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Review article

A review of medical therapy for proton pump inhibitor nonresponsive gastroesophageal reflux disease

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SUMMARY. **Up to 40% of patients report persistent gastroesophageal reflux disease (GERD) symptoms despite proton pump inhibitor (PPI) therapy. This review outlines the evidence for medical therapy for PPI nonresponsive GERD. A literature search for GERD therapies from 2005 to 2015 in PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews identified 2928 unique citations. Of those, 40 unique articles specific to the impact of PPI metabolizer genotype on PPI response and the use adjunctive medical therapies were identified. Thirteen articles reported impacts on CYP genotypes on PPI metabolism demonstrating lower endoscopic healing rates in extensive metabolizers; however, outcomes across genotypes were more uniform with more CYP independent PPIs rabeprazole and esomeprazole. Twenty-seven publications on 11 adjunctive medications showed mixed results for adjunctive therapies including nocturnal histamine-2 receptor antagonists, promotility agents, transient lower esophageal sphincter relaxation inhibitors, and mucosal protective agents. Utilizing PPI metabolizer genotype or switching to a *CYP2C19* independent PPI is a simple and conservative measure that may be useful in the setting of incomplete acid suppression. The use of adjunctive medications can be considered particularly when the physiologic mechanism for PPI nonresponse is suspected. Future studies using adjunctive medications with improved study design and patient enrollment are needed to better delineate medical management options before proceeding to antireflux interventions.**

KEY WORDS: **adjunctive medication, rapid metabolizer, refractory gastroesophageal reflux disease.**

ABBREVIATIONS: CYP: cytochrome p450; EAE: esophageal acid exposure; EE: erosive esophagitis; ESO: esomeprazole; FDA: Food and Drug Administration; FSSG: Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease; GABA: γ-aminobutyric acid; GERD: gastroesophageal reflux disease; H2RA: histamine-2 receptor antagonisthetero; EM: extensive metabolizer; homoEM: heterozygous extensive metabolizer; LAN: lansoprazole; NERD: nonerosive reflux disease; OME: omeprazole; PM: poor metabolizer; PPI: proton pump inhibitor; PPINR: PPI nonresponder; RBZ: rabeprazole; RCT: randomized controlled trial; TLESR: transient lower esophageal sphincter relaxation.

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INTRODUCTION

Up to 40% of patients report persistent gastroesophageal reflux disease (GERD) symptoms despite proton pump inhibitor (PPI) therapy.[1] The clinical approach to PPI nonresponsive GERD is unclear and heterogeneous, with some patients referred for invasive antireflux interventions and others continued on the same or an increased PPI dose. Although pharmaceutical options are available to target physiologic mechanisms of PPI nonresponse such as transient lower esophageal sphincter relaxation (TLESR) with reflux, incomplete acid suppression, impaired esophageal clearance mechanisms, and delayed gastric emptying, the role of these adjunctive medications is not well delineated in the literature.

Targeting these mechanisms with medications may improve symptoms and eliminate the need for antireflux interventions. For instance, stimulation of γ-aminobutyric acid (GABA) type B receptors by medications such as baclofen may decrease TLESR related acidic and nonacidic reflux episodes.[2] Since genetic polymorphisms of CYP isoenzyme *CYP2C19* result in distinct metabolizer groups with extensive metabolizers (homoEM) having lower plasma PPI levels and subsequently lower intragastric pH compared to heterozygotes (heteroEM) and poor metabolizers (PM), specific PPIs (e.g. rabeprazole (RBZ) and esomeprazole (ESO)) that are more independent of *CYP2C19* metabolism may provide better acid suppression in homoEM.[3–7] Histamine-2 receptor antagonists (H2RAs) are another choice for added gastric acid suppression by blocking the histamine-2 receptors of parietal cells, particularly in cases of nocturnal acid breakthrough that occurs in up to 75% of patients on PPI.[8] Agents with prokinetic properties such as selective 5-HT_4-receptor agonists (e.g. mosapride, revexepride, and prucalopride) and selective dopamine receptor antagonists (e.g., domperidone) are proposed as adjunctive medications for PPI nonresponse in setting of delayed gastric emptying.[9–11] In addition, domperidone has been shown to increase lower esophageal sphincter pressure.[12] Providing esophageal mucosal protection from acidic and nonacidic contents is another potential approach to PPI nonresponse. Irsogladine is a selective phosphodiesterase-4 inhibitor that provides mucosal protection by activating gap junction intercellular communication.[13,14] Rebapimide is an amino acid derivative of 2(1H)-quinolinone with complex mechanisms for gastroesophageal mucosal protection: promotion of ulcer healing, scavenging of oxygen radicals, and inhibition of immunoinflammatory responses.[15] Lastly, mirgeal is an alginic acid delivery system that contains glycyrrhetinic acid and anthocyanosides (both of which have mucosal protective properties).[16,17]

Thus, pharmaceuticals are available to target various mechanisms of PPI refractory GERD. The objective in this study is to perform a systematic search and provide a narrative review of the evidence for pharmaceutical options in cases of PPI nonresponse.

MATERIALS AND METHODS

Search strategy

We conducted targeted systematic literature searches of articles published in English from 2005 to 2015 in PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews on July 10, 2015 (see Supplementary Material for a detailed description of the search strategy and query results). Of 3,259 records retrieved, we removed 331 duplicate records and uploaded the remaining 2,928 records to Covidence for title and abstract screening. Through manual review of the citations of studies meeting inclusion criteria, we identified six additional studies that underwent the same screening process (Fig. 1).

Study and participant selection

The initial study screening of title and abstract was assessed by a single author (LH). All trials evaluating the efficacy of PPI therapy or adjunctive medical therapy for the management of GERD in adults were eligible for full-text review. After the initial screen, 202 studies underwent independent full-text screening by two authors (LH, AJT). Only full-text articles available in English were included. All study types, including case reports, were eligible for review.

The predetermined objective was to limit the review to study participants with objective evidence of PPI refractory GERD. However due to the significant paucity of such studies, studies that enrolled participants irrespective of how the diagnosis of GERD was made, including self-reported symptoms, positive symptom questionnaire, presence of erosive esophagitis (EE) on endoscopy, or abnormal pH study.

Studies including the following were excluded: subjects <18 years old, specific subsets of patients (i.e., systemic sclerosis), and primary endpoints of extraesophageal symptoms. Studies utilizing dietary or herbal supplements were also excluded. Studies evaluating hepatic cytochrome p450 (CYP) genotypes needed to report either symptomatic or physiologic responses to PPI therapy according to genotype. Adjunctive medication studies were only included if the medication of interest was used in conjunction with PPI therapy, irrespective of previous PPI response. Any disagreements during study selection were resolved by a third author (RY).

