

# Pharmaceutical principles of acid inhibitors: unmet needs

---

Krznarić, Željko; Ljubas Kelečić, Dina; Rustemović, Nadan; Vranešić Bender, Darija; Ostojić, Rajko; Markoš, Pave; Scarpignato, Carmelo

Source / Izvornik: **Digestive Diseases, 2011, 29, 469 - 475**

Journal article, Accepted version

Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

<https://doi.org/10.1159/000331515>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:915594>

Rights / Prava: [In copyright](#) / [Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-08-28**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine  
Digital Repository](#)





## Središnja medicinska knjižnica

**Krznarić Ž., Ljubas Kelečić D., Rustemović N., Vranešić Bender D.,  
Ostojić R., Markoš P., Scarpignato C. (2011) *Pharmaceutical principles  
of acid inhibitors: unmet needs. Digestive Diseases*, 29 (5). pp. 469-  
75. ISSN 0257-2753**

<http://www.karger.com/DDI>

<http://dx.doi.org/10.1159/000331515>

<http://medlib.mef.hr/1438>

University of Zagreb Medical School Repository

<http://medlib.mef.hr/>

## **Pharmaceutical principles of acid inhibitors: unmet needs**

Z. Krznaric<sup>1</sup>, D. Ljubas Kelecic<sup>2</sup>, N. Rustemovic<sup>1</sup>, D. Vranesic Bender<sup>2</sup>, R. Ostojic<sup>1</sup>, P. Markos<sup>3</sup> C. Scarpignato<sup>4</sup>

<sup>1</sup>University of Zagreb, School of Medicine, Department of Gastroenterology and Hepatology, University Hospital Centre Zagreb, Zagreb, Croatia

<sup>2</sup>Centre of Clinical Nutrition, University Hospital Centre Zagreb, Zagreb, Croatia

<sup>3</sup>Department of Gastroenterology and Hepatology, University Hospital Centre Zagreb, Zagreb, Croatia

<sup>4</sup>Laboratory of Clinical Pharmacology, School of Medicine and Dentistry, University of Parma

### **Corresponding author:**

Zeljko Krznaric, MD, PhD, FEBGH

Department of Gastroenterology and Hepatology University Hospital Centre Zagreb,

Kispaticeva 12

10000 Zagreb, Croatia

Tel.: +385- 98-35-54-54

Fax: +385- 24-20-100

E-mail: [zeljko.krznaric1@zg.t-com.hr](mailto:zeljko.krznaric1@zg.t-com.hr)

## **ABSTRACT**

Despite the well established benefits of currently approved delayed release proton pump inhibitors (PPIs) in the treatment of acid related diseases, the unmet needs are still present and although often frustrating, they challenge clinicians. The unmet needs relate to the lack of complete control of acid secretion with oral PPI administration in the management of patients with gastro-oesophageal symptoms. These substantial groups of patients, who do not respond completely to standard doses of PPIs, are non-responders; and their lack of response should be considered as PPIs failure. Several mechanisms could explain PPI failure: differences in pharmacokinetics, PPIs formulation, dosing time and diet, noncompliance, transient lower oesophageal sphincter relaxations (TLESRs), oesophageal hypersensitivity, and nocturnal acid breakthrough. To increase QoL of these patients and avoid multiple medical consultations and unnecessary investigations, we have to go one step forward, to use combine therapy or look towards new treatments beyond acid suppression.

**Key words:** unmet needs, acid inhibition, proton pump inhibitors (PPIs), gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD), Barrett's oesophagus, nocturnal acid breakthrough (NAB), rebound acid hypersecretion

## **INTRODUCTION**

The development of the PPIs and their introduction in the late 1980s enabled significant improvement in the management of various acid-related upper gastrointestinal disorders. Because of their efficiency, minimal side effects and general safety for long-term treatment, today they are the most common prescribed drugs in the treatment of acid-peptic diseases. A meta-analysis of 43 studies on gastro-oesophageal reflux disease (GERD), including 7635 patients, demonstrated a more complete and twice as fast esophagitis healing and heartburn relief with PPIs vs. histamine receptor antagonists (H2RAs).<sup>1</sup>

