopidogrel alone.^{11,12} However, these were prone to bias; for example, in both studies cited, patients taking a PPI and clopidogrel had worse cardiovascular risk profiles and more comorbidity than those not on a PPI. Because these were not randomized trials, it may be that patients with worse disease, and at presumed greater risk of GI bleeding, were more likely to have been given PPI cotherapy. As of March 2010, there were no published, peer-reviewed data from prospective, randomized trials. However, O'Donoghue and colleagues¹³ did make a post hoc analysis of prospectively collected data from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, which had randomized more than 13,000 patients with acute

coronary syndrome (ACS) to clopidogrel or prasugrel. Although TRITON-TIMI 38 was not a randomized comparison of PPI cotherapy with no cotherapy in patients receiving clopidogrel, a large number of patients in the trial had been on PPI cotherapy. O'Donoghue and colleagues¹³ did not identify any adverse cardiovascular outcomes in the patients treated with clopidogrel who had received PPI cotherapy compared with those who had not. Furthermore, they identified a small but statistically significant reduction in all-cause mortality among the patients treated with clopidogrel on PPI cotherapy. To date, Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) is the only randomized study to have compared PPI cotherapy with no cotherapy in patients taking clopidogrel. However, this trial was terminated prematurely for financial reasons and, at the time of writing, had not been reported in full. It randomized patients to a fixed-dose combination of clopidogrel and omeprazole or to clopidogrel alone after a myocardial infarction, other ACS, or coronary stent placement.¹⁴ Patients who had received the combination of omeprazole and clopidogrel in COGENT did not have demonstrably worse cardiovascular outcomes than those who received clopidogrel alone. The patients who had received omeprazole had a significantly lower rate of adverse GI outcomes than those who did not.

As of March 2010, there is no definitive clinical evidence that PPI cotherapy with clopidogrel is a risk factor for adverse cardiovascular outcomes.¹⁵ Patients taking clopidogrel who have additional risk factors for GI bleeding should receive PPI cotherapy.¹⁰ However, in November 2009, the FDA announced its analysis of some pharmacodynamic and pharmacokinetic studies conducted by the manufacturers of clopidogrel.¹⁶ These showed that omeprazole cotherapy was associated with reduced serum levels of clopidogrel's active metabolite and with a reduction in clopidogrel's in vitro antiplatelet effect. Based on these studies, the FDA recommended that omeprazole (and esomeprazole) be avoided among patients taking clopidogrel. Similar studies are currently being conducted with other PPIs.

Clostridium difficile and Other Enteric Infections

Clostridium difficile is a spore-forming bacterium; its nosocomial acquisition is associated with significant morbidity and it is also emerging as an important community-acquired pathogen.^{17,18} Several published studies have investigated the association between PPI use and *C difficile* infection. The proposed mechanism for the increased risk is that gastric acid suppression allows ingested spore survival in the upper GI tract and eventual proliferation in the colon.¹⁹ There is also some evidence that PPIs cause leukocyte inhibition, which may contribute to an increase in various enteric infections, including *C difficile*.²⁰

Aseeri and colleagues²¹ published a retrospective case-control study of 94 patients with nosocomial *C difficile* infection. Multivariate analysis in which factors such as antibiotic use, sex, and age were controlled for, determined an odds ratio (OR) for PPI use and *C difficile* infection of 3.6 (95% confidence interval [CI] 1.7–5.3). In another case-control study, Yearsley and colleagues²² investigated 155 patients with nosocomial *C difficile* infection. There was an increased risk of *C difficile* infection with PPI therapy (OR 1.9; 95% CI 1.1–3.3).²² To determine the effects of PPIs on community-acquired *C difficile*, Dial and colleagues¹⁹ conducted a population-based case-control study of 1233 patients and found an adjusted rate ratio of 2.9 (95% CI 2.4–3.4) for *C difficile* infection among patients using PPIs. Based on the available data, there seems to be a weak association between PPI use and *C difficile* infection, both nosocomial and community-acquired, although causality has not been established.