Outcomes

The primary outcomes of interest were: (1) Improvement in GERD symptoms as assessed by a validated symptom questionnaire or patient report, and

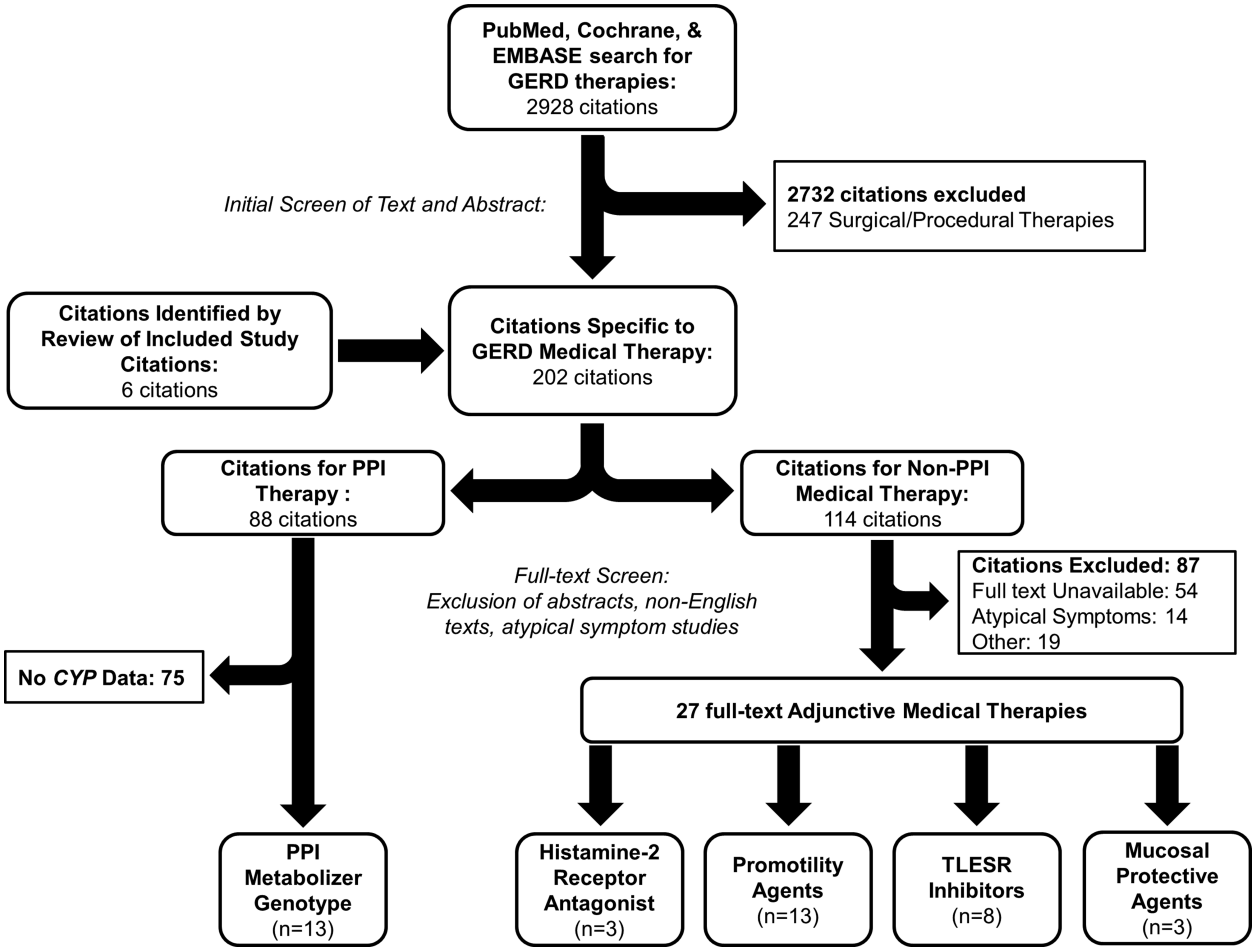

Fig. 1 Search results for GERD medical therapies between 2005 and 2015 of PubMed, Cochrane, and EMBASE databases and screening process. TLESR, transient lower esophageal sphincter relaxation.

(2) Physiologic parameters including distal esophageal acid exposure (EAE; % time pH < 4), DeMeester score, reflux events, and EE healing.

Data extraction and reporting

Two authors (LH, AJT) independently extracted data using a standardized data extraction form which contained the items: (1) general information: study title, authors, date; (2) study characteristics: design, intervention, and duration of follow-up; (3) patient characteristics: number of patients enrolled, diagnosis of GERD, history and response to PPI therapy; (4) primary outcome measurements: symptomatic and objective response as defined above.

RESULTS

PPI metabolizer genotypes

Of the 88 articles evaluating PPI therapy, 13 articles reported response according to *CYP2C19* genotype. GERD was diagnosed by EE on endoscopy in 11 studies, positive pH study in one, and by symptoms in another.

CYP2C19-dependent PPIs

In patients with healed EE treated with lansoprazole (LAN) 15 mg daily, symptom recurrence was greater in homoEM (89%) compared to PM (50%), and correspondingly, the 6 month remission rate of EE was lower in homoEM (62%) compared to PM (100%) (Table 1).[18,19] OME 10 mg or 20 mg resulted in comparable endoscopic healing rates of EE (73% vs. 80%, respectively) and symptoms response rates (96% vs. 100%) at 12 months in both homoEM and PM.[20] Conversely, in patients with EE treated with OME 20 mg twice daily for 4 weeks, homoEM demonstrated lower endoscopic healing rates (55% vs. 81%, respectively) and symptom remission rates (43% vs. 95%) than heteroEM.[21] Lastly, symptom response rates in obese patients with EE treated with pantoprazole 40 mg daily for 8 weeks varied between homoEM (68%), heteroEM (74%), and PM (100%), but this difference diminished with double-dose PPI (82%, 95%, and 100%, respectively).[22] Double-dose PPI treatment also resulted in significantly higher rates of symptom

Table 1 PPI metabolizer genotypes—CYP2C19-dependent PPIs

References	Study design	CYP genotypes (*n*)	Symptomatic response	Physiologic parameters
Kawamura *et al.*[18]	Multicenter cohort of 82 Japanese patients with EE and mucosal healing after 8 weeks PPI treated with LAN 15 mg daily for 6 months	• HomoEM: 26 • HeteroEM: 41 • PM: 15	Symptom remission • HomoEM: 92.0% (24/26) • HeteroEM: 90.2% (37/41), P = NS* • PM: 100% (15/15), P = NS*	EE remission • Total: 76.8% (63/82) • HomoEM: 61.5% (16/26) • HeteroEM: 78.0% (32/41), $P < 0.01$* • PM: 100% (15/15), $P < 0.01$*
Furuta *et al.*[19]	Cohort of 124 Japanese patients with EE and mucosal healing after 8 weeks LAN 30 mg treated with maintenance LAN 30 mg if Sx >1/week or ↓ to15 mg if Sx < 1/week. Dose ↑ to 30 mg if Sx recurred on lower dose, follow-up not specified	• HomoEM: 54 • HeteroEM: 56 • PM: 14	Symptom recurrence on LAN 15 mg • HomoEM: 88.9% (26/18) • HeteroEM: 78.6% (22/28), $P = 0.02$* • PM: 50.0% (4/8), $P = 0.01$* Patients requiring LAN 30 mg • HomoEM: 96.3% (52/54) • HeteroEM: 89.3% (50/56) • PM: 71.4% (10/14), $P = 0.01$*	Not reported
Ohkusa *et al.*[20]	Multicenter cohort of 121 Japanese patients with recurrent EE requiring long-term PPI therapy treated with OME 10 mg or 20 mg, follow-up 6 months (n = 100), 12 months (n = 69)	• HomoEM: 46 • HeteroEM: 53 • PM: 20 • Unknown: 2	Symptom improvement/recurrence @ 12 months • HomoEM: 96.2% (25/26) • HeteroEM: 96.0% (24/25) • PM: 100.0% (15/15)	EE healing @ 12 months • HomoEM: 73.1% • HeteroEM: 84.0% • PM: 80.0%
Zendehdel *et al.*[21]	Cohort of 82 Iranian patients with EE treated with OME 20 mg twice daily for 4 weeks, comparison between homoEM vs. heteroEM as only 1 PM	• HomoEM: 58 • HeteroEM: 23 • PM: 1	Resolution of symptoms • HomoEM: 43% • HeteroEM: 95%, $P < 0.01$	EE healing (≥1 change LA classification) • HomoEM: 12/22 • HeteroEM: 13/16
Chen *et al.*[22]	Randomized trial of 200 overweight/obese Taiwanese patients with EE LA Class A/B treated with double-dose PAN (40 mg twice daily) or standard-dose PAN (40 mg daily) + placebo for 8 weeks	Double dose • HomoEM: 42 • HeteroEM: 41 • PM: 17 Standard dose • HomoEM: 39 • HeteroEM: 45 • PM: 16	SSR (asymptomatic for last 7 days) PP Double dose • HomoEM: 82.1% (32/39) • HeteroEM: 94.9% (37/39) • PM: 100% (17/17) Standard dose • HomoEM: 68.4% (26/38) • HeteroEM: 73.7% (28/38) • PM: 100% (16/16)	Not reported