However, in last ten years many articles regarding the unmet needs of acid suppression have been published indicating that currently available PPIs have notable limitations and are still far from the ideal antisecretory compound. The unmet needs relate to the lack of complete control of acid secretion with oral PPIs administration in the management of patients with gastro-oesophageal symptoms, non-variceal upper gastrointestinal bleeding, nonsteroidal anti-inflammatory drugs (NSAIDs) and GIT mucosa injury, and *Helicobacter pylori* infection.<sup>2-5</sup>

The question is whether the current PPIs still have hidden potential or unmet clinical needs require to be addressed with newer agents capable of achieving rapid and long-lasting acid suppression?<sup>6</sup>

### **Differences in PPIs pharmacokinetics**

Differences in PPIs pharmacokinetics, bioavailability, elimination half-life and metabolism have been observed and could be the answer for the differences in clinical outcomes.<sup>7</sup> PPI products currently available on the market (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) all contain basic structural framework, 2-pyridylmethylsulfinylbenzimidazole pharmacophore, varying only in the specific side ring substitution. Tenatoprazole, a new PPI, has an imidazopyridine ring.

PPIs pKa of about 4.0 enables their accumulation only in the acidic secretory canaliculus of the stimulated parietal cell, where they are converted into thiophilic intermediates that bind to cysteine sulfhydryl groups on the luminal aspect of the proton pump to form covalent disulfide bonds. This covalent inhibition of the enzyme by the thiophilic sulfenamide results in a specific and long-lasting impairment of gastric acid secretion. The antisecretory effect of the drugs reflects their short plasma half-life (ranging from 1 to 1.5 hours), the number of active pumps during that time, and the recovery of pumps following biosynthesis and reversal of inhibition.<sup>8</sup> Tenatoprazole, a new PPI that has a 5- to 7-fold longer elimination half-life than other current PPIs, could be potentially more useful for the treatment of GERD and NAB.<sup>4,9</sup> One of the latest comparisons of pharmacodynamic and pharmacokinetic profiles of tenatoprazole and esomeprazole has shown **significantly** greater and more prolonged dose-dependent 24-h and nocturnal acid suppression with S-tenatoprazole-Na than esomeprazole. S-tenatoprazole-Na may provide greater clinical efficacy compared with current PPIs for patients with ineffective once-daily therapy.<sup>10</sup>

### **PPIs formulation**

PPIs are often referred as prodrugs, although they do not require enzymatic activation. They are acid-labile, weak bases formulated as delayed-release enteric-coated preparations. Enteric coating is protecting PPIs from premature acid degradation in the stomach so that absorption can occur in the proximal small intestine. Because of that, there is a delay in absorption and onset of their antisecretory effect.<sup>11</sup> Lansoprazole fast disintegrating tablet (LFDT), so called "patient-friendly" and more convenient formulation of lansoprazole which can be taken with or without water, was the first PPI to be made available as an orally disintegrating tablet (ODT).<sup>12</sup> Unfortunately, no significant differences in symptom relief between lansoprazole ODT and esomeprazole were reported in patients with non-erosive reflux disease.<sup>13</sup> Few years ago, immediate-release omeprazole has been introduced. It consists of pure, non enteric-coated omeprazole powder along with sodium bicarbonate,

which acts as a buffer against gastric acid degradation. The absence of an enteric coating facilitates rapid absorption. Studies have shown that immediate-release omeprazole when compared to delayed-release omeprazole, has a higher mean peak plasma concentration ( $C_{(max)}$  1019 ng/mL vs 544 ng/mL) and a significantly shorter mean time to reach significantly shorter  $t_{max}$  (25 minutes vs 127min).<sup>14</sup> In the management of nocturnal acid breakthrough (NAB), repeated once-daily (bedtime) dosing with immediate-release omeprazole produced significantly better results than repeated once daily (pre-dinner) or twice-daily dosing with delayed-release pantoprazole. Twice daily dosing (prebreakfast and bedtime) with immediate-release omeprazole 20 and 40mg achieved the best night-time control of gastric acidity.<sup>15</sup>

