EXPERT RECOMMENDATIONS

An Expert Review and Recommendations on the Rational Use of Proton Pump Inhibitors: Indian Perspective

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Abstract

Background: Proton pump inhibitors (PPIs) are the mainstay of treatment for acid peptic diseases (APDs), but are often irrationally prescribed in clinical practice. Appropriate prescription of PPIs is needed to optimize outcomes, and minimize risks and cost burden on the healthcare system.

Objective: To review available literature on efficacy and safety of proton pump inhibitors (PPIs) and give recommendations for rational use of PPIs from an Indian perspective.

Methods: Twelve healthcare professionals (9 gastroenterologists, 1 cardiologist, 1 orthopedist, 1 clinical pharmacologist) comprised the expert group; members disclosed conflicts of interest. The creation of the expert review was through a process that included meetings (in-person, online, telephone) where each professional contributed their experiences with regards to efficacy and safety of PPIs. Articles published between the years 2000 and 2017 were reviewed for evaluation of safety and efficacy of PPIs in treatment of various APDs.

Conclusion: This expert review provides key recommendations for decision making in order to minimize the irrational use of PPIs. Some significant recommendations include: patients with GERD and acid-related complications should take a PPI for minimum 12 weeks for healing of esophagitis, and for maximum up to 48 weeks for symptom control. Patients with Barrett's esophagus should take long-term PPI. Patients at high risk for ulcer-related bleeding from NSAIDs including aspirin should take a PPI if they continue to take NSAIDs. Best practice recommendations are meant to merely assist with decision making in conjunction with patients' clinical history, and are not intended to dictate mandatory rules.

Introduction

Acid peptic diseases (APDs) are prevalent worldwide; changing lifestyles and dietary habits may be attributable to the rising disease burden. A systematic review of 28 studies indicated ethnic and geographical variations in prevalence of gastroesophageal reflux disease (GERD) [18.1–27.8 % in North America, 8.8–25.9 % in Europe, and 2.5–7.8 % in East Asia].[1] A survey of 1000 clinicians from India showed a high prevalence of GERD (39.2%), peptic ulcer disease (PUD, 37.1%) and non-ulcer dyspepsia (25.2%) with nearly 50% of patients requiring prompt endoscopy.[2] Specific symptoms need to be identified accurately in order to avoid under-diagnosis or over-treating APDs.

Medications available for treating these acid related diseases are proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RA), antacids, sucralfate and prostaglandin analogues. The PPIs available in the Indian market for clinical use are dexlansoprazole, dexrabeprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.[3] Their CDSCO (Central Drugs Standard Control Organization) approved indications are presented in Table 1.

Irrational prescription has been rampant with PPIs being prescribed to patients not presenting with valid indications warranting PPI use.[5,6] A study by Churi *et al.* (2014) showed intravenous (IV) PPIs being inappropriately prescribed to 89.2% of internal medicine ward patients and 34.04% of surgery ward patients.[7] Parenteral PPIs, being relatively expensive compared to oral PPIs and H2RAs, can significantly increase the cost for patients in hospitals. In another study at a tertiary care teaching hospital in Raichur, Karnataka, 50% of PPIs were orally prescribed to patients.[8] Improper utilization of PPIs can lead to adverse effects, which in turn may result in an economic burden on patients seeking treatment. Quality variability across formulations manufactured by different companies may be an issue peculiar to India. In view of these concerns, the current expert recommendations have been developed to assist physicians in the rational use of PPIs.

Methods

The expert review team (ERT) comprised of 12 experts- 9 gastroenterologists, an orthopedist, a cardiologist and a clinical pharmacologist. All ERT members had

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Table 1: Approved PPIs and their Indications in India as per the CDSCO

Indications	Esomeprazole (10, 20, 40 mg)	Ome-prazole (20,40 mg)	Lansoprazole (30mg)		Pantoprazole (10,20,40 mg)		Rabe-prazole (10,20 mg)	Dex-lansoprazole (30,60 mg)	Dex-rabeprazole (5,10,30 mg)	Ilaprazole (5,10 mg)
Route	Oral	Oral	Oral	Injection	Oral	Injection	Oral	Oral	Oral	Oral
GERD	✓	✓			✓	✓	✓	✓	✓	
Erosive esophagitis	✓	✓		✓				✓		
Reflux esophagitis			✓			✓				
Peptic Ulcer Disorder	✓					✓				
Gastric Ulcer	✓	✓	✓		✓	✓	✓		✓	
Duodenal Ulcer	✓	✓	✓		✓	✓	✓		✓	✓
Prophylaxis of NSAID induced ulcer	✓									
Zollinger-Ellison syndrome	✓		✓		✓	✓	✓			
Eradication of H. pylori	✓	✓								

Data extracted from CDSCO.[4]

Table 2: Review of clinical studies of efficacy of various PPIs in GERD (ERD and NERD)