*Compared to HomoEM.
EE, erosive esophagitis; heteroEM, heterozygous extensive metabolizer; homoEM, homozygous extensive metabolizer; mo, month; LA, Los Angeles; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; PM, poor metabolizer; PP, per protocol; PPI, proton pump inhibitor; RCT, randomized controlled trial; SSR, sustained symptomatic response; Sx, symptoms; wk, week.

Table 2 PPI metabolizer genotypes—CYP2C19-independent PPIs and comparison

References	Study design	CYP genotypes (n)	Symptomatic response	Physiologic parameters
Ariizumi *et al.*[23]	Multicenter cohort of 103 Japanese patients with EE treated with RBZ 10 mg for 8 weeks	• HomoEM: 36 • HeteroEM: 50 • PM: 17	Symptom resolution • HomoEM: 93.8% (30/32) • HeteroEM: 79.1% (34/43) • PM: 81.3% (13/16)	EE healing • HomoEM: 86.1% (31/36) • HeteroEM: 92% (46/50) • PM: 82.4% (14/17)
Kinoshita *et al.*[24]	Multicenter, double-blind RCT of Japanese patients with NERD treated with RBZ 10 mg ($n = 98$), RBZ 5 mg ($n = 88$), or placebo ($n = 88$) for 8 weeks, comparing response according to CYP genotypes	RBZ 10 mg • HomoEM: 32 • HeteroEM: 52 • PM: 17 RBZ 5 mg • HomoEM: 34 • HeteroEM: 40 • PM: 19	Symptom resolution RBZ 10 mg • HomoEM: 44% (14/32) • HeteroEM: 44% (23/52) • PM: 41% (7/17) RBZ 5 mg • HomoEM: 32% (11/34) • HeteroEM: 38% (15/40) • PM: 32% (6/19)	Not reported
Yamano *et al.*[25]	Cohort of 19 Japanese patients with m-LA class M ($n = 3$) or LA class ≥A ($n = 16$) treated with RBZ 10 mg for 8 weeks	• HomoEM: 5 • HeteroEM: 8 • PM: 6	Not reported	Intragastric pH > 4 • HomoEM: 58.4% • HeteroEM: 53.1% • PM: 71.5% m-LA classification (N/M/A/B/C) • HomoEM: Pre: 0/0/1/3/1 Post: 0/5/0/0/0 • HeteroEM: Pre: 0/1/2/3/2 Post: 5/3/0/0/0 • PM: Pre: 0/2/0/3/1 Post: 3/3/0/0/0
Takeuchi *et al.*[26]	Cohort of 60 Japanese patients with EE treated with OME 20 mg daily for ≥8 weeks. If FSSG ≥ 8 at 8 weeks, patients ($n = 17$) switched to RBZ 20 mg for 8 weeks	• Homo/HeteroEM: 14 • PM: 3	Symptom improvement (FSSG < 8) • Homo/HeteroEM: 14.3% (2/14) • PM: 66.7% (2/3)	Not reported
Hsu *et al.*[27]	Cohort of 184 Taiwanese patients with EE treated with ESO 40 mg for 8 weeks then ESO on-demand until symptom relief for 12 weeks (total 20 weeks follow-up)	• HomoEM: 60 • HeteroEM: 98 • PM: 26	Symptom relapse • HomoEM: 65% (39/60) • HeteroEM: 52% (51/98) • PM: 69.2% (18/26)	Persistent EE • HomoEM: 43.3% (26/60) • HeteroEM: 50% (49/98) • PM: 34.6% (9/26)
Schwab *et al.*[28]	Case-control of 205 European patients with EE LA A/B treated with ESO 40 mg for 4 weeks comparing EE healing according CYP2C19 genotype	• HomoEM: 148 • HeteroEM: 51 • PM: 6	ΔUASQ Score • HomoEM: -14.2 • HeteroEM/PM: −12.9, $P = 0.48$	EE Healing • HomoEM: 50.7% (75/148) • HeteroEM/PM: 43.9% (25/57)
Comparison of response to CYP219-dependent and independent PPIs				
Nagahara *et al.*[29]	Multicenter randomized trial of 99 Japanese patients with EE and baseline GOS ≥ 4 treated with OME 20 mg ($n = 101$) or RBZ 10 mg ($n = 98$) for 4 weeks	OME 20 mg • HomoEM: 36 • HeteroEM: 40 • PM: 23 • Unknown: 2 RBZ 10 mg • HomoEM: 37 • HeteroEM: 42 • PM: 19	Symptom relief day 4–7 in PM • OME: 62.5%–66.9% vs. RBZ: 31.6%, $P < 0.03$ Sustained Symptom relief @ 2–4 weeks • NS for homo/EM and heterEM, values not provided • 2 weeks: OME: 78.3% vs. RBZ: 42.1%, $P = 0.02$ • 4 weeks: OME: 95.7% vs. RBZ: 68.4%, $P = 0.02$	Not reported

Table 2 *continued*

References	Study design	CYP genotypes (n)	Symptomatic response	Physiologic parameters
Saitoh *et al.*[30]	Cohort of 99 Japanese patients with EE with mucosal healing after 8 weeks of RBZ 10 mg, OME 20 mg or LAN 30 mg and asymptomatic subsequently treated with RBZ 10 mg ($n = 45$), OME 20 mg ($n = 28$) or LAN 15 mg ($n = 26$) for 6 months	• HomoEM: 25 • HeteroEM: 56 • PM: 18	Recurrence of symptoms (QUEST > 4) • HomoEM: 38.5% • HeteroEM: 10.9%, $P < 0.01$* • PM: 5.6%, $P < 0.01$* • RBZ: 4.4% vs. OME 25% vs. LAN 30.8%	Not reported

*Compared to HomoEM.