## **Dose**

There are differences in PPIs bioavailability after single and repeated dose. Early complete heartburn relief with proton pump inhibitors for the entire day occurs in only 30% of patients after their first PPI dose and in 9% of patients after placebo. Although PPIs might provide benefit from the first day of therapy, most patients will not have symptom relief with 1 or 2 days of PPI therapy.<sup>16</sup> The first published comparative pharmacodynamic trial comparing standard doses of esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole has shown that esomeprazole at the standard dose of 40 mg once daily provided more effective control of gastric acid at steady state than standard doses of other PPIs in patients with symptoms of gastroesophageal reflux disease.<sup>17</sup> The bioavailability of rabeprazole on day 1 is greater than with other PPIs, and this may translate into faster onset of symptom relief for patients with gastro-oesophageal reflux disease. On the other hand, the bioavailability of esomeprazole increases 3-fold at day 5, and it has been shown that on day 5, esomeprazole provided significantly more effective control of gastric acid than other PPIs. The exact clinical significance of these observations remains to be determined.<sup>18</sup> Differences in hepatic metabolism of PPIs due to cytochrome P450 2C19 genetic polymorphisms may

influence clinical outcomes. In *Helicobacter pylori* eradication, a significantly lower eradication rate was seen in extensive metabolisers with omeprazole and lansoprazole but not with rabeprazole. The oesophagitis healing rate was lower in extensive metabolisers with lansoprazole but not with rabeprazole.<sup>7</sup>

### **Nutritional intake and food timing**

There is sufficient evidence to support the relationship between being obese/overweight and GERD, expressed as specific symptoms and endoscopic features. Furthermore, available evidence suggests that controlled weight loss is able to induce a significant improvement in GERD symptoms and/or in GERD clinical-endoscopic manifestations. It is a common belief that some foods may induce or worsen GERD symptoms. In daily clinical practice, this belief leads to advising patients to avoid the suspect foods. Since GERD symptoms are most commonly reported postprandial, the role of diet components in inducing symptoms has been suggested. However, different and conflicting results exist in the literature for identifying the most "refluxogenic" foods. Clinical studies have shown a decrease in LES pressure and an increase in esophageal acid exposure in response to the ingestion of food rich in fats, chocolate and carminatives. Also, studies demonstrated that fried foods, spicy foods and alcohol are the most common precipitating factors of heartburn.<sup>19</sup> According to the study of El-Serag et al. there is a positive association between high fat intake, and GERD symptoms as well as erosive esophagitis, while a high-fibre diet seemed to reduce reflux symptoms. The effects of fat on GERD symptoms and erosive esophagitis were dependent on BMI since this was statistically significant only in overweight individuals.<sup>20</sup> While some authors have suggested that alcohol is an independent risk factor for GERD-related symptoms, others have not found such a relationship. Similar observation was for ingestion of coffee; while intraesophageal infusion of coffee in patients with acid sensitivity may induce heartburn, two large epidemiological studies have found no association between coffee drinking and GERD.<sup>21,22</sup>



Effectiveness of a PPI is also dependent on food timing and food intake. As gastric acid secretion is maximally stimulated by food ingestion, maximal PPI efficacy should be achieved when they are taken before a meal. Hatlebakk's study has shown an advantage in daytime intragastric pH control when a morning dose of omeprazole or lansoprazole were taken before breakfast compared with no breakfast. Therefore, intake of medication in relation to meals, specially may be important to optimize their effect and avoid therapeutic failure.<sup>23</sup>

PPIs are most often prescribed for intake in the morning and in most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition, and a second dose, which is occasionally necessary, should be administered before the evening meal.<sup>2</sup>