Author, Year	Study Design	Study Drugs and Sample Size	Outcome
GERD: ERD			
Li et al. 2017	PRSIMA-compliant network meta-analysis	Dexlansoprazole (60 mg), Esomeprazole (40 mg), Esomeprazole (20 mg), Pantoprazole (40 mg), Lansoprazole (30 mg), Rabeprazole (20 mg), Omeprazole (20 mg) N=25,088	• Esomeprazole 40 mg showed significantly higher healing rate at 4 weeks [versus omeprazole 20mg, lansoprazole 30 mg, rabeprazole 20 mg, pantoprazole 40 mg] and at 8 weeks [versus omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg] • Heartburn relief was significantly better with esomeprazole 40 mg compared to omeprazole 20 mg and lansoprazole 30 mg • Dexlansoprazole 60 mg exhibited the significantly increased withdrawal rates compared with omeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, and rabeprazole 20 mg
Zheng et al. 2009	RCT	Omeprazole (20 mg; n=68), Lansoprazole (30 mg; n=69), Pantoprazole (40 mg; n=69), Esomeprazole (40 mg; n=68); Esomeprazole (40 mg)	• No significant differences were seen between the groups in the rate of endoscopic healing of reflux esophagitis at week 8 • Complete resolution of heartburn in reflux esophagitis patients treated with esomeprazole for 5 days compared with omeprazole, lansoprazole and pantoprazole
Edwards et al. 2006	Systematic review and meta-analysis	Lansoprazole (30 mg), Omeprazole (20 mg), Pantoprazole (40 mg), Rabeprazole (20 mg) N=14,800	• Healing rates of reflux esophagitis showed a significant benefit in favor of esomeprazole at 4 weeks (RR 0.92; 95%CI: 0.90, 0.94; P < 0.00001) and 8 weeks (RR 0.95; 95% CI: 0.94, 0.97; P < 0.00001) • Magnitude of benefit esomeprazole offers over other standard dose PPIs increases with the severity of the underlying reflux esophagitis
Gralnek et al. 2006	Meta-analysis of RCTs	Esomeprazole (40 mg), Omeprazole (20 mg), Omeprazole (40 mg), Lansoprazole (30 mg), Pantoprazole (40 mg) N=15,316	• Esomeprazole conferred an 8% (RR, 1.08; 95% CI, 1.05–1.11) relative increase in the probability of GERD symptom relief at 4 weeks • At both 4 and 8 weeks, a 10% (RR, 1.10; 95% CI, 1.05–1.15) and 5% (RR, 1.05; 95% CI, 1.02–1.08) relative increase in the probability of healing with esomeprazole versus alternative PPIs observed
Nagahara et al. 2014	RCT	Omeprazole (20 mg QD; n=106), Rabeprazole (10 mg QD; n=103)	• Sufficient and sustained relief of reflux symptoms observed in 46.5–61.4% of patients in the omeprazole 20 mg group than in the rabeprazole 10 mg group (39.8–52.0 %) on days 3–7 • After 2 and 4 weeks, proportion of patients achieving sufficient relief of reflux symptoms was similar in the omeprazole 20 mg and rabeprazole 10 mg groups
Delchier et al. 2009	RCT	Rabeprazole (20 mg QD; 104), Rabeprazole (10 mg BID; 103), Omeprazole (20 mg QD; 103)	• Rabeprazole 20 mg in two different dosing schedules is as effective as omeprazole 20 mg QD with regard to efficacy and tolerability in patients with erosive GERD • No significant differences between the three treatment groups with regard to healing rate at either 4 or 8 weeks
Liu et al. 2017	Meta-analysis	Lansoprazole (15 mg, 30 mg, 60 mg), Omeprazole (10 mg, 20 mg, 40 mg) N=8752	• For healing outcome, lansoprazole 60 mg per day (RR=1.29, 95% CI [1.01, 1.66], I^2=79.3%, P=0.028) or 30 mg per day (RR=1.59, 95% CI [1.28, 1.99], I^2=NA, P=NA) was more effective than 15 mg per day • For symptom relief, significant difference between 20 mg per day and 10 mg per day of omeprazole was observed (RR=1.21, 95% CI [1.06, 1.39], I^2=53.9%, P=0.089)
Srikanth et al. 2014	Prospective RCT	Pantoprazole (40 mg; n=55), Esomeprazole (40 mg; n=55)	• Esomeprazole provided significantly greater healing than pantoprazole after 4 weeks in patients with all grades of erosive esophagitis severity (56.36% vs. 49.09 %; P<0.18) • Both groups of patients were healed after up to 8 weeks of treatment (Esomeprazole; 94.54% vs. Pantoprazole; 70.90 %; p<0.23)
Moraes-Filho et al. 2014	RCT	Pantoprazole-Mg (40 mg; n=290), Esomeprazole (40 mg; n=288)	• At 4 weeks, complete resolution occurred in 61% patients in each group and in 81% and 79% of patients in the pantoprazole-Mg and esomeprazole groups at 8 weeks for patients with erosive GERD • At 8 weeks, symptom relief with pantoprazole-Mg was significantly greater than that with esomeprazole (91.6% vs. 86.0%, P = 0.037) • Mucosal healing rates were high and not significantly different in both treatment groups
Vedamanickam et al. 2017	Open, comparative clinical trial	Esomeprazole (40 mg; n=70), Rabeprazole (20 mg; n=70)	• At the end of 8th week, 90% relief from GERD-symptoms was noted with esomeprazole and 92% relief was noted in rabeprazole group • Upper GI endoscopy revealed 84% healing rate in esomeprazole group and 82% healing rate in rabeprazole group • At the end of 24 months, 78% patients in esomeprazole group and 64% in rabeprazole group were symptom free

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Table 2: Review of clinical studies of efficacy of various PPIs in GERD (ERD and NERD) *(Contd...)*

Author, Year	Study Design	Study Drugs and Sample Size	Outcome
GERD: NERD			
Chen et al. 2016	Network meta-analysis	Dexlansoprazole (30 mg, n=315; 60 mg, n=315), Omeprazole (10 mg, n=555; 20 mg, n=555), Lansoprazole (15 mg, n=276; 30 mg, n=277), Esomeprazole (20 mg, n=782; 40 mg, n=523), Rabeprazole (5 mg, n=93; 10 mg, n=445; 20 mg, n=197); Placebo (n=1929)	• Compared with placebo groups, all interventions except rabeprazole 5 mg showed a significantly increased rate of symptomatic relief • Omeprazole 20 mg group was associated with a higher rate of symptomatic relief in contrast to omeprazole 10 mg group (OR: 1.89, 95% CI: 1.34, 2.67; P= 0.0005) or rabeprazole 5 mg group (OR: 2.51, 95%CI: 1.16, 5.42; P= 0.019) • For the rate of adverse events, there was no significant difference among all interventions
Sung et al. 2016	Open-label, multi-center	Esomeprazole (40 mg), Placebo N=92	• The sum score of heartburn and regurgitation decreased significantly from 72.51 to 32.55 after 4 weeks of treatment (P⊛0.001) • Patients with severe symptoms at baseline had significantly higher symptom improvement rate in comparison to patients who had milder symptoms
Fock et al. 2005	RCT	Esomeprazole (20 mg; n=64), Rabeprazole (10 mg; n=63)	• At 4 weeks, rabeprazole and esomeprazole were comparable with regards to the primary endpoint of time to achieve 24-h symptom free interval for heartburn 8.5 days vs 9 days and regurgitation 6 days vs 7.5 days • Rabeprazole 10 mg has a similar efficacy and safety profile as esomeprazole 20 mg in Asians with NERD
Dean et al. 2004	Systematic review of placebo-controlled RCTs	Omeprazole (10 mg;20 mg), Esomeprazole (20 mg; 40 mg); Rabeprazole (10 mg; 20 mg); Placebo N=1854	• Therapeutic gain of PPI therapy over placebo ranged from 30-35% for sufficient heartburn control and from 25-30% for complete heartburn control • PPIs provide a more modest therapeutic gain in patients with NERD as compared with those with erosive esophagitis