EE, erosive esophagitis, ESO, esomeprazole, FSSG, Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease; GOS, Global Overall Symptom scale, heteroEM, heterozygous extensive metabolizer; homoEM, homozygous extensive metabolizer; mo, month, LA, Los Angeles; LAN, lansoprazole; OME, omeprazole, NS, not significant, PM, poor metabolizer, PPI, proton pump inhibitor; RBZ, rabeprazole; RCT, randomized controlled trial; UASQ, Upper abdominal symptom questionnaire, wk, week.

response in heteroEM compared to daily dosing and similarly, there was a trend toward increased symptom response with twice daily dosing for homoEM.[22]

CYP2C19 independent PPIs

For patients with EE treated with RBZ 10 mg daily for 8 weeks, homoEM, heteroEM, and PM had similar EE healing rates (86%, 92%, and 82%) and symptom resolution (94%, 79%, and 81%) (Table 2).[23] Likewise, response rates for patients with nonerosive reflux disease (NERD) at 4 weeks were similar across genotypes when treated with RBZ 5 mg (homoEM 32%, heteroEM 38%, and PM 32%) or 10 mg (44%, 44%, and 41%, respectively).[24] In another study, no difference in intragastric pH or EE healing rates was observed between genotypes in patients treated with RBZ 10 mg daily for 8 weeks.[25] Switching PPINR from OME 20 mg to RBZ 20 mg daily was not an effective strategy as there were similar response rates between homoEM/heteroEM and PM (14% vs. 67%), though the study was limited by the small number of PPINR ($n = 17$).[26] In regards to ESO, patients treated with ESO 40 mg daily for 8 weeks, homoEM, hetero EM, and PM had similar rates of persistent EE (43%, 50%, and 35%, respectively) and symptom relapse (65%, 52%, and 69%).[27] Likewise, EE healing rates in patients treated with ESO 40 mg daily were similar regardless of CYP polymorphism.[28]

Comparison of CYP2C19-dependent and independent PPIs

When comparing OME 20 mg and RBZ 10 mg daily in patients with EE, symptomatic relief at 4 weeks was greater in the OME PM group (96%) than in the RBZ PM group (68%); however, symptom response did not differ between the homoEM and hetero EM groups.[29] Additionally, complete resolution of symptoms at four weeks did not differ across genotypes.[29] For patients with healed EE treated with RBZ 10 mg, OME 20 mg, or LAN 15 mg daily, symptom recurrence rate differed by *CYP2C19* genotype (homoEM 39%, heteroEM 11%, and PM 6%); recurrence rate was significantly lower with RBZ (4%) than OME (25%) or LAN (31%), but subgroup analysis according to genotype was not performed for each PPI.[30]

Adjunctive medical therapies

Of 114 citations reporting non-PPI medical therapy for GERD, 87 citations were excluded and 27 studies were reviewed. Twelve studies were excluded because of lack of co-PPI therapy.

Histamine-2 receptor antagonists

A 2009 Cochrane review found that additional bedtime H2RA therapy increases duration and degree of intragastric pH; however, the review did not address EAE or control of symptoms (Table 3).[31] In a retrospective cohort study, addition of nighttime ranitidine

Table 3 Adjunctive histamine-2 receptor antagonist therapy

References	Study design	Diagnosis of GERD	PPI history	Symptomatic response	Physiologic response
Wang *et al.*[31]	Cochrane review of eight RCTs evaluating nocturnal H2RA for gastric acid breakthrough in addition to once or twice daily PPI	Included normal participants, GERD and peptic ulcer disease	N/A	Not reported	Short term (<4 weeks) • 7 trials ($n = 127$):↓ in NAB (RR 0.43 CI 0.25–0.72) Long term (>1 week) • 1 trial ($n = 10$): no difference in NAB (RR 0.75 CI 0.41–1.36)
Rackoff *et al.*[32]	Retrospective cohort study ($n = 41$) using phone survey to assess efficacy of nocturnal ranitidine 300 mg or famotadine 40 mg for >1 month plus twice daily PPI (various PPIs used)	pH testing: 37/41 EE: 2/41 Both: 2/41	Not reported	Overall symptoms • Improved in 72% (28/39) Nocturnal symptoms • Improved in 74% (25/34) Discontinuation rate (>1 month) • 13% (5/39) due to tachyphylaxis	Not reported
Mainie *et al.*[33]	Retrospective analysis of 100 patients using twice daily PPI (various PPIs used, $n = 42$) or PPI + nocturnal famotidine, ranitidine, or cimetidine (dose not provided, $n = 58$)	Not reported	Nonresponse to twice daily PPI	Subjects with NAB • PPI: 64% vs. PPI + H2RA: 17% (χ^2 21.95, $P < 0.01$) EAE (% time pH < 4) • PPI: 3.3 vs. PPI + H2RA: 1.9 ($P = 0.49$)	+ Symptom Index Nonacid • PPI: 26% vs. PPI + H2RA: 31% + Symptom Index Acid • PPI: 10% vs. PPI + H2RA: 0%

CI, confidence interval; EAE, esophageal acid exposure, EE, erosive esophagitis; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; NAB, nocturnal acid breakthrough; N/A, not applicable; PPI, proton pump inhibitor; RCT, randomized controlled trial; RR, relative risk.

300 mg or famotidine 40 mg improved overall symptoms (72%) and nighttime symptoms (74%); though, 13% discontinued H2RA after 1 month due to tachyphylaxis.[32] When compared to PPI alone, addition of nighttime H2RA for PPINR significantly reduced nocturnal acid breakthrough (17% vs. 64%) and percent intragastric time pH < 4 (18% vs. 31.5%).[33] EAE (1.9 vs. 3.3) and positive symptom index (SI) for acid reflux (0% vs. 10%) were lower but not significantly different.[33]

Promotility agents

Mosapride Three RCTs published from 2005 to 2013 found no improvement in GERD symptoms with adjunctive mosapride therapy (Table 4).[34–36] These studies were included in a 2013 systematic review reporting that mosapride combination therapy with PPI is no more effective than PPI alone.[37] However, in a subgroup analysis, patients with more severe symptoms experienced a slight benefit compared to placebo.[35] Two subsequent studies similarly found no improvement in GERD symptoms with combination mosapride therapy, also noting lower response rates in NERD as compared to EE.[38,39] While the aforementioned studies failed to show significant benefit with adjunctive mosapride therapy across all GERD patients, three open-labeled trials evaluated the effect of mosapride specifically in PPINR. Miyamoto *et al.* reported in two separate studies that PPINR had improved symptom response with mosapride combination therapy (79%–98%), including PPINR with NERD (Frequency Scale for Symptoms of Gastroesophageal Reflux Disease (FSSG) score pretreatment: 17.4 vs. PPI monotherapy: 14.6 vs. combination therapy: 7.7).[40,41] Futagami *et al*. also found combination therapy improved symptoms in PPINR with NERD and delayed gastric emptying; however, there was no difference in acid exposure time, frequency of acid reflux, or esophageal peristalsis after combination therapy.[42]

Prucalopride In a study of four female PPINR with chronic constipation, 2 mg prucalopride daily resulted in reduced total and nonacid reflux episodes with concordant symptom improvement (Table 5).[43]