## **WHAT DO WE KNOW ABOUT UNMET NEEDS?**

### **Gastro-oesophageal reflux disease**

GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms, with or without mucosal damage, and/or complications.<sup>24</sup> A systematic review of the epidemiology of GERD has demonstrated 10-20% prevalence, defined by at least weekly heartburn and/or acid regurgitation, in the Western world and less than 5% in Asia. The incidence in the Western world is approximately 5 per 1000 person years.<sup>25</sup> Although, the proton pump inhibitors are highly effective for the majority of patients with erosive oesophagitis and considered the mainstay treatment for GERD, significant therapeutic challenges still exist,. Surveys among primary-care physicians (PCPs) indicate a number of areas of controversy and confusion related to the management of GERD. It was found that most PCPs prescribe PPIs for GERD without prior authorization and without first using an H2RA and many of them give an H2RA with once-daily PPI treatment for patients with nocturnal heartburn. The appropriate advice regarding the importance of PPIs use and food intake was in less than 64% of patients.<sup>26</sup> The conclusion of recently published review from Yuan and Hunt was that a substantial number of patients fail to respond adequately to

once or even twice daily PPI and that there is no standard definition of PPI failure in GERD as well as a universally accepted definition for treatment success.<sup>27</sup>

The prevalence of PPI failure differs from patients with nonerosive reflux disease (NERD) and those with erosive oesophagitis. PPIs provide a more modest therapeutic gain in patients with NERD as compared with those with erosive oesophagitis. Total response rates at 4 weeks were significantly higher for patients with erosive oesophagitis compared with NERD (56% vs. 37%).<sup>28</sup> Studies in the different phenotypic presentations of GERD suggest that the overall prevalence of PPI failure is approximately 30%.<sup>29</sup> Meta-analysis of symptomatic GERD patients found that in about two-thirds of patients, reflux symptoms are not adequately controlled after the first dose of a PPI, and nearly 50% patients still suffer symptoms 3 days later.<sup>30</sup>

### **Nonerosive reflux disease**

**NERD** is the most common form of GERD. In a primary care setting up to 70% of patients with typical symptoms of GERD have NERD. The closest entity to NERD that is examined by available epidemiologic studies is defined by the presence of GERD symptoms in the absence of esophageal erosions or Barrett's esophagus.<sup>32</sup> NERD is often characterized with troublesome symptoms that affect the quality of life similar to that reported by patients with erosive oesophagitis. GERD patients with NERD are relatively refractory to the pharmacodynamic effects of proton pump inhibitors on the postprandial integrated gastric acidity,<sup>33</sup> suggesting that their symptoms may be generated by different mechanisms than acid as in erosive oesophagitis.

The proportion of NERD patients responding to a standard dose of PPIs is approximately 20–30% lower than what has been documented in patients with erosive oesophagitis.<sup>29,31,31</sup> Progression to erosive gastroesophageal reflux disease (ERD) occurs in about 5% of NERD cases per year, despite standard therapy. Factors that are consistently and independently

influencing this progression are smoking and the lack of a continuous PPI therapy during the follow-up period.<sup>34</sup>

Recently, biopsies established that subjects with heartburn and PPI-responsive NERD, like those with erosive esophagitis, have lesions within the esophageal epithelium known as dilated intercellular space (DIS), suggesting that DIS might be involved in development of persistent symptoms.<sup>35</sup> Dexlansoprazole MR a novel, modified-release formulation of dexlansoprazole, which incorporates dual delayed- release technology designed to prolong the serum concentration- time profile, and thus provides extended acid-suppression, has been recently assessed in NERD patients.<sup>37</sup> In 4-week, double-blind, placebo-controlled study with 947 NERD patients dexlansoprazole 30 mg/day for 4 weeks was shown to be superior to placebo in providing 24-hour heartburn-free days and nights (54.9% vs. 17.5% and 80.8% vs. 51.7%, respectively).<sup>38</sup>

### **Erosive oesophagitis**

Erosive oesophagitis accounts for about 20-30% of patients with GERD demonstrates 6-15% of PPI (once daily) treatment failure. Patients with more severe grades of erosive oesophagitis have demonstrated a higher PPI failure rate than those with less severe disease.<sup>29</sup> Nonresponse of erosive esophagitis increases with severity of erosive esophagitis grading. The nonhealed rate for Los Angeles grade C and grade D erosive esophagitis on standard dose PPIs suggests that approximately 40% of moderate (C) and 51% severe (D) erosive esophagitis were unhealed after 4 weeks and 18% of C and 27% of D at 8 weeks.<sup>39</sup>