PPI- proton pump inhibitor, GERD- gastro-esophageal reflux disease, ERD- erosive reflux disease. NERD- non-erosive reflux disease, RCT- randomized controlled trial, RR- relative risk, OR- odds ratio, CI- confidence interval, GI- gastrointestinal

expertise in the clinical management of patients taking PPIs. PubMed database was used to ensure studies of safety and efficacy of PPIs published between the years 2000 and 2017 were captured.

The search was made using the following Medical Subject Headings (MeSH) terms- Anti-inflammatory Agents- Non-Steroidal, Drug Interactions, Dyspepsia, Deprescriptions, Histamine Antagonists, Drug-related Side Effects and Adverse Reactions, Acute Kidney Injury, Proton Pump Inhibitors, Helicobacter pylori, Gastrointestinal Motility, Benzamides/metabolism, Dopamine Antagonists, Parasympathomimetics, Cardiovascular Diseases/complications, dexlansoprazole, dexrabeprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole. The ERT reviewed published as well as unpublished literature on PPI safety and efficacy in Indian population and gave recommendations on the rational use of PPIs in alignment with those provided by the American Gastroenterological Association (AGA) 2017.

The expert review is presented here under efficacy of PPIs in various indications, safety of PPIs including drug interactions, selecting appropriate PPIs, deprescribing PPIs and Indian recommendations for rational use of PPIs. Recommendations were articulated by the ERT.

Efficacy of PPIs

Gastro-esophageal Reflux Disease (GERD)

The most effective treatment choice for frequent GERD symptoms are PPIs, which provide effective symptomatic relief in about 56-76% patients,[9] and esophageal lesion healing rate of 80-85% at 8 weeks.[10] The standard doses of PPIs once daily (QD) should be best taken 30-60 minutes before breakfast. Despite the well-recognized efficacy, approximately 30% of GERD patients remain symptomatic on this dose with a possibly increased risk of other complications such as Barrett's esophagus.[11] Although PPIs are an effective option in gastric acid control, a subgroup of patients such as those with non-erosive reflux disease (NERD) may remain refractory to standard PPI treatment.[12] Table 2 summarizes a review of clinical studies of the efficacy of various PPIs in GERD.

Peptic Ulcer Disease (PUD)

Defects in the gastrointestinal (GI) mucosa that may also extend through the muscularis mucosa can be attributed to peptic ulcers (gastric and duodenal).[13] PPI therapy for ulcer bleeding in the Asian population has been more efficacious than in Western countries.[14] With endoscopy being a treatment most utilized for bleeding peptic ulcers, PPI therapy can significantly reduce re-bleeding in patients after endoscopy.[15] The link between the pathogenesis of upper GI diseases and the presence of *H. pylori* infection has been investigated to understand the relation of its eradication with peptic ulcer healing. It is crucial to diagnose whether patients suffering from PUD have an *H. pylori* infection to aid in a treatment strategy.

PPIs decrease acid secretion by inhibiting the H^+-K^+-ATPase. However, a correlation between higher or lower doses affecting healing of NSAID-induced ulcers is unclear. The local and systemic action of NSAIDs on the gastric mucosa combined with the failure of mucosal protective defense is the pathogenic process for development of NSAID related gastroduodenal ulcers. As these risks are dose- and time-dependent, high-dose and long-term NSAID users may have a higher risk of developing peptic injury.[16] Furthermore, reduction in ulcer re-bleeding, surgery and mortality has been observed in patient with ulcer bleeding and on PPI therapy.[17,18] Table 3 summarizes a review of clinical studies of the efficacy of various PPIs in PUD, eradication of *H. pylori* and prophylaxis of NSAID-induced ulcers.

Functional Dyspepsia (FD)

With a global prevalence of 11-29.2% for functional dyspepsia (no organic cause to explain symptoms),[19] dyspeptic symptoms have been reported in the Indian community ranging from 7.6-

Table 3: Review of clinical studies of efficacy of various PPIs in PUD, eradication of *H. pylori* and prophylaxis of NSAID-induced ulcers