Similarly, diminished gastric acid secretion is postulated to increase the risk of other enteric infections. Garcia Rodriguez and colleagues²³ studied a retrospective cohort of 6414

patients with age- and sex-matched controls to investigate the risk of culture-positive bacterial enteric infections with PPI use. They found a dose-dependent relationship with a relative risk (RR) of 2.9 (95% CI 2.5–3.5) between gastroenteritis and PPI use. A meta-analysis evaluating 6 observational studies comprising 11,280 patients found a significant association between PPI use and bacterial enteric infection (OR 2.55; 95% CI 1.53 and 4.26).²⁴ The investigators also found a quantitatively smaller association between use of H₂-receptor antagonists (H₂RAs) and bacterial enteric infection. Taken together, these observations suggest an association between acid suppression and enteric bacterial infections. H₂RAs are associated with a lower risk than PPIs, so there may be some degree of dose response. However, the magnitude of the increased risk is small. In general, when estimates of effect sizes from observational studies are small, they should not be interpreted as proving causation; they imply an association and might be considered to generate hypotheses.

Pneumonia

Gastric acid suppression has also been associated with the development of both community-acquired and nosocomial pneumonia. The proposed mechanism of infection is through the ability of bacteria to colonize the upper GI tract because of the increase in gastric pH with PPI therapy.²⁵ The association between PPI use and leukocyte inhibition may also play a role.²⁰ In a population-based cohort study of 364,683 individuals, Laheij and colleagues²⁶ reported that PPI use was associated with community-acquired pneumonia (CAP) (RR 1.89; 95% CI 1.36–2.62). This association was dose-dependent, with patients on higher doses of PPI having a higher risk of developing CAP.²⁶ However, there were significant confounders in this study, which did not control for the presence of GERD or chronic obstructive pulmonary disease in their cohort. Sarkar and colleagues²⁷ subsequently conducted a nested case-control study of 80,066 patients, in which those who were started on a PPI within the 30 days preceding the diagnosis of CAP had a higher risk than those who had been on long-term PPI treatment. The highest risk of CAP was seen within the first 2 days of PPI therapy (OR 6.53; 95% CI 3.95–10.80). The association between CAP and short-term, but not long-term, PPI use may be an example of protopathic bias, in which patients presenting to their health care providers with certain symptoms were inappropriately prescribed a PPI.

Herzig and colleagues²⁸ investigated the risk of nosocomial pneumonia and PPI use in a prospective cohort of 63,878 patients who were not ventilated and who were hospitalized for at least 72 hours. The OR for developing nosocomial pneumonia for patients on PPIs was 1.3 (95% CI 1.1–1.4) in a multivariate analysis and the association was strongest with aspiration than for nonaspiration pneumonia.

Based on these studies, there may be a slightly increased risk of both CAP and nosocomial pneumonia associated with PPI use. However, the magnitude of the observed effect is small and at least some of the studies were prone to confounding.

Rebound Hypersecretion

One of the consequences of acid suppression with a PPI is hypergastrinemia, which in turn causes enterochromaffinlike cell hyperplasia and may, ultimately, lead to parietal cell hyperplasia. Thus, the potential exists for increased gastric acid secretory capacity compared with that which existed before the introduction of the PPI. This potential has led to concern about the possibility of rebound acid hypersecretion when stopping PPIs after prolonged use.^{29,30}

Reimer and colleagues³¹ conducted a randomized, double-blind, placebo-controlled study in 120 asymptomatic individuals to investigate the possibility of new upper GI symptoms,

possibly related to rebound acid hypersecretion, after 8 weeks of therapy with esomeprazole. They found that heartburn and dyspeptic symptoms were statistically significantly increased among the subjects who had discontinued esomeprazole compared with those who had discontinued placebo, with onset approximately 2 to 4 weeks after stopping the PPI. This study claimed that some previously asymptomatic individuals temporarily develop upper GI symptoms (possibly caused by rebound acid hypersecretion, which was not measured) after withdrawal of a PPI. However, these symptoms were temporary and of a minor nature and should not dissuade physicians from prescribing a PPI to patients with legitimate symptoms expected to respond to acid suppression. At least 1 further study has reported similar findings to Reimer and colleagues.³¹ Niklasson and colleagues³² reported more severe symptoms after PPI withdrawal, but these were also more transient than those detected by Reimer and colleagues. The clinical significance of these findings has been questioned.³³