Revexepride In two RCTs, adjunctive revexepride was no more effective than placebo in symptom control for PPINR. In a phase II trial, Shaheen *et al.* found no significant improvement in heartburn or regurgitation-free days over 8 weeks of revexepride dose escalation compared to placebo, and similarly, Tack *et al.* found no consistent improvement in symptoms or reflux parameters measured by pH impedance testing with revexepride versus placebo.[44,45]

Domperidone In a double-blinded RCT, domperidone 10 mg three times daily plus OME twice daily provided superior symptom relief compared to OME alone (delta FSSG score 7.5 vs. 4.6); however, post-treatment FSSG scores were identical between groups (19.3 vs. 19.3).[46]

Transient lower esophageal sphincter relaxation inhibitors

A 2014 meta-analysis of nine RCTs reported that baclofen reduces the incidence of GERD, EAE, and TLESRs, though studies were not limited to PPI co-therapy or PPINR (Table 6).[47] In PPI responsive patients, the addition of baclofen 20 mg three times daily reduced the total number of reflux episodes in patients with and without hiatal hernia (>3 cm) but had no effect on acidic reflux episodes or esophageal acid exposure time.[48] In symptomatic GERD patients treated with OME daily plus either baclofen 10 mg twice daily or placebo, baclofen significantly reduced the rates of heartburn (4% vs. 46%) and regurgitation (4% vs. 54%, respectively).[49] Arbaclofen and lesogaberon were designed to overcome the unfavorable pharmacokinetics and side effect profile of baclofen but development was halted due to disappointing results.[50–56]

Mucosal protective agents

In patients with EE who achieved symptomatic relief with PPI therapy, symptom recurrence rate at 12 months was lower in patients treated with rebapimide 300 mg daily plus LAN daily (20%) than LAN monotherapy (52%) (Table 7).[57]

An RCT found no difference in symptom control between adjunctive irsogladine and placebo (FSSG score 9.0 vs. 11.2); however, subgroup analysis using the Japanese modified LA classification found significantly improved FSSG scores for those with no minimal change compared to placebo (LA class N, 7.8 vs. 12.5).[58] Neither rebapimide nor irsogladine are currently approved by the US Food and Drug Administration (FDA).

Mirgeal, an alginic acid delivery system containing glycyrrhetinic acid and anthocyanosides (both of which have mucosal protective properties), in combination with PPI provided greater symptom control for PPINR with NERD as compared to alginic acid plus PPI.[16,17,59]

DISCUSSION

We performed a systematic literature search and present a narrative review of 40 studies from 2005 to 2015 regarding the impact of PPI metabolizer genotypes on PPI response and the use adjunctive medical therapies for PPINR. In addition to reviewing the current literature, this paper importantly highlights the critical deficiency of high-quality outcomes based

Table 4 Adjunctive mosapride therapy

References	Study design	Diagnosis of GERD	PPI history	Symptomatic response	Physiologic response
Cho *et al.*[34]	Double-blind, RCT trial comparing ESO 40 mg + mosapride 10 mg tid ($n = 24$) vs. ESO 40 mg + placebo ($n = 19$), follow-up 4 weeks	EGD or abnormal pH testing with typical reflux symptoms (baseline EE: mosapride 46% vs. placebo 37%)	Not reported	>50% improvement in 6-point Likert scale off medication or reduction in symptom severity to mild/absent • Mosapride: 79.2% (19/24) vs. placebo: 68.4% (13/19), $P = 0.65$	LES length and basal pressure unchanged in both groups Distal esophageal amplitude ↑ with mosapride (pre: 81 vs. post: 89, $P = 0.049$), otherwise no significant changes in esophageal peristalsis in either group on HRM.
Hsu *et al.*[35]	Double-blind, randomized, placebo controlled crossover trial comparing LAN 30 mg + mosapride 5 mg tid. ($n = 50$) vs LAN 30 mg + placebo ($n = 46$) × 4 weeks, then crossover × 4 weeks	EE demonstrated on EGD	Excluded if PPI use within 1 month of enrollment	Δ FSSG Score at 4 weeks • Mosapride: −13.42 vs. placebo: −10.85 ($P = 0.10$) Δ FSSG Score for baseline FSSG > 18 at 4 weeks • Mosapride: −18.2 vs. placebo: −12.9 ($P = 0.04$) Stable/improved FSSG score at 8 weeks • Mosapride: 88.6% vs. placebo: 82% ($P = 0.40$)	Not reported
Miwa *et al.*[36]	Double-blind, RCT comparing OME 10 mg + mosapride 5 mg tid ($n = 97$) vs. OME 10 mg + placebo ($n = 95$), follow-up 4 weeks	Typical GERD symptoms >2/week ≤1 week of enrollment and normal EGD ≤ 1 year	Excluded if PPI use ≤ 1 week of enrollment	Δ VAS scale (10 cm scale) • Mosapride: −3.8 vs. placebo: −3.4 ($P = 0.13$) Δ GSRS • Mosapride: −0.8 vs. placebo: −0.8 ($P = 0.86$)	Not reported
Liu *et al.*[37]	Systematic review of seven trials (4 RCTs, 3 open label trials specific to PPINR) evaluating combination mosapride + PPI therapy	Excluded studies if specific description of GERD diagnosis not provided	N/A	Using a fixed-effects model, adjunctive mosapride did not ↑ responder rate compared to PPI alone (PRR 1.132, 95% CI 0.934–1.372)	Not reported
Yamaji *et al.*[38]	Open-label, RCT comparing OME 10 mg + mosapride 5 mg tid ($n = 22$) vs. OME 10 mg ($n = 28$), follow-up 4 weeks	Reflux symptoms >2/week (unspecified timeframe) with EGD ≤ 3 months of enrollment (EE: 18/50)	Excluded if using PPI	Δ FSSG • Mosapride + OME: −6.82 vs. OME: −6.46 ($P = 0.93$) Δ FSSG Reflux-related Symptoms • Mosapride + OME: −5.86 vs. OME: −4.89 ($P = 0.49$)	Not reported
Lim *et al.*[39]	Double-blind, RCT of patients with normal gastric emptying comparing mosapride 5 mg tid + PAN 40 mg ($n = 15$) vs. PAN 40 mg + placebo ($n = 15$), follow-up 8 weeks	GERD diagnosed by Montreal criteria with normal gastric emptying	Excluded if using PPI	• 'Gastroesophageal reflux symptoms improved after treatment and there was no significant difference between two groups'—numbers not provided	$\frac{1}{2}$ gastric emptying time Mosapride + PAN • Pre: 61.2 Post: 65.0 ($P = 0.54$) PAN + placebo • Pre: 57.5 Post: 88.5 ($P = 0.02$)