Author, Year	Study Design	Study Drugs and Sample Size	Outcome
Peptic Ulcer Disease			
Hu et al. 2017	Pairwise and network meta-analysis of RCTs	Omeprazole (20 mg; 40 mg), Lansoprazole (15 mg; 30 mg; 60 mg), Rabeprazole (20 mg), Pantoprazole (40 mg), Ilaprazole (10 mg) N=6,188	• No significant difference in the healing rate for duodenal ulcer treated with different PPIs in different doses except Pantoprazole 40 mg versus Lansoprazole 15 mg (RR = 3.57; 95% CI= 1.36–10.31) and Lansoprazole 30 mg versus Lansoprazole 15 mg (RR = 2.45, 95% CI = 1.01-6.14) • Pantoprazole 40 mg was more effective compared with other regimens, although most of the difference was insignificant and Lansoprazole 15 mg had a lower healing rate versus other regimens • No significant difference for the rate of adverse effects between different PPIs in different doses
Zeng et al. 2015	Meta-analysis	Lansoprazole, Omeprazole, N=774	• No significant differences between patients treated with lansoprazole combinations and omeprazole combinations in terms of healing rate (RR = 1.04, 95% CI = 0.99-1.09, P = 0.93) • Significant differences between those treated by lansoprazole combination and omeprazole combination in terms of H. pylori eradication rate (RR = 1.09, 95% CI = 1.01-1.18, P = 0.04) • Lansoprazole and omeprazole exhibit similar efficacy in the treatment of H. pylori associated duodenal ulcers
Ji et al. 2014	Meta-analysis	Ilaprazole (10 mg), Omeprazole (20 mg), Esomeprazole (40 mg), N=1481	• No difference in the 4 week healing rate between ilaprazole and other PPIs [89.7% vs 87.0%; RR= 1.02; 95%CI: 0.98-1.06; Z = 1.00; P = 0.32] • Ilaprazole can be recommended as a therapy for acid-related disorders, especially in Asian populations
H. pylori Eradication			
Xin et al. 2016	Network meta-analysis	Rabeprazole, Esomeprazole, Omeprazole, Lansoprazole, Pantoprazole, Antibiotic regimens: Levofloxacin/Moxifloxacin/ Bismuth-containing interventions	• In triple therapy, esomeprazole was found to be the most effective PPI, followed by rabeprazole, while no difference was observed among the three old generations of PPI for the eradication of H.pylori • Moxifloxacin or levofloxacin-based triple therapy were both associated with greater effectiveness than bismuth-based therapy as a second-line treatment • PPIs and use of moxifloxacin or levofloxacin within triple therapy as second-line treatment were associated with greater effectiveness
McNicholl et al. 2012	Meta-analysis	Esomeprazole (40 mg; 20 mg), Rabeprazole (40 mg;20 mg;10 mg), Pantoprazole (40 mg), Lansoprazole (30 mg), Omeprazole (20 mg), N=5,998	• Higher eradication rates for esomeprazole than for first-generation PPIs: 82.3% vs. 77.6%; OR = 1.32 (1.01–1.73); NNT = 21 • Esomeprazole and rabeprazole show better overall H. pylori eradication rates than first-generation PPIs
Wang et al. 2006	Meta-analysis	Esomeprazole (40 mg; 80 mg), Omeprazole (40 mg), Pantoprazole (80 mg), Antibiotic regimens: clarithromycin + amoxicillin or clarithromycin + metronidazole, N=2,159	• No statistically significant difference in eradication rates between esomeprazole-based and other PPI-based regimens (OR 1.17, 95% CI: 0.89, 1.54, p=0.25) • Analysis of low-dose (20 mg BID) esomeprazole and high-dose (40 mg BID) esomeprazole showed no significant differences in H. pylori eradication rates between esomeprazole-based and other PPI-based regimens (OR 1.20, 95% CI: 0.92, 1.56, p=0.17 and OR 3.21, 95% CI: 0.31, 32.93, respectively) • Esomeprazole-based triple therapy may be as effective as omeprazole-based therapy in eradicating H. pylori
Gisbert et al. 2004	Meta-analysis	Esomeprazole (20 mg), Omeprazole (20 mg), Antibiotic regimens: Clarithromycin (250 mg;500 mg), Metronidazole (400 mg;500 mg), Amoxicillin (1 g)	• Mean H. pylori eradication rates (intention-to-treat) with esomeprazole plus antibiotics was 85% and 82% when omeprazole was used (OR 1.19; 95%CI 0.81–1.74) • Mean cure rates with dual regimens (esomeprazole plus clarithromycin) were 51 and 54%, respectively, by intention-to-treat and by per-protocol • Corresponding figures with triple regimens (esomeprazole + clarithromycin + either amoxicillin or metronidazole) were 82% (intention-to-treat) and 86% (per-protocol) • Esomeprazole-based triple therapy is highly effective for the eradication of H. pylori infection and offers comparable efficacy to omeprazole-based therapy
Hawkey et al. 2003	RCT	RCA (n=87), OCA (n=86), RCM (n=85), OCM (n=87), (R, rabeprazole 20 mg; O, omeprazole 20 mg; C, clarithromycin 500 mg; A, amoxicillin 1000 mg; M, metronidazole 400 mg)	• Overall eradication rates (per protocol/intention-to-treat) were 87%/77% and 85%/75% with rabeprazole and omeprazole, respectively (insignificant) • RCA produced a somewhat higher eradication rate than OCA (94% vs.84%; difference, 9.8%; 95%CI -0.7% to +20.4%), whereas RCM produced a lower eradication rate than OCM (79% vs. 86%; difference, 8.1%; 95%CI -21.4% to +5.1%) • Ulcer healing rates were > 90% with H. pylori eradication
Gisbert et al. 2003	Meta-analysis	Rabeprazole (10 mg;20 mg), Omeprazole (20 mg), Lansoprazole (30 mg) Antibiotic regimens: Levofloxacin (500 mg), Tinidazole (500 mg), Metronidazole (250 mg; 400 mg;500 mg), Clarithromycin (250 mg; 400 mg; 500 mg; 800 mg), Amoxicillin (500 mg;750 mg;1 g;2 g), N=5,544	• Eradication rates: 14-day rabeprazole–amoxicillin, 73%; rabeprazole–amoxicillin–clarithromycin for 3, 5, 7 and 10 days, 44%, 72%, 78% and 75%, respectively; low-dose rabeprazole (20 mg/day), amoxicillin and clarithromycin for 7 days, 81%; high-dose rabeprazole (40 mg/day), amoxicillin and clarithromycin for 7 days, 75%; 7-day rabeprazole–clarithromycin–nitroimidazole, 85% • The eradication rate with rabeprazole plus antibiotics was 79%; it was 77% with other proton pump inhibitors (OR 1.15; 95%CI, 0.93–1.42) • Low doses of rabeprazole (10 mg b.d.), when administered with two antibiotics, may be sufficient to eradicate H. pylori infection • Rabeprazole achieves similar H. pylori eradication rates to omeprazole and lansoprazole when co-prescribed with antibiotics
Prophylaxis of NSAID-induced Ulcers			
Scheiman et al. 2011	RCT (OBERON)	Low-dose acetylsalicylic acid (75-325 mg), Esomeprazole (40 mg, n=817;20 mg, n=804), Placebo (n=805)	• After 26 weeks, esomeprazole (40 mg and 20 mg) significantly reduced the cumulative proportion of patients developing peptic ulcers • The 1.5% of esomeprazole 40 mg and 1.1% of esomeprazole 20 mg recipients, compared with 7.4% of placebo recipients, developed peptic ulcers (both p<0.0001 vs placebo) • Acid-suppressive treatment with once-daily esomeprazole 40 mg or 20 mg reduces the occurrence of peptic ulcers in patients at risk for ulcer development who are taking low-dose ASA