Bone Health

In 2006, Yang and colleagues³⁴ published a nested case-control study investigating the risk of hip fracture with PPI use. They identified 13,566 patients with hip fractures and found that greater than 1 year of PPI use was associated with an adjusted OR of 1.44 (95% CI 1.30–1.59). This risk appeared to increase with PPI dose and with duration of treatment. One theoretic mechanism for the increase in hip fractures was that gastric acid suppression decreases dietary calcium absorption and, in time, this may lead to relative demineralization of bone, osteopenia, osteoporosis, and an increased fracture risk.³⁵ A retrospective matched cohort study of 15,792 patients found that PPI use was only associated with hip fracture after more than 6 years of exposure (adjusted OR 1.92; 95% CI 1.16–3.18).³⁶ Corley³⁷ conducted a retrospective case-control study using the Kaiser Permanente database for Northern California. He matched more than 33,000 individuals with hip fracture with more than 130,000 controls. Greater than 2 years of PPI use was associated with a 30% increase in the rate of hip fracture (OR 1.30; 95% CI 1.21–1.39). In addition, greater than 2 years of H₂RA use was also associated with a slightly increased risk (OR 1.18; 95% CI 1.08–1.28). Corley³⁷ was able to demonstrate a positive dose-response relationship between PPI use and hip fracture but did not identify any duration-response relationship.

However, a recent study by Targownik and colleagues³⁸ conducted both a cross-sectional and longitudinal analysis investigating bone mineral density in 2193 and 2549 patients, respectively. The longitudinal study investigated change in bone mineral density in a 1- to 3-year span. The cross-sectional study found no significant relationship between bone density and PPI use. Similarly, PPI use did not have a significant effect on bone mineral density in patients in the longitudinal analysis. Another nested case-control study by Kaye and Jick³⁹ found no association between PPI use and hip fracture in 1098 patients.

There are slightly inconsistent results among the different retrospective studies of PPI use and fractures. However, most studies suggest a weak positive association, and some criteria for causation are also fulfilled, notably a dose-response relationship and, at least in most of the studies, a duration-response relationship. Although there was a once-plausible biologic rationale to explain the association, the recent findings by Targownik and colleagues³⁸ call this into question. Patients who have a genuine requirement for PPI treatment should receive it in the lowest effective dose. At this time, there is no recommendation to provide patients with additional bone mineral density monitoring or more than routine calcium and vitamin D supplementation.⁸

B₁₂ Deficiency

Vitamin B₁₂ deficiency, if left untreated or undetected, has potentially serious and irreversible systemic consequences.⁴⁰ An early report of a possible association between B₁₂

deficiency and PPI use (>1 year), was made by Valuck and Ruscin⁴¹ in their case-control study of 53 patients greater than 65 years old and 212 age- and sex-matched controls. However, this association has been questioned based on a cross-sectional study published by den Elzen and colleagues,⁴² which recruited 125 patients more than 65 years of age on PPI therapy for greater than 3 years and used their partners who were not on PPI therapy as the control group. The study patients had serum B₁₂ levels measured and compared with those of their partners. Multivariate analysis, controlling for age, sex, *H pylori* status, and C-reactive protein, showed no statistical difference in B₁₂ levels between patients and their partners. Based on these data, there is no evidence of a discernable association with PPI use and the development of B₁₂ deficiency.⁴³

Side Effects, Anaphylaxis, and Allergy

As a class, PPIs are well tolerated with few reported side effects,⁴⁴⁻⁴⁶ the most common being headache, constipation, diarrhea, dizziness, and rash.¹⁻⁶ There have been several case reports and series of anaphylactic and allergic reactions to PPI therapy. The largest published case series described 9 patients with adverse reaction to omeprazole: urticaria/angioedema in 7 and anaphylaxis in 2.⁴⁷ Most of these patients had positive pin-prick tests suggesting immunoglobulin E-mediated allergy. Four patients also had a positive pin-prick test to pantoprazole. However, lansoprazole was well tolerated, suggesting a lack of a class effect with anaphylactic reactions.