Table 4 *continued*

References	Study design	Diagnosis of GERD	PPI history	Symptomatic response	Physiologic response
Miyamoto *et al.*[40]	Open label cohort study, 163 patients (EE: 52, NERD: 111) treated with RBZ 10 mg then offered at 12 and 24 weeks: (1) stop treatment, (2) continue PPI, (3) step-down to H2RA, (4) combination with mosapride 5 mg tid if dissatisfied	Reflux symptoms ≥2/week, abnormal FSSG score, and normal EGD	Not reported	• 79.1% (129/163) satisfied at 12 weeks improved to 98.2% (160/163) at 24 weeks with 16.6% choosing mosapride therapy	Not reported
Miyamoto *et al.*[41]	Open label, subgroup analysis of 117 PPINR with NERD after 2 weeks of various PPI therapies treated with adjunctive mosapride therapy 5 mg tid for 4 weeks	Reflux symptoms, abnormal FSSG, normal EGD	Nonresponse (FSSG improvement <50%) after 2 weeks of PPI therapy	FSSG Score • Pretreatment: 17.4 • PPI alone: 14.6 • PPI + mosapride: 7.7 ($P < 0.01$) Overall satisfaction: 67.% (79/117)	Not reported
Futagami *et al.*[42]	Open-label analysis of PPINR with NERD ($n = 44$) treated with OME 20 mg + mosapride 5 mg tid, with gastric emptying analysis by ^{13}C-acetate breath test	QUEST score >4, typical symptoms >2/week for ≥6 months, normal EGD	Non-response (QUEST >4) after 4 weeks of OME 20 mg	Mosapride improved reflux symptoms in PPINR with delayed gastric empyting ($T_{max} > 65$ minutes) compared to those with normal gastric emptying ($T_{max} <$ 65 minutes), values not provided	Mosapride improved gastric emptying (T_{max}) in 83% (20/24) of PPINR with delayed gastric emptying. No change in EAE in 9 PPINR with delayed gastric emptying after mosapride (0.1 vs. 0.07)

EAE, esophageal acid exposure; EE, erosive esophagitis, EGD, esophagogastricduodenoscopy; ESO, esomeprazole, FSSG, Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease; GERD, gastroesophageal reflux disease; GSRS, gastrointestinal symptom rating scale; LAN, lansoprazole; LES, lower esophageal sphincter; NERD, nonerosive reflux disease; OME, omeprazole; PAN, pantoprazole; PPI, proton pump inhibitor; PPINR, PPI non-responder; PRR, pooled relative risk; QUEST, Questionnaire for the diagnosis of reflux disease; RBZ, rabeprazole; RCT, randomized controlled trial, tid, three times daily; VAS, visual analog scale; wk, week.

Table 5 Other adjunctive promotility therapies

References	Study design	Diagnosis of GERD	PPI history	Symptomatic response	Physiologic response
Prucalopride					
Nennstiel *et al.*[43]	Case report of four chronically constipated females with GERD treated with prucalopride 2 mg daily ± PPI ($n = 3$), unclear follow-up time	Symptom based questionnaire and pH testing	Symptoms despite 'standard PPI therapy' for at least 4 weeks	Improvement in symptoms in all four patients using symptom based questionnaire	↓ in all reflux episodes and non-acid/weakly acidic episodes in all 4 patients
Revexepride					
Tack *et al.*[44]	Phase II, RCT comparing revexepride 0.5 mg tid + PPI (various regimens, $n = 34$) vs. placebo + PPI ($n = 31$), follow-up 4 weeks	≥25 liquid-containing reflux events in 24 hours on pH/impedance on PPI, EGD <5 years w/o LA class C/D esophagitis	Reflux symptoms while on minimal labeled dose PPI for ≥6 weeks	LS mean Δ in PAGI-SYM • Revexepride −0.44 vs. placebo −0.35 ($P = 0.67$) LS mean Δ in PAGI-QOL ≤0.21 for both treatment groups ($P = 0.48$)	Δ liquid-containing reflux events • Revexepride −17.6 vs. placebo −16.3 ($P = 0.869$) No significant change from baseline between study arms for acidic, weakly acidic or alkaline reflux except for weakly acidic episodes in recumbent period (LS mean change −10.9% vs 11.82%, $P = 0.02$)
Shaheen *et al.*[45]	Phase II, RCT comparing PPI (various regimens) + placebo ($n = 122$), revexepride 0.1 mg tid ($n = 119$), 0.5 mg ($n = 118$), or 2 mg ($n = 118$), follow-up 8 weeks	6 month history of reflux symptoms, EGD ≤ 2 years, excluding patients with LA class B/C/D esophagitis	Persistent symptoms of regurgitation on at least daily PPI, excluded if no response to PPI	Regurgitation-free days ↑ in all four studies groups from baseline (15.0%–18.8%) to week 8 (62.3–70.5%) but differences between placebo were not significant (0.1 mg $P = 0.13$, 0.5 mg $P = 0.06$, 2 mg $P = 0.65$)	Not reported
Domperidone					
Ndraha *et al.*[46]	Randomized, double-blind trial comparing OME 20 mg twice daily + domperidone 10 mg tid ($n = 30$) vs. OME 20 mg twice daily ($n = 30$), follow-up 2 weeks	Heartburn and/or regurgitation for unspecified time	Not reported	FSSG Domperidone + OME • Pre: 26.7 Post: 19.3 ($P < 0.01$) OME • Pre: 23.9 Post: 19.3 ($P < 0.01$) Δ in FSSG • Domperidone + OME: 7.5 vs. OME: 4.6 ($P = 0.02$)	Not reported

EGD, esophagogastricduodenoscopy; FSSG, Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease; GERD, gastroesophageal reflux disease; LA; Los Angeles; LS, lease square; OME, omeprazole; PAGI-SYM, patient assessment of upper gastrointestinal disorders-symptom severity index; PAGI-QOL, patient assessment of upper gastrointestinal disorders-quality of life; PPI, proton pump inhibitor, RCT, randomized controlled trial, tid, three times daily; VAS, visual analog scale, wk, weeks.