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Table 3: Review of clinical studies of efficacy of various PPIs in PUD, eradication of *H. pylori* and prophylaxis of NSAID-induced ulcers *(Contd...)*

Author, Year	Study Design	Study Drugs and Sample Size	Outcome
Mizokami et al. 2009	Multi-center study	Rabeprazole (10 mg;20 mg), Diclofenac sodium (25-100 mg), Loxoprofen (60-180 mg), Lornoxicam (12-18 mg) N=38	• Endoscopic cure rate in 38 patients in the efficacy analysis (endoscopic evaluation) was 71.1% (27/38) • Among the 38 patients, 35 had gastric ulcer with a cure rate of 71.4% (25/35), and 3 had duodenal ulcer with a cure rate of 66.7% (2/3) • Treatment efficacy of rabeprazole for NSAID-induced ulcer under continuous NSAID administration was confirmed
Graham et al. 2002	RCT (MUCOSA)	Lansoprazole (15 mg, n=136; 30 mg, n=133), Misoprostol (200 µg, 134) Placebo (n=134)	• Patients receiving lansoprazole (15 mg or 30 mg) remained free from gastric ulcer longer than those who received placebo (P<.001), but for a shorter time than those who received misoprostol • By week 12, the percentages of gastric ulcer–free patients were as follows: placebo, 51% (95% CI, 41.1%-61.3%); misoprostol, 93% (95% CI, 87.2%-97.9%); 15-mg lansoprazole, 80% (95% CI, 72.5%-87.3%); and 30-mg lansoprazole, 82% (95% CI, 75.0%-89.6%) • A significantly higher proportion of patients in the misoprostol group reported treatment-related adverse events and early withdrawal from the study

PPI- proton pump inhibitor, RCT- randomized controlled trial, RR- relative risk, OR- odds ratio, CI- confidence interval, NSAID- non-steroidal anti-inflammatory drug, ASA- acetyl salicylic acid

49%.[20] A meta-analysis of 7 RCTs by Wang *et al*. (2007) showed PPIs to be more effective than placebo in reducing FD symptoms in patients (Relative Risk Reduction[RRR], 10.3%; 95% CI, 2.7%–17.3%), with a significant difference in the efficacy for patients with ulcer-like (RRR, 12.8%; 95% CI, 7.2%–18.1%) and reflux-like dyspepsia (RRR, 19.7%; 95% CI, 1.8%–34.3%).[21] Furthermore, a systematic review of 23 RCTs to study PPIs with respect to global symptoms of dyspepsia revealed similar efficacy rates of low-dose as well as standard-dose PPIs.[22]

The major PPIs that have been explored for the treatment of dyspepsia are omeprazole, esomeprazole and lansoprazole. Results from the BOND (n=642) and OPERA (n=606) randomized clinical trials revealed complete relief of symptoms achieved in 38.2% of the 20 mg omeprazole group (p=0.002) and in 36.0% of the 10 mg omeprazole group (p=0.02) compared with 28.2% in the placebo group of patients with dyspepsia.[23] The ENTER trial showed a significant efficacy of 4-week esomeprazole (40 mg) for symptom relief compared to placebo, but no statistically significant difference at 8 weeks (P=0.009).[24] Peura *et al*. (2004) showed significantly greater symptomatic relief at 8 weeks in FD patients with lansoprazole (15 mg or 30 mg OD) compared with placebo (P<0.001).[25]

Safety of PPIs

Adverse events (AEs) with PPI Use

Proton pump inhibitors are well tolerated in patients with the frequency of adverse effects being <5%; the most common being headache, diarrhea, abdominal pain and nausea.[26] The American Gastroenterological Association (AGA) has outlined an evidence of potential adverse events based on the GRADE methodology. Some of the reported potential PPI-associated adverse effects identified in observational studies are kidney disease, bone fracture, myocardial infarction, *C. difficile* infection, pneumonia, micronutrient deficiencies, dementia, GI malignancies.[27] However, the quality of evidence is low to very low which most likely is attributed to a stratification bias which predisposes to these conditions, independent of PPI exposure. Retrospective database analyses cannot correct for this type of potential bias unless the database was constructed from the onset.[27] Table 4 highlights some of the most commonly observed adverse effects with PPI use.

There are many published articles highlighting the long-term safety concerns of PPIs. However, the US FDA has issued PPI class warnings only for three conditions *viz*. *Clostridium difficile*–associated diarrhea (released in the year 2012), low magnesium levels (year 2011), and possible increased risk of fractures of the hip, wrist, and spine (year 2011). However, these associations of harm have not been accepted as valid in more recent expert consensus reports.[27,44]

The alleged safety concerns highlighted with the long-term use of PPIs are class effects and not specific to any PPI molecule. The choice of PPI and duration of its use should be based on clinical condition of the patient under treatment and associated comorbid conditions.[45]

Drug Interactions with PPIs

The concomitant prescription of PPIs with other drugs may pose a risk to patients due to PPI metabolic interactions. The safety profiles of various PPIs need to be thoroughly understood with respect to a patient's medical history in order to avoid unwanted outcomes. Pharmacokinetic mechanisms by which PPIs exhibit drug-drug interactions are by altering drug absorption, modifying hepatic metabolism via either enzyme inhibition or induction, and affecting renal elimination of concomitant drugs.[46] PPIs have also been observed to reduce the oral bioavailability of anti-retroviral drugs such as atazanavir, darunavir and fosamprenavir by about 50%; thereby requiring their concomitant use with PPIs to be restricted.(46) Some prominent drugs and their pharmacokinetic effects with concomitant PPI use have been highlighted in Table 5.