### **Barrett's oesophagus**

The prevalence of Barrett's oesophagus is 6–12% of all patients who present for endoscopy with GERD-related symptoms, and 0.25–3.9% in unselected cases undergoing upper endoscopy.<sup>40</sup> Barrett's esophagus is considered to follow a progression from intestinal metaplasia to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and finally to

esophageal adenocarcinoma in a subset of patients. Conservative management, involving symptom control and periodic endoscopic surveillance to exclude progressive disease, is recommended for patients with Barrett's esophagus without evidence of dysplasia or cancer. Lifestyle modifications can be helpful to increase esophageal acid clearance and decrease the incidence of reflux events.<sup>41</sup>

### **Atypical symptoms**

GERB can be presented with atypical or extraesophageal symptoms, including asthma, unexplained chronic cough, laryngitis, oropharyngitis, nocturnal wheeze, chronic sore throat, dental erosions, and noncardiac chest pain. Empiric trial using proton pump inhibitors is still the recommended initial approach to those suspected of having reflux as the cause for extraesophageal symptoms such as asthma, chronic cough or laryngitis, although, recent randomized placebo-controlled studies have been disappointing in showing benefit of acid suppressive therapy.<sup>42-46</sup>

### **Nocturnal acid breakthrough**

NAB has been arbitrarily defined as the presence of gastric pH below 4 for at least 1h during the night – in patients on PPI therapy. This is physiological phenomenon that has been observed in 75% of all individuals (GERD patients as well as healthy subjects) taking PPI twice a day.<sup>45</sup> Recent US survey of GERD patients taking PPIs clearly emphasized that over 80% of the patients reported night symptoms during the previous 30 days and 23.4% described symptoms as severe or very severe.<sup>46</sup> In total, 22% of responders were on PPI b.i.d. and 42% supplemented prescribed PPIs by OTC PPIs, H2RAs, or antacids. Among patients on PPI b.i.d., 39.1% increased the dose due to poor symptom control at night.<sup>47</sup> Increased night time acidity leads to more severe GERD symptoms and could be associated with obstructive sleep apnea.<sup>48</sup> Due to the short plasma half life (1-2 h) delayed release PPIs do not have effect on acid suppression 5 hours after evening dose because there is no drug

available to inhibit acid pumps synthesized during the night time hours so intragastric pH may remain less than 4 for up to a third of the night<sup>49</sup> Therefore, acid secretion after midnight is not controlled even with the most aggressive acid-suppressive therapy. Therapeutic approach that included the addition of histamine-2 receptor antagonist (H2RA) at bedtime was introduced and quickly adopted. In summary, the presence of NAB in patients treated with a PPI is a physiological phenomenon that has yet to demonstrate an association with clinical parameters, such as symptoms or erosive esophagitis.

### **Rebound acid hypersecretion**

Rebound is defined as an increase in gastric acid secretion above pre-treatment levels following discontinuation of antisecretory therapy. Rebound is clinically important because it seems that it contributes to the recurrence of GERD.<sup>50</sup> There are four mechanisms to explain rebound : up regulation of H2-receptors, hypergastrinaemia-stimulating histamine release by enterochromaffin-like (ECL) cells, increase of parietal cell mass and up regulation of H<sup>+</sup>/K<sup>+</sup>-ATPase activity.<sup>51</sup> Increased gastric acid secretion is well described after stopping the long-term use of histamine H2- receptor antagonists,<sup>52,53</sup> but its occurrence after the prolonged use of PPIs is controversial, it seems that there is no strong evidence for a clinically relevant increased acid output after PPI therapy is stopped.<sup>51-53</sup> Three uncontrolled trials nevertheless suggested an increase in acid secretory capacity in H. pylori negative subjects after 8 weeks of treatment.<sup>54-56</sup> In this situation rebound hypersecretion after attempting to stop the PPI, could result in GERD symptoms worsening and therefore resulting in prolongation of the PPIs use.<sup>52</sup> Perhaps the advice should be to never abruptly stop PPI therapy but to always step down to half strength and then to intermittent therapy if full symptom control is obtained. Whether on-demand therapy may also lead to rebound is unknown, but deserves to be evaluated.<sup>2</sup>