Table 6 Adjunctive transient lower esophageal sphincter relaxation inhibitors

Reference	Study Design	Diagnosis of GERD	PPI History	Symptomatic Response	Physiologic Response
Baclofen					
Li *et al.*[47]	Meta-analysis of 9 RCT with a total of 283 GERD and healthy subjects not limited to PPI2014 co-therapy	"[NERD], hypersensitive esophagus, or functional heartburn"	Concurrent PPI (daily or twice daily) use, response not reported	Significant ↓ in the incidence of GERD with baclofen as compared to placebo (SMD: −0.65 95% CI −0.94, −0.36, $P < 01$), incidence not defined.	Significant ↓ in acid reflux time (SMD: −1.14; 95% CI −1.72, −0.52, $P < 0.01$) and TLESR (SMD: −3.65; 95% CI: −4.30, −3.00; $P < 0.01$) with baclofen.
Beaumont *et al.*[48]	Double-blind, randomized, placebo controlled cross-over trail ($n = 23$) comparing baclofen 20 mg tid + PPI (various regimens) ×12 days then placebo + PPI ×12 days, subgroup analysis of those with and without hiatal hernia	Patients with typical GERD symptoms	Not reported	Few symptoms reported during both placebo and baclofen: 5 patients recorded 27 symptoms during placebo and 8 patients recorded 34 symptoms during baclofen.	No Hiatal Hernia • Reflux episodes: Pre: 694 Post: 475 ($P < 0.01$) • Acid reflux: Pre: 219 Post: 174 ($P =$ NS) • EAE: Pre: 0.7% Post: 0.3% ($P =$ NS) Hiatal Hernia >3 cm • Reflux episodes: Pre: 1157 Post: 644 ($P = 0 < 01$) • Acid reflux: Pre: 253 Post: 185 ($P =$ NS) • EAE: Pre: 2.1% Post: 2.5% ($P =$ NS)
Abbasinazari *et al.* [49]	Double-blind, RCT comparing baclofen sustained release 10 mg twice daily + OME 20 mg ($n = 15$) vs placebo + OME 20 mg ($n = 28$), follow-up 2 wk	Diagnosis based on symptoms and Mayo Gastroesophageal Reflux Questionnaire	Not reported	Patients with HB • Baclofen 4% (1/25) vs placebo 46.4% (13/28), $P < 0.01$ Patients with RG • Baclofen 4% (1/25) vs placebo 53.6% (15/28), $P < 0.01$	Not reported
Arbaclofen					
Vakil *et al.*[52]	Phase II, RCT comparing PPI (various regimens) + placebo ($n = 75$) vs arbaclofen 20 mg ($n = 75$) or 40 mg daily ($n = 67$) or 20 mg ($n = 69$) or 30 mg ($n = 67$) twice daily, follow-up 6 wk	Diagnosis of GERD by gastroenterologist, excluded patients with EE	Partial response with daily PPI for 4 wk, excluded if using twice daily PPI	LS mean Δ in HB events/week • Arbaclofen −69.4–77.7% vs placebo −68% ($P =$ NS for all arbaclofen doses) *Post-hoc* analysis excluding mild symptoms found ↓ in HB events/wk for all arbaclofen doses compared to placebo ($P < 0.05$)	Not reported
Lesogaberan					
Miner *et al.*[53]	Phase II, randomized, placebo controlled 4-way crossover trial comparing PPI (various regimens) + placebo ($n = 24$) vs PPI + lesogaberan 30 mg ($n = 18$), 90 mg ($n = 17$), 120 mg ($n = 20$) or 240 mg ($n = 18$) ×2 doses over 24 hours	History of GERD symptoms ≥6 months, symptoms as measured by RESQ-7	Partial response to PPI, excluded if no response to PPI	Not reported	Dose-dependent ↓ in reflux episodes with lesogaberan (mean Δ −26.2–52.8%, $P < 0.05$) Significant ↓ in EAE with 30 mg, 120 mg, and 240 mg lesogaberan (−65.7–73.9%, $P < 0.05$)

Table 6 *continued*

Reference	Study Design	Diagnosis of GERD	PPI History	Symptomatic Response	Physiologic Response
Boeckxstaens *et al.*[54]	Phase II, RCT comparing lesogaberan 65 mg twice daily + PPI (various regimens, $n = 113$) vs placebo + PPI ($n = 111$), follow-up 4 wk	History of GERD ≥6 weeks on PPI, symptom recall over 7 days as reported in RDQ	Persistent symptoms despite ≥6 wk PPI	Response rate (≤1 24 h period with HB or RG not more than mild intensity during last 7 days of treatment) • Lesogaberan 16% vs placebo 8% ($P = 0.02$) ↓ of symptom intensity similar between groups (Δ RDQ for HB+RG (1.0 vs 0.9)	Not reported
Shaheen *et al.*[55]	Phase II, RCT comparing PPI daily (various regimens) + placebo ($n = 122$) vs PPI + lesogaberan 60 mg ($n = 121$), 120 mg ($n = 109$), 180 mg ($n = 114$) or 240 mg ($n = 114$) twice daily, follow-up 4 wk	History of GERD symptoms ≥6 months, symptoms as measured by RESQ-7	Persistent symptoms despite 4 wk of daily PPI, twice daily and no response to PPI excluded	Response rate (≥3 days/wk with not more than mild symptoms) significant only for 240 mg (26.2% vs 17.9%, $P < 0.1$), difference from placebo corresponding to <1 additional day/wk with not more than mild symptoms	Not reported

CI: confidence interval, EAE: esophageal acid exposure, EGD: esophagogastricduodenoscopy, EE: erosive esophagitis, FSSG: Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease, GERD: gastroesophageal reflux disease, HB: heartburn, LS: least square, NERD: non-erosive reflux disease, NS: not significant, OME: omeprazole, PPI: proton pump inhibitor, RCT: randomized controlled trial, RESQ-7: 7-day recall Reflux Symptom Questionnaire, RQD: Reflux Disease Questionnaire, RG: regurgitation, SMD: standard mean difference, tid: three times daily, TLESR: transient lower esophageal sphincter relaxations, wk: week.

studies for this prevalent and burdensome patient population.

The data for PPI metabolizer genotypes suggest that homoEMs with EE have lower rates of endoscopic healing, remission and symptom response when treated with *CYP2C19*-dependent PPIs, whereas response is similar regardless of genotype when treated with the more *CYP2C19* independent PPIs RBZ and ESO. Despite the deficiency of head-to-head trials examining outcomes of *CYP2C19*-dependent and independent PPIs between genotypes, the existing data suggest that *CYP2C19* polymorphism is an important factor in endoscopic healing and response rates in patients with EE. In fact, the homoEM genotype has been shown to be an independent risk factor for PPI nonresponse in those with EE.[60] Thus, it would be reasonable to assess a patient's genotype or switch to a *CYP2C19* independent PPI to optimize acid suppression in cases of PPI nonresponse and persistent pathologic acid exposure. This may explain improvement in GERD symptoms and quality of life in PPINR patients after being switched to ESO.[61–63] This approach may be particularly effective for populations with a higher prevalence of homoEM, which is more common among Caucasians (59.7%–69.9%) as compared to Asian populations (27.7%–41.6%.)[64] Nevertheless, genotyping is often not readily available and is unlikely a cost-effective strategy. While cost effectiveness of *CYP2C19* genotyping for PPIs has not been specifically studied like it has with antiplatelet therapy, extrapolating the data to GERD is inappropriate given the consequences of therapy failure between diseases.[65] Alternatively, using the *CYP2C19* independent PPI ilaprazole as initial therapy for duodenal ulcer disease rather than OME in Chinese patients, even homoEM, was cost effective, supporting a suggesting the more simple approach of using or switching to CYP2C19 independent PPIs when cost is a concern.[66] Future studies utilizing such strategies are needed as the only study utilizing this strategy was significantly limited by its small sample size.[26] It is important to note that these studies are almost exclusively limited to patients with EE, and the impact of CYP genotypes on PPI response in NERD is not well described.

Data for adjunctive medical therapy show limited efficacy of these therapies. Nighttime H2RAs may suppress NAB as evidenced by greater acid suppression and symptom improvement; however, tachyphylaxis limits long-term use.[67] A select group of PPINR may benefit from adjunctive promotility agents though results are inconsistent. Mosapride is the most well-studied agent with conflicting evidence and is also not FDA approved. A case report suggests that GERD symptoms improve with prucalopride for patients with constipation. Kessing *et al.* have also shown improved EAE and gastric emptying in healthy subjects but larger studies

