omeprazole having an OE of 1.00), the relative potencies of standard-dose pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole have been estimated at 0.23, 0.90, 1.00, 1.60, and 1.82 OEs, respectively (52,53).

PPIs can bind only to proton pumps that are actively secreting acid. Because meals stimulate proton pump activity, enteric-coated PPIs control intragastric pH best when given before a meal (30–60 minutes before breakfast for once-daily dosing and 30–60 minutes before breakfast and dinner for twice-daily dosing (54,55)). Bedtime dosing is discouraged because this is less effective than a predinner dose in acid control (56).

Dexlansoprazole, a dual delayed release PPI, in which first absorption is in the duodenum, then partially further down the small bowel, seems to have similar efficacy in pH control regardless of meal timing. An omeprazole-sodium bicarbonate combination that is not enteric-coated provides good control of intragastric pH in the first 4 hours of sleep when dosed at bedtime (57). There seems to be a wide variation in individual intragastric pH control between PPIs, a rationale for considering switching PPIs in patients with incomplete response (58). In a study of 282 patients with persistent heartburn on lansoprazole 30 mg once daily who were randomized either to double the dose of lansoprazole or to switch to esomeprazole 40 mg once daily, the 2 strategies were equally effective, with approximately 55% of patients in both groups experiencing a decrease in the percentage of heartburn-free days (59). Studies suggest that genetic differences in CYP2C19 metabolism affect PPI response; however, genetic testing in this regard has no established role in practice. If one is considering a PPI switch, changing to a PPI that does not rely on CYP2C19 for primary metabolism (rabeprazole) might be considered.

Maintenance PPI therapy should be administered for patients with GERD complications including severe EE (LA grade C or D) and Barrett's esophagus (60). For patients without EE or Barrett's esophagus who continue to have symptoms when PPI therapy is discontinued, consideration can be given to on-demand therapy in which PPIs are taken only when symptoms occur and discontinued when they are relieved (61,62). Two-thirds of patients with non-erosive disease responsive to PPIs will demonstrate symptomatic relapse when PPIs are stopped. With LA grade C esophagitis, nearly 100% will relapse within 6 months (63). Recurrence of EE after discontinuation can occur in as little as 1–2 weeks, particularly in patients with previous LA grade C EE (18). Patients with LA grade C or D EE should remain on long-term PPI therapy to maintain healing.

In some cases, patients with NERD and otherwise non-complicated GERD can be managed successfully with on-demand or intermittent PPI therapy. In 1 RCT, 83% of patients with NERD randomized to 20 mg of omeprazole on demand were in remission at 6 months compared with 56% of patient on placebo (64). In a systematic review of RCTs comparing on-demand PPI vs placebo, symptom-free days for patients with NERD in the on-demand arm were equivalent to rates for patients on continuous PPI therapy, and both on-demand and continuous PPIs were superior to placebo. On-demand PPI therapy was not better than continuous PPI therapy for patients with EE. Step-down therapy to H2RAs is another acceptable option for management, particularly in patients with NERD (65,66).

Use of the lowest effective dose is recommended and logical but must be individualized. One area of controversy relates to abrupt PPI discontinuation and potential rebound acid hypersecretion, resulting in increased reflux symptoms. Although rebound acid hypersecretion has been demonstrated to occur in healthy controls, strong evidence for an increase in symptoms after abrupt PPI withdrawal is lacking (67–69).

H2RA taken at bedtime

Medical options for patients with GERD with incomplete symptom response on PPI therapy are limited. The addition of bedtime H2RA has been suggested for patients on PPIs with persistent nocturnal symptoms. This approach gained popularity after several studies demonstrated improved overnight intragastric pH control with the addition of an H2RA (70), although a well-performed study demonstrated loss of pH control (tachyphylaxis) after a month of bedtime H2RA therapy (71). Based on these data, use of a bedtime H2RA may be beneficial if dosed on an as-needed basis for patients with nocturnal symptoms and for patients with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment.

Prokinetics

There are limited data on the use of prokinetic agents for patients with GERD. Metoclopramide has been shown to increase LES pressure, enhance esophageal peristalsis, and augment gastric emptying. However, data on its efficacy in GERD are scant, and significant adverse events have been reported with long-term and high-dose metoclopramide use, including central nervous system side effects such as drowsiness, agitation, irritability, depression, dystonic reactions, and tardive dyskinesia (72,73). Thus, we do not recommend using metoclopramide solely for the treatment of GERD. Prucalopride, a 5 HT agonist US Food and Drug Administration (FDA)-approved for treatment of constipation, was shown in 1 off-label use study to improve gastric emptying and reduce esophageal acid exposure in patients with GERD. In the future, this may be a potential add-on therapy for patients with GERD on PPIs found to have delayed gastric emptying (74).

Baclofen

Baclofen, a $GABA^B$ agonist, reduces the transient LES relaxations that enable reflux episodes. Baclofen decreases the number of postprandial acid and nonacid reflux events, nocturnal reflux activity, and belching episodes (75–77). A trial of baclofen at a dosage of 5–20 mg 3 times a day can be considered in patients with objective documentation of continued symptomatic reflux despite optimal PPI therapy. Short-term RCTs have demonstrated symptomatic improvement with baclofen (75–77). A randomized, placebo-controlled trial of medical therapy (including baclofen) vs antireflux surgery for PPI-refractory heartburn found no significant benefit for baclofen compared with placebo at 1 year, but the study was not sufficiently powered to detect a small but potentially important effect for baclofen (24). Usage is limited by side effects of dizziness, somnolence, and constipation.

Sucralfate

Sucralfate is a mucosal protective agent, but few data document its efficacy in GERD. Limited studies have suggested similar efficacy to H2RAs, but there are no comparative data to PPIs nor any combination studies with these agents. Sucralfate is largely unabsorbed and has no systemic toxicity. There is little to recommend for this agent in GERD outside of pregnancy.

Treatment of GERD during pregnancy

A small RCT found that sucralfate was superior to dietary and lifestyle modifications for relieving heartburn and regurgitation in pregnant women (78). Approximately two-thirds of pregnant women experience heartburn. It has been recommended that treatment of GERD during pregnancy should start with lifestyle