Another reported adverse reaction to PPI therapy is acute interstitial nephritis (AIN). In a systematic review, Sierra and colleagues⁴⁸ identified 64 cases of PPI-associated AIN, 59 of which were proven by biopsy. All of the PPIs, except for dexlansoprazole (which was not available at that time), were implicated, suggesting a class effect. In addition, there was improvement in renal function by a mean of 35.5 weeks after withdrawal of PPI therapy, but creatinine levels did not return to baseline.⁴⁸ Evidence for causality in the cases reviewed was often poor; in general, patients have not been challenged with reintroduction of the suspected PPI, for obvious reasons. However, these adverse effects are tempered by the extremely low overall rate of adverse reactions, estimated at 0.01% in one case series.⁴⁹

Pregnancy

Given the widespread use of PPIs, there is concern about their possible effects on the developing fetus. Omeprazole is listed by the FDA as a pregnancy class C medication, whereas all other currently available PPIs are class B, which still denotes a possible serious risk to the fetus.¹⁻⁶ Gill and colleagues⁵⁰ recently published a systematic review evaluating the risk of PPI use in pregnancy. Among 1530 PPI-exposed subjects compared with 133,410 controls, they found no association between major fetal malformations, spontaneous abortions, or pre-term delivery. This lack of association was also apparent when omeprazole alone was investigated.

However, there is some suggestion that acid suppression alone may have an adverse effect on an exposed fetus. In a recent, large, case-control study investigating children with asthma, Dehlink and colleagues⁵¹ found a relationship between maternal gastric acid suppression with a PPI or H₂RA and the development of childhood asthma (OR 1.43; 95% CI 1.29–1.59). The postulated mechanism, based on animal model data, is that acid suppression increases type 2 helper cell bias in their offspring, thus predisposing to increased atopy.⁵¹ Based on these data, the immediate fetal developmental risk of PPIs may be negligible. However, possible risks to the fetus that may only become manifest in childhood require further study.

A summary containing our assessment of the clinical relevance of the various proposed adverse effects of PPIs is given in Table 1.

H₂RAS

Cimetidine, ranitidine, famotidine, and nizatidine are commonly used and widely available medications used to treat acid-related disorders. They are generally well tolerated and have a low incidence of side effects,⁵²⁻⁵⁴ with the most commonly ascribed being diarrhea, dizziness, and headache. The estimated incidence of drug-related side effects is 5% to 8%.^{52,53} However, in a pooled analysis the side effects were no greater than placebo treatment for ranitidine and famotidine.⁵²

The H₂RA with the most reported DDIs is cimetidine, because it is the most potent inhibitor of the cytochrome P450 system and the H₂RA that has been in clinical use for the longest time. The potential exists for interactions with medications that are extensively metabolized by cytochrome P450 and have a narrow therapeutic index, such as warfarin, theophylline, and phenytoin. However, the incidence of clinically relevant DDIs with cimetidine is extremely low, and all the H₂RAs, including cimetidine, are now widely available for purchase without a prescription. The affinity of ranitidine for the cytochrome P450 system is approximately one-sixth that for cimetidine, whereas famotidine and nizatidine have no apparent cytochrome P450 interaction.⁵⁵

In the study by Yu and colleagues,⁵⁶ neither the cross-sectional bone mineral density cohort nor the prospective fracture cohort showed any relationship between H₂RA use and bone health.

Transient rebound hypersecretion has been shown after stopping H₂RAs, although the mechanism of this remains unclear.⁵⁷

The association between H₂RA use and CAP was studied in the case-control study by Laheij and colleagues²⁶ in 475 subjects and 4690 controls. The association had an adjusted OR of 1.43 (95% CI 1.14–2.23). However, Rodriguez and colleagues⁵⁸ investigated the relationship between CAP and H₂RA use in 278 patients and 241 controls and found no significant relationship between rates of pneumonia and H₂RA use within the prior 31 days. Herzig and colleagues²⁸ found no association between hospital-acquired pneumonia and H₂RA use in their prospective cohort of 5686 subjects and 30,956 controls.