## **Quality of life (QoL)**

Heartburn and acid regurgitation are the cardinal symptoms of GERD.<sup>57</sup> It is well known that severity and frequency of these symptoms are associated with impaired QoL.<sup>58,59</sup> Generic measurements have shown that GERD patients even have a lower QoL than patients with chronic ischemic heart disease.<sup>60</sup>

Today, PPIs as the most commonly prescribed drugs in case of GERD play an important role in patients QoL. The German prospective cohort study (ProGERD) with over 6000 GERD patients determined that the quality of life of individuals with reflux disease, in terms of both physical and psychosocial aspects of wellbeing, was significantly lower than that of the general population. Problems with eating and drinking, vitality and pain were defined as most significant to impair the QoL. However, it was shown that this can easily be relieved or even eliminated within a short period of time (2 weeks) by treatment with esomeprazole, irrespective of whether the patient is suffering from non-erosive or erosive GERD or Barrett's oesophagus.<sup>59</sup> Three years later, results of the first study that involved endoscopy in the general population, suggest that the presence or absence of oesophagitis does not appear to predict impairment of QoL.<sup>60</sup> Recently, one study demonstrated that the QoL associated with the reflux oesophagitis and NERD subtypes may be more related to psychological factors (anxiety and depression) than to symptom severity.<sup>61</sup>

## **BEYOND ACID SUPPRESSION: MANAGEMENT OF FAILURE**

Logical step forward would be the next generation of drugs, which suppress gastric acidity. A number of new drugs are currently being investigated. Potassium-competitive acid blockers (P-CABs) are potassium competitive inhibitors of the ATPase.<sup>5</sup> Considering the main differences in the mechanism of action between P-CABs and PPIs, a clinically relevant fact is that P-CABs have a full effect after the first dose. Potassium competitive antagonists and gastrin (CCK2) receptor antagonists reached clinical testing, but did not fulfil all clinical

expectations. Dual approach, using PPIs in combination with TLESR- targeted agents, would reduce the time that patients need to achieve heartburn control and minimize possible ceiling effect of PPI therapy.<sup>62</sup> Since PPIs have no effect on TLESR, new add-on medication therapies will be of great interest for pharmaceutical companies in the future.

The type B gamma-aminobutyric agonists (GABA (B)) receptor agonists are new medications, which are currently undergoing clinical trials to establish their potential to reduce TLESR and reflux episodes, increase basal lower esophageal sphincter pressure and reduce swallowing. Limitations are small human phase 1 and 2 trails, and significant side-effects, particularly those affecting liver and central nervous system. Discovery of analogues with an improved side effect profile is warranted.

The metabotropic glutamate receptor (mGluR) antagonists have similar mechanism of action as GABA (B) agonists. Their research is currently in the phase of animal studies, except for one human proof-of-concept study.<sup>63</sup>

Endoscopic antireflux procedures were introduced with great enthusiasm at the beginning of this century but after all a recent AGA Institute medical position statement recommended that "current data suggest that there are no definite indications for endoscopic therapy for GERD at this time".<sup>64</sup>..

## **CONCLUSION**

The proton pump inhibitors are a group of drugs that reduce the secretion of gastric acid, and are highly successful in treating of patients suffering from acid related diseases.

Unfortunately, there are still significant number of patients that have persistent dyspeptic symptoms and decrease QoL despite use of PPI's. The unmet needs of PPI's relate to the lack of complete control of acid secretion with oral PPI administration in the management of patients with gastro-oesophageal symptoms, non-variceal upper gastrointestinal bleeding, NSAID gastrointestinal injury and *Helicobacter pylori*. To increase QoL of these patients and

avoid multiple medical consultations and unnecessary investigations, we have to go one step forward, to use combine therapy or look towards new treatments beyond acid suppression. Beside the acid suppression, there are different potential targets in patophysiological mechanisms of GERD and acid related diseases where we can act in order to accomplish the support to those patients. The role of those new medications and endoscopic procedures remains to be proved, before placing as an add-on therapy to PPIs.