Selection of Appropriate PPIs

In order to appropriately prescribe a drug to a patient, factors such as the efficacy, safety, suitability and cost need to be taken into account by the prescriber. The WHO recommends that when two drugs appear to be similar, factors such as thorough clinical investigations, pharmacokinetic profile and reliability of local manufacturing facilities need to be taken into account for selection.[48] While efficacy is a critical decider for many prescribers, unnecessary prescription of a stronger or more sophisticated PPI to treat a large number of patients, and taking side effects into secondary consideration, may provide minimal benefit. Moreover, kinetic characteristics that could be irrelevant to the drug profile, but stressed to promote an expensive drug often lead to cheaper alternatives

Table 4: Summary of studies that report adverse events with adjusted odds ratio or hazard ratio

Author, Year and Country	Results	Adjusted OR/HR and 95%CI
Bone Fractures		
Chiu et al., 2010, Taiwan (28)	Risk of hip fracture for ≤28 defined daily doses* of PPI	OR 1.04 (0.73–1.49)
	Risk of hip fracture for 29–70 defined daily doses* of PPI	OR 1.67 (1.11–2.51)
	Risk of hip fracture for ≥70 defined daily doses* of PPI	OR 2.51 (1.77–3.55) (p value for trend <0.0001)
Ding et al., 2014, USA (29)	Risk of any fracture with use of PPI	HR 1.27 (1.12–1.43; p=0.0002)
	Risk of major osteoporotic fractures with use of PPI	HR 1.28 (1.09–1.51; p=0.003)
	Risk of hip fracture with use of PPI	HR 1.32 (1.01–1.71; p=0.04)
	Risk of vertebral fracture with use of PPI	HR 1.69 (1.26–2.27; p=0.0005)
Lee et al., 2013, Korea (30)	Risk of hip fracture with PPI use	OR 1.34 (1.24–1.44)
	Risk of hip fracture with PPI use not on bisphosphonate treatment	OR 1.30 (1.19–1.42)
	Risk of hip fracture with PPI use and on bisphosphonate treatment	OR 1.71 (1.31–2.23)
Clostridium difficile infection		
Tleyjeh et al., 2012, USA (31)	Risk of C. difficile infection with use of PPI	OR 1.51 (1.26–1.83)
McDonald et al., 2015, Canada(32)	Risk of C. difficile infection recurrence within 90 days with continuous use of PPI for age older than 75 years	HR 1.5 (1.1–2.0; p<0.01)
Vitamin B12 Deficiency		
Lam et al., 2013, USA(33)	Risk of vitamin B12 deficiency with ≥2-year supply of PPI	OR 1.65 (1.58–1.73)
	Risk of vitamin B12 deficiency with ≥2-year supply of H2RA	OR 1.25 (1.17–1.34)
Jung et al., 2015, USA(34)	Risk of vitamin B12 deficiency with ≥10 months of PPI/H2RA	HR 1.83 (1.36–2.46; p value 0.00)
Kidney Diseases		
Leonard et al., 2012, UK (35)	Risk of acute interstitial nephritis with use of PPI	OR 3.20 (0.80–12.79)
Xie et al., 2016, USA (36)	PPI group had an increased risk of incident eGFR <60 ml/min/1.73 m^2	HR 1.22 (1.18–1.26)
	Risk of incident CKD	HR 1.28 (1.23–1.34)
Dementia		
Gomm et al.,2016, Germany(37)	Risk of incident dementia with use of PPI	HR 1.44 (1.36–1.52; p<0.001)
Community-Acquired Pneumonia (CAP)		
Gulmez et al., 2007, Denmark(38)	Risk of CAP with current use of PPI	OR 1.5 (1.3–1.7)
	Risk of CAP with past use of PPI	OR 1.2 (0.9–1.6)
	Risk of CAP with recent initiation of PPI	OR 5.0 (2.1–11.7)
Johnstone et al., 2010, Canada and Europe(39)	Risk of CAP with use of PPI	OR 1.36 (1.12–1.65; p<0.001)
Meijvis et al., 2011, Netherlands(40)	Risk of CAP with past PPI exposure	OR 1.2 (0.72–2.1; p=0.46)
	Risk of CAP with current PPI exposure	OR 1.6 (1.2–2.2; p<0.01)
	Risk of CAP with initiation of PPI in last 30 days	OR 3.1 (1.4–7.1; p<0.01)
Lambert et al., 2015, USA, Canada, Asia, Europe(41)	Risk of CAP with ambulatory PPI therapy	Pooled OR 1.49 (1.16–1.92; p<0.001)
	Risk of hospitalization for CAP with PPI therapy	Pooled OR 1.61 (1.12–2.31)
Hypomagnesemia		
Danziger et al., 2013, USA(42)	Risk of hypomagnesemia with use of PPI	OR 1.54 (1.22-1.95; p<0.001)
Cheungpasitporn et al., 2015, USA(43)	Risk of hypomagnesemia with use of PPI	Pooled RR 1.43 (1.08-1.88)

Notes: *Defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. The studies mentioned above include case-control, prospective/retrospective cohort, meta-analyses and systematic review studies. Abbreviations: OR, odds ration; HR, hazard ratio; RR, relative risk; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonists; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CAP, community-acquired pneumonia

being underutilized.[48]

Special populations such as elderly, children, pregnant women and those with kidney or liver disease need to be closely followed-up when initiating treatment with PPIs.

The cost of a drug needs to be taken into account based on the clinical setting as patients in resource limited countries. In India, most patients have inadequate access to health insurance and medical reimbursement schemes thereby limiting their affordability for more expensive medications because most of the healthcare expenditure is out of pocket.[49] Although the safety and efficacy across PPIs are relatively similar, differences in their cost can play a major role in governing their utilization across clinical settings in India.

Certain PPIs, particularly branded drugs, may be expensive as compared to generics, therefore, the social status of the patient, length of the treatment, the total cost of the treatment apart from efficacy and safety, need to be taken into account when initiating a drug therapy for a patient. Long-term PPI therapy may be required in underprivileged sections of the society, and prescribing drugs purely based on efficacy, safety and tolerability may diminish patient adherence due to unaffordable healthcare costs. This in turn would increase the burden of unwanted complications that would lead to increased economic burden on a hospital, and ultimately, the country.