H₂RAs have also been implicated in the development of community-acquired *C difficile* infection, by Dial and colleagues¹⁹ in their case-control study of 83 subjects and 367 controls (adjusted OR 2.0; 95% CI 1.6–2.7). However, there was no evidence of increased risk of other enteric infections in the study by Rodriguez and colleagues,²³ although the systematic review and meta-analysis by Leonard and colleagues²⁴ did suggest a slight increase in risk.

For many of the suspected adverse effects preliminarily attributed to H₂RA use and ascribed to an acid-suppressing effect, the estimates of effect size are small and generally lower than those found with PPIs. This suggests that pharmacologic acid suppression is associated with slight increases in the rates of these events. H₂RAs suppress acid to a lesser extent than PPIs and are associated with even lower degrees of risk. However the H₂RAs have been available since the late 1970s and have had an excellent record of safety and tolerability. It would be surprising if data showing any serious unintended consequence of H₂RA use were to emerge now or in the future.

Uncommon reported reactions to H₂RAs include AIN and hepatotoxicity. There have been 41 reported cases of H₂RA-induced AIN in the literature, with 28 being proven by biopsy.⁵⁹ The patients usually presented with fever and fatigue and were found to have sterile pyuria, proteinuria, and increased erythrocyte sedimentation rate. All the patients described in the series rapidly improved after withdrawal of the medication. H₂RA-related hepatotoxicity and hepatitis have also been rarely reported, with an estimated rate of 0.06%. Ranitidine has been the most commonly implicated, with rates up to 1% of all exposed patients. Normalization of liver function tests typically occurred 1 to 6 weeks after withdrawal of therapy.^{59,60}

H₂RAs are commonly used in pregnancy to control reflux symptoms and seem to have no adverse effects on the fetus.^{61,62} Magee and colleagues⁶¹ investigated H₂RA use among 178 women and matched controls in the first trimester of pregnancy and found no difference in adverse fetal outcomes. Ruigomez and colleagues⁶² analyzed a large population-based cohort of pregnant women who were exposed to cimetidine or ranitidine (or omeprazole) during the first trimester and found no increase in nongenetic congenital malformations with exposure to any of these medicines.

MISCELLANEOUS MEDICINES FOR ACID-RELATED DISORDERS

Sucralfate, magaldrate, and calcium carbonate are commonly used medicines to treat acid-related disorders and are generally safe with few reported side effects. Sucralfate's main side effects are constipation, the potential for aluminum toxicity in patients with impaired renal function, and the possibility of DDIs by decreasing the bioavailability of several other medicines, including fluoroquinolones, H₂RAs, and phenytoin.⁶³ The only significant reported side effect with magaldrate has been mild, self-limiting diarrhea, estimated at 2% in one small series of patients.⁶⁴ Calcium carbonate is a generally benign drug, with only isolated reports of increased total body calcium levels in patients with renal insufficiency, typically with dosages greater than 6 g per day.⁶⁵

SAFETY OF DRUGS USED TO TREAT FGIDS

In the United States, lubiprostone is currently the only FDA-approved medicine to treat irritable bowel syndrome (IBS). It is used in constipation-predominant IBS (IBS-C) and is also approved for the management of chronic constipation. The major side effects in the phase 3 clinical trials of 1171 patients with IBS-C were GI-related (nausea, diarrhea, and abdominal distention) with an incidence of 19% versus 14% in the placebo arm.⁶⁶ The rates of drug discontinuation because of adverse effects were similar between the lubiprostone and placebo arms (25% vs 23%, respectively).⁶⁶

Antispasmodics are frequently used to treat many GI complaints presumed to be related to disturbed motility or smooth muscle spasm (typically, IBS). Dicyclomine and hyoscyamine are commonly used in IBS; although the package inserts note numerous side effects related to their anticholinergic properties, there are no published studies of serious adverse effects.^{67,68}

Loperamide is commonly used for self-treatment of diarrhea. In 2 separate studies conducted in adults and children, there were no differences in rates of adverse events between groups given loperamide or placebo.^{69,70}