Table 7 Adjunctive mucosal protective therapies

Reference	Study Design	Diagnosis of GERD	PPI History	Symptomatic Response	Physiologic Response
Rebapimide					
Yoshida *et al.*[57]	Open-label randomized trial comparing recurrence rate of symptoms in patients with EE LA class A/B after 8 wk of PPI treated with LAN 15 mg + rebamipide 300 mg ($n = 20$) vs LAN 15 mg ($n = 21$), follow-up 1 year	EE LA class A/B with QUEST ≥4 and GSRS acid reflux score ≥5	Symptom relief after 8 wk of LAN 30 mg, OME 20 mg or RBZ 10 mg	Relapse of Symptoms (GSRS ≥5) • Rebamipide + LAN 20% (4/20) vs LAN 52.4% (11/21), $P < 0.05$	Not reported
Irsogladine					
Suzuki *et al.*[58]	RCT comparing irsogladine + RBZ ($n = 49$) vs placebo + RBZ ($n = 48$) in patients with NERD, doses not provided, follow-up 4 wk	FSSG ≥8 with normal EGD	"Persistent GERD symptoms", not further defined, no PPI use within 4 weeks	Post-treatment FSSG • Irsogladine 9.0 vs placebo 11.2 ($P = 0.15$) Post-treatment FSSG for modified LA class N • Irsogladine 7.8 vs placebo 12.5 ($P = 0.04$)	Not reported
Mirgeal					
Di Pierro *et al.*[59]	Open-label randomized trial comparing Mirgeal + PAN 20 mg twice daily ($n = 29$) vs alginate 500 mg twice daily + PAN 20 mg twice daily ($n = 29$), follow-up 4 wk before PPI discontinued, excluded analysis without co-PPI therapy	Typical or atypical GERD symptoms, normal EGD	Persistent symptoms, not further defined	VAS (10-point scale) for HB • Mirgeal 1.96 vs alginate 3.41 ($P < 0.05$) VAS (10-point scale) for RG • Mirgeal 2.00 vs alginate 1.16 ($P = $ NS) Mean Global Outcome (10-point VAS across 7 symptoms) • Mirgeal 8.8 vs alginate 14.2 ($P = 0.0012$)	Not report

EGD: esophagogastroduodenoscopy, EE: erosive esophagitis, FSSG: Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease, GERD: gastroesophageal reflux disease, GSRS: Gastroesophageal Symptom Rating Scale, LA: Los Angeles, HB: heartburn, LAN: lansoprazole, NERD: non-erosive reflux disease, PAN: pantoprazole, PPI: proton pump inhibitor, QUEST: Questionnaire for the diagnosis of reflux disease, RBZ: rabeprazole, RCT: randomized controlled trial, RG: regurgitation, VAS: visual analog scale.

evaluating subjects with pathologic acid exposure and/or delayed gastric emptying is needed.[68] In one study, adjunctive domperidone reduced FSSG scores better than PPI alone but the posttreatment FSSG score was identical to placebo. Domperidone is not FDA approved and carries significant arrythmogenic risks.[69] Although GABA agonists physiologically inhibit TLESRs, these properties translate to, at best, minimal clinical improvement in GERD symptoms. This approach may be particularly beneficial for patients with abnormally high reflux events of non- or weakly acidic reflux. Frequent dosing requirement and non-insignificant central nervous system depressant effects limit the use of GABA agonists, of which baclofen remains the only commercially available agent at this time. Finally, mucosal protective agents show some promise for treating PPINR, particularly NERD, though more rigorous trials are needed before routine use in clinical practice.

A major limitation to this review is the critical deficiency of high quality of studies in regard to participant enrollment and study design. The high variability of subjective measure reporting makes study comparison difficult. Additionally, only two studies on adjunctive medications explicitly used twice daily dosing of PPIs in their study design and some even included PPI naïve patients. These study designs raise major concerns about the external validity of these studies to PPI nonresponsive populations, as adjunctive medications are not typically pursued until patients are on double dose daily PPI. Only 18.5% ($n = 5$) of the adjunctive medication studies enrolled patients with proven pathologic acid exposure by EGD or pH testing. This distinction is important as up to 35% of patients classically defined as PPINR are found to have an alternative explanation for their symptoms, including functional and hypersensitivity disease.[70] Inclusion of these participants likely dilutes the therapeutic effects of these medications.

Even more so, given the heterogeneity of mechanisms that contribute to PPI nonresponse, an approach to phenotype patients according to the specific mechanism of persistent pathologic esophageal reflux is warranted. Phenotyping patients based on pH-impedance testing have already been shown to predict outcomes for patients treated with PPIs.[71] However, only two of the 27 studies on adjunctive medications used baseline physiologic testing for patient enrollment or subgroup analysis that specifically addressed the proposed pharmacodynamic mechanism of an agent. Futagami *et al.* compared reflux symptoms in patients with delayed and normal gastric emptying treated with mosapride, and Tack *et al.* enrolled patients with abnormal number of liquid reflux events to be treated with arbaclofen.[42,44] The meager therapeutic benefits reported by the studies in this review may be a reflection of inappropriate patient selection. It would be logical that a precision approach using physiologic studies such as pH testing or esophageal manometry to preselect patients based on the pharmacodynamic target of the medication may demonstrate greater patient responses to these medications. Therefore, the use of old or new reflux inhibitors, prokinetics, and mucosal protective agents deserves to be readdressed using an approach of more careful patient selection that specifically targets a patient's physiologic profile.

Continued research efforts are underway on the use of other adjunctive medications in this population. Published after our literature search, an RCT reported symptomatic improvement in PPINR at 7 days treated with adjunctive gaviscon, an alginate formulation that forms a protective raft over the esophageal mucosa for 7 days.[72] Tegaserod is a novel prokinetic that is currently being studied as an adjunctive agent for PPINR, though the results of the trial are yet to be published.[73] Lastly, vonoprazan is a novel potassium-competitive acid blocker that has demonstrated more potent and sustained acid suppressive effects than the PPIs LAN, ESO, and RBZ.[74,75] Metabolized primarily via *CYP3A4*, vonoprazan is also not plagued by genetic polymorphisms of *CYP2C19* that impact EE healing and recurrence rates with certain PPIs.[76] While not specifically studied in PPINR, vonoprazan has been shown to be noninferior to LAN for the treatment of EE and given its more favorable pharmacodynamic and pharmacogenetic properties, may offer another therapeutic option for PPI nonresponse.[77]

Synthesizing the data presented, first off clinicians should pursue pH testing in patients not responding to double-dose PPI therapy to evaluate for objective evidence of pathologic GERD. In patients with pathologic PPI refractory GERD and nonresponse to a double-dose *CYP2C19*-dependent PPI, it may be reasonable to switch to a *CYP2C19* independent PPI. If switching PPI is ineffective, it is essential to evaluate for other disorders that may cause persistent symptoms or pathologic reflux such as Zollinger-Ellison, bile acid reflux, or eosinophilic esophagitis that PPIs alone may not address. In addition, pH testing and high-resolution manometry may provide important information related to bolus clearance, reflux episodes, TLESRs, and the integrity of the antireflux barrier.

In conclusion, management of PPINR has become an increasing challenge for gastroenterologists. Foremost, objective evidence of pathologic GERD is required to classify a patient as PPI refractory. Excluding functional disorders, esophageal hypersensitivity, and alternate mechanisms for reflux symptoms is critical as these patients should be managed differently from those with pathologic reflux. In patients failing a double-dose *CYP2C19*-dependent

PPI, utilizing PPI metabolizer genotype when available or switching to a *CYP2C19* independent PPI is a simple and conservative measure. pH testing and high-resolution manometry may provide important information related to bolus clearance, reflux episodes, TLESRs, and the integrity of the antireflux barrier, and direct targeted treatment approaches, though future studies are needed to better characterize mechanistic phenotypes and outcomes of PPINRs.

SUPPLEMENTARY DATA

Supplementary data are available at *DOTESO* online.

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