De-prescribing PPIs

Although PPIs have a number of benefits and are viewed as safe, inappropriate prescription or prolonged usage with limited or no benefit can potentially cause adverse reactions. Deprescribing refers to stopping, stepping down or reducing the doses of PPIs by discontinuing/tapering, abruptly stopping/tapering, substituting with an H2RA prescription, or prescribing intermittent/on-demand PPI use.[50] This process may be initiated when medication may be causing harm or showing no benefit to the user. An evidence-based guideline developed by Farrell *et al.* (2017) recommend de-prescription of PPIs in adults undergoing treatment for heartburn, or mild to moderate GERD, or esophagitis for a minimum of 4 weeks, and have symptom resolution.[50] However, in

Table 5: Common drugs and their pharmacokinetic interaction effect with common PPIs

	Concomitant medication	Changes in the effect	Cause of the interaction	Clinical significance
All PPIs	Itraconazole, ketoconazole, Digoxin	↓	Decreased absorption	Decreased antimycotic effect
		↑	Increased absorption	Increased risk of toxicity
Omeprazole				
Absorption	Nifedipine	↑	Increased absorption	
CYP2C19-mediated interactions	Ticlopidine	↑ PPI effect	Inhibition of omeprazole 5′-hydroxylation, decreased elimination	Increased inhibition of gastric acid secretion
	Contraceptives	↑ PPI effect		Increased inhibition of gastric acid secretion
	Fluvoxamine	↑ PPI effect		Increased inhibition of gastric acid secretion
	Phenytoin	↑	Inhibition of omeprazole 5′-hydroxylation, decreased elimination	Increased risk of phenytoin toxicity
	Warfarin	↑		Increased risk of bleeding
	Carbamazepine	↑	Inhibition of the CYP2C19-mediated metabolism	Increased risk of carbamazepine toxicity
	Diazepam	↑		Increased sedative effect
			Decreased clearance	
			Decreased warfarin clearance	
			Decreased degradation	
			Decreased degradation, competitive inhibition of CYP2C19	
CYP3A4-mediated interactions	Ketoconazole	↑ PPI effect	Inhibition of the CYP3A4-mediated metabolism of PPIs	Increased inhibition of gastric acid secretion
	Dapsone	↑		Increased risk of toxicity
	Clarithromycin	↑ PPI effect	Probable inhibition of CYP3A4, decreased dapsone clearance	Increased inhibition of gastric acid secretion
	Salicylates	↑		Unknown
	Cyclosporine	↑	Inhibition of CYP3A4-mediated metabolism	Increased risk of cyclosporine toxicity
			Increased absorption	
			?	
Lansoprazole				
	Theophylline	↓	Increased degradation due to the CYP1A2 induction	Unknown
	Clarithromycin	↑ PPI effect		Increased inhibition of gastric acid secretion
	Tacrolimus	↑	Inhibition of CYP3A4-mediated metabolism	Increased risk of tacrolimus toxicity
			Decreased degradation, inhibition of CYP2C19	
Pantoprazole				
	Methotrexate	↑	?	Increased risk of toxicity
Rabeprazole				
	Clarithromycin	↑ PPI effect, ↑ antibiotic effect	Higher plasma concentrations of clarithromycin and rabeprazole	Beneficial to Helicobacter eradication
Esomeprazole				
	Phenytoin	↑	Decreased clearance	Increased risk of toxicity
	Diazepam	↑	Decreased degradation	Increased sedative effect
	Warfarin	↑	Decreased warfarin clearance	Increased risk of bleeding
	Clarithromycin	↑ PPI effect	Inhibition of CYP3A4-mediated metabolism	Increased inhibition of gastric acid secretion

↓ - Decrease; ↑- Increase; ?- unknown; PPI- proton pump inhibitor. Adapted with permission from Hagymási *et al.* 2011.(47)

adults with Barrett's esophagus, severe esophagitis (GRADE C or D) and documented history of bleeding GI ulcers, de-prescription should be based on patient's history and medical judgement.

The American College of Gastroenterology (ACG) 2013 guideline for treatment of GERD, recommends an initial therapy of PPIs for 8 weeks, followed by discontinuation with a need for maintenance therapy to be assessed.[51] Reducing the PPI to the lowest effective dose before discontinuation, while exploring a symptom management strategy that could include on-demand PPIs, could improve the stepping-down approach for clinicians and decrease potential long-term adverse effects in patients.[50] Long term continuation of PPIs is appropriate for risk reduction of nonsteroidal anti-inflammatory (NSAID) prophylaxis in appropriate patients.[52,53]

Fixed Dose Combinations of PPIs with Prokinetic Drugs

In India, the combination of PPI and prokinetic agent is being increasingly used by medical practitioners in patients with severe and resistant GERD.[54] Although PPIs lower acid production, have high healing rates, and rates of resolution of reflux symptoms at 4 weeks, the downside is their inability to improve underlying disturbance in gut motility or improve tone of cardiac sphincter; causing relapse in most cases.[55]

The ACG 2013 guideline recommends that therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should not be used in GERD patients without diagnostic evaluation (conditional recommendation, moderate level of evidence).[51] Prokinetic therapy with metoclopramide in addition to PPI therapy is another option often considered for patients with incomplete response to PPI therapy. For the small number of patients who may

Table 6: Expert Panel Recommendations on Best Practices for PPIs Use in India

Best Practice Advice 1: Patients with GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture) should take a PPI for minimum 12 weeks for healing of esophagitis and for maximum up to 48 weeks for symptom control.
Rationale: PPIs are highly effective in healing esophagitis and for GERD symptom control, and this benefit is likely to outweigh PPI-related risks. There is also good evidence that patients with acid related complications such as peptic stricture are best treated with continued PPI.