Alosetron is a selective 5-hydroxytryptamine type 3 (5-HT₃) antagonist used to treat IBS with diarrhea that is unresponsive to other therapeutic approaches.⁷¹ Constipation was the most common adverse event seen in clinical trials, with a frequency of 20% to 29%; this appeared to be dose-dependent.⁷¹ The drug was temporarily removed from the market in

2000 because of rare cases of severe constipation and resultant mucosal ischemia requiring surgery.^{72,73} The drug was subsequently reintroduced with prescription and dosage restrictions because of these safety concerns.⁷⁴ In a randomized, placebo-controlled trial of 705 patients, there was a dose-dependent 9% to 19% incidence of constipation with alosetron use, and 1 episode of ischemic colitis.⁷⁵

Prokinetic Agents

Metoclopramide is a proximal gut prokinetic that induces acetylcholine release by activating 5-hydroxytryptamine type 4 (5HT₄) receptors while also acting as an antagonist for dopamine D₂ receptors centrally.⁷⁶ Common safety concerns with metoclopramide result from its antidopaminergic effects. Acute dystonic reactions have been reported in 0.2% to 6% of patients, typically within 48 hours of initiating therapy.⁷⁶ The incidence of (sometimes irreversible) tardive dyskinesia has been estimated as between 1% and 15%, typically occurring after more than 3 months of continuous use.^{76,77} Prolonged treatment can also result in a Parkinson-like syndrome, which typically subsides within 2 to 3 months of discontinuation.^{76,77}

Domperidone is a D₂ receptor antagonist that primarily acts to increase motility in the upper gut.⁷⁸ QT prolongation has been a concern with domperidone administration, although there are few data on the incidence of ventricular arrhythmias.⁷⁸

Renzapride is a recently developed prokinetic that is primarily used for IBS with constipation. Lembo and colleagues⁷⁹ evaluated its efficacy in a placebo-controlled, double-blind, randomized trial of 1798 patients. The most common side effects possibly related to renzapride were diarrhea, abdominal pain, nausea, and flatulence, although the incidences were not significantly greater than with placebo. However, in a long-term (>12 weeks) arm of the study of 971 patients, 3 patients on renzapride developed ischemic colitis.⁷⁹

Tegaserod is a selective 5HT₄ agonist that was developed for IBS-C, chronic constipation, and functional dyspepsia. Its use was suspended in 2007 because of concerns about an increase in ischemic cardiovascular events based on a review of phase III clinical trial data. However, subsequent data from a case-control study of 2603 tegaserod users found no increase in cardiac events.⁸⁰ Chey and colleagues⁸¹ evaluated the safety and efficacy of tegaserod in 780 patients in separate 1-year extension studies. The most commonly reported adverse event was diarrhea, with an incidence of approximately 10%, which was generally moderate and led to discontinuation in only 5.9% of patients. Adverse cardiovascular events that were potentially drug related had an incidence of less than 1%.

SUMMARY

Most of the drugs reviewed here have low risks of serious adverse events. At the time of writing, concerns about the interaction between PPIs and clopidogrel were foremost in the minds of prescribers. Other possible consequences of long-term PPI use have also been discussed in detail because these drugs are extremely widely used and because some of the proposed adverse effects can have serious consequences. Clinicians need to be aware of the safety profiles of the drugs they frequently prescribe in their practices. All prescribing decisions are essentially based on a risk-benefit analysis, whether conscious or subconscious. Evidence of benefit is essential, and this must be balanced with an understanding of (even very low) levels of risk.

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Table 1

Potential safety issues associated with PPI use

Safety Issue	Clinical Significance
Cytochrome P450 interaction	Negligible
Clopidogrel interaction	Unclear
<i>Clostridium difficile</i> infection	Probable
Other enteric infections	Probable
Pneumonia	Probable
Rebound hypersecretion	Negligible
Fractures	Negligible
Idiosyncratic reactions (AIN, hepatitis)	Rare
Anaphylaxis	Rare
Pregnancy risk	Likely negligible