Best Practice Advice 2: Patients with uncomplicated GERD including NERD who respond to short-term (less than 6 weeks) use of PPIs, should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should be advised to undergo investigations to help distinguish GERD from a functional syndrome.
Rationale: Short-term PPIs are highly effective for uncomplicated GERD. Most patients with uncomplicated GERD respond to short-term PPIs and are subsequently able to reduce PPIs to less than daily dosing. Because patients who cannot reduce PPIs face lifelong therapy, we would consider testing for an acid-related disorder in this situation. Patients who do not respond to PPIs often do not have GERD.

Best Practice Advice 3: The patients with atypical symptoms of GERD such as non-cardiac chest pain may be given a 2-week trial of PPI. If they do not respond, they should be investigated to prove if they have GERD related chest pain.
Rationale: Most cases of non-cardiac chest pain may be related to reflux or esophageal motility disorder. A trial of PPI helps to differentiate.

Best Practice Advice 4: Patients with Barrett's esophagus should take long-term PPI.
Rationale: PPIs have a clear symptomatic benefit and a possible benefit in slowing progression of Barrett's. There is likely to be a net benefit for long-term PPIs in these patients

Best Practice Advice 5: Patients at high risk for ulcer-related bleeding from NSAIDs including aspirin should take a PPI if they continue to take NSAIDs
Rationale: PPIs are highly effective in preventing ulcer-related bleeding in appropriately selected patients who take NSAIDs including aspirin.

Best Practice Advice 6: The dose of long-term PPIs should be periodically re-evaluated so that the lowest effective PPI dose can be prescribed to manage the condition.
Rationale: Long-term PPI users often receive PPIs at doses higher than necessary to manage their condition. Since PPI reduction is often successful, it is logical to periodically reevaluate PPI dosing so that the minimum necessary dose is prescribed.

Best Practice Advice 7: Long-term PPI users should not use probiotics to prevent infection.
Rationale: There is no evidence for the use of probiotics to prevent infections in long-term users of PPIs.

Best Practice Advice 8: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the Recommended Dietary Allowance (RDA).
Rationale: There is no evidence for or against use of vitamins or supplements beyond the RDA in long-term users of PPIs. If patients have proven or suspected nutritional deficiency then it is reasonable to supplement vitamins and minerals regardless of PPI use.

Best Practice Advice 9: Long-term PPI users should not be routinely screened or monitored for bone mineral density, magnesium, or vitamin B12. Low threshold for testing should be kept for those with any clinical features suspicious of or in presence of other risk factor(s) for deficiency of magnesium or b12 or of osteoporosis.
Rationale: There is no evidence for or against dedicated testing for patients taking long-term PPIs. Such screening (e.g., for iron or vitamin B12 deficiency) is of no proven benefit.

Best Practice Advice 10: Patients on long-term PPI should not be routinely (yearly) monitored for serum creatinine unless there are other risks for renal monitoring.
Rationale: Based on the current literature, there is a small idiosyncratic risk of renal toxicity such as AIN with PPIs. Current data does not support routine monitoring for the vast majority of users.

Best Practice Advice 11: Specific PPI formulations should not be selected based on potential risks.
Rationale: There is no convincing evidence to rank PPI formulations by risk.

Best Practice Advice 13: Patients with dyspepsia who have predominant acid related symptoms (epigastric pain syndrome) should receive short-term PPI.
Rationale: There is likely to be a net benefit for short-term PPIs in these patients.

benefit from a prokinetic, another option is domperidone, a peripherally acting dopamine agonist.[51] The ACG 2017 guideline recommends that dyspepsia patients under the age of 60 not responding to PPI or *H. pylori* eradication therapy should be offered prokinetic therapy (very low quality evidence).[56]

The combination of prokinetic and PPI therapy regimen versus PPI monotherapy has been investigated to understand safety and efficacy profiles. Ren *et al*. (2014) analyzed 12 RCTs where participants were treated with 5-HT agonists, GABA-B receptor agonists, dopamine-receptor antagonists, each with PPI therapy. A reduction in the number of reflux episodes in GERD [95%CI: -5.96-(-1.78), P = 0.0003] with the combined therapy was observed, however, the effect on acid exposure time was insignificant (95%CI: -0.37-0.60, P = 0.65).[57] A double blind randomized clinical trial conducted by Ndraha *et al*. (2011) among sixty dyspeptic patients having heartburn and/or regurgitation revealed a statistically significant improvement with a combination of omeprazole and domperidone in GERD patients with high frequency scale of symptoms for GERD (FSSG) score, compared to omeprazole monotherapy (P=0.02).[58]

The use of prokinetics have had variable success in patients with functional dyspepsia however, they fail to promote healing of esophagitis leaving them inadequate for GERD treatment.[54] Despite a positive outcome, further studies with different PPI and prokinetic combinations need to be conducted to understand the utility of the FSSG score for the addition of a prokinetic to PPI therapy in different populations. Adverse drug reactions such as headache, lethargy, giddiness, diarrhea, xerostomia and QT prolongation have been found in studies involving metoclopramide and levosulpiride, and the former four AEs have been also been found in domperidone.[59] A prospective, randomized study by Jain et al. (2017) revealed superiority of levosulpiride (25 mg TID) over domperidone (10 mg TID) in patients with FD (n=182), but reported more adverse effects than the latter.[60] Further, the impact of prokinetic therapy on clinical outcomes such as pneumonia, mortality and ICU length stay in critically ill patients remains unclear.[61]

A safe and effective prokinetic agent, over PPI therapy, may be an appropriate empiric choice when heartburn occurs with symptoms of impaired gastric emptying.[62] In clinical practice, although agents such as PPIs are effective in acute treatment and are preferred for maintenance therapy, a 'step-down' approach may allow them to be replaced with either a prokinetic agent or H2RA.[62]

Expert Panel Recommendations

The Clinical Practice Updates Committee of the American Gastroenterological Association (AGA) in 2017 formulated 10 best practice recommendations based on expert opinions and related publications for the treatment of GERD, Barrett's esophagus and NSAID bleeding prophylaxis.[27] The expert panel has adapted AGA recommendations with Indian context as shown in the Table 6.

Conclusion

This expert review provides key recommendations for decision making in order to minimize the irrational use of PPIs. Best practice recommendations are meant to merely assist with decision making in conjunction with patients' clinical history, and are not intended to dictate mandatory rules.

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