### References:

1. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology* 1997; 112:1798–810.
2. Tytgat GNJ. Are there unmet needs in acid suppression? *Best Practice & Research Clinical Gastroenterology*. 2004; 18:67–72.
3. Hunt RH. Review article: the unmet needs in delayed-release proton-pump inhibitor therapy in 2005. *Aliment Pharmacol Ther* 2005; 22 (3):10–19.
4. Scarpignato C, Pelosini I. Review article: the opportunities and benefits of extended acid suppression. *Aliment Pharmacol Ther*. 2006; 23(2):23-34.
5. Scarpignato C, Pelosini I, Di Mario F. Acid Suppression Therapy:Where Do We Go from Here? *Dig Dis* 2006;24:11-46
6. Scarpignato C, Hunt RH. Proton pump inhibitors: the beginning of the end or the end of the beginning? *Current Opinion in Pharmacology* 2008; 8:677–684.
7. Fock KM, Ang TL, Bee LC, et al. Proton pump inhibitors: Do differences in pharmacokinetics translate into differences in clinical outcomes? *Clin Pharmacokinet*. 2008; 47:1-6.
8. Roche VF. TEACHERS' TOPICS. The Chemically Elegant Proton Pump Inhibitors. *American Journal of Pharmaceutical Education* 2006; 70(5): Article 101.



9. Hunt RH, Armstrong D, James C, et al. Effect on intragastric pH of a PPI with a prolonged plasma half-life: comparison between tenatoprazole and esomeprazole on the duration of acid suppression in healthy male volunteers. *Am J Gastroenterol* 2005; 100:1949- 1956.
10. Hunt RH, Armstrong D, Yaghoobi M, James C. The pharmacodynamics and pharmacokinetics of S-tenatoprazole-Na 30 mg, 60 mg and 90 mg vs. esomeprazole 40 mg in healthy male subjects. *Aliment Pharmacol Ther.* 2010; 31(6):648-57.
11. Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD. An overview of their pharmacology, efficacy and safety. *Pharmacological Research* 2009; 59:35–153.
12. Baldi F, Malfertheiner P. Lansoprazole Fast Disintegrating Tablet: A New Formulation for an Established Proton Pump Inhibitor. *Digestion* 2003;67:1–5
13. Baldi F, Ghersi S, Cavoli C, Torresan F. A comparison of the new lansoprazole orally disintegrating tablets (LODT) tablets with esomeprazole in patients with non erosive reflux disease. *Gastroenterology* 2005; 128(2):A523–524.
14. Howden CW. Review article: immediate-release proton-pump inhibitor therapy – potential advantages. *Aliment Pharmacol Ther* 2005; 22(3):25-39.
15. Castell D, Bagin R, Goldlust B, et al. Comparison of the effects of immediate- release omeprazole powder for oral suspension and pantoprazole delayed- release tablets on nocturnal acid breakthrough in patients with symptomatic gastroesophageal reflux disease. *Aliment Pharmacol Ther* 2005; 21:1467-74.
16. McQuaid KR, Laine L. Early heartburn relief with proton pump inhibitors: a systematic review and meta-analysis of clinical trials. *Clin Gastroenterol Hepatol* 2005; 3(6):553-63.
17. Miner P, Katz Jr. PO, Chen Y, Sostek M. Gastric Acid Control With Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole: A Five-Way Crossover Study. *Am J Gastroenterol* 2003; 98:2616- 2620.

18. Hellstrom PM, Vitols S. The choice of proton pump inhibitor: does it matter? *Basic Clin Pharmacol Toxicol* 2004; 94:106-11.
19. Festi D, Scaiola E, Baldi F, et al. Body weight, lifestyle, dietary habits and gastroesophageal reflux disease *World J Gastroenterol* 2009;15(14):1690-1701.
20. El-Serag HB, Satia JA, Rabeneck L. Dietary intake and the risk of gastro-oesophageal reflux disease: a cross sectional study in volunteers. *Gut* 2005; 54:11-17.
21. Stanghellini V. Relationship between upper gastrointestinal symptoms and lifestyle, psychosocial factors and comorbidity in the general population: results from the domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterol Suppl* 1999; 231:29-37.
22. Wang JH, Luo JY, Dong L, Gong J, Tong M. Epidemiology of gastroesophageal reflux disease: a general population-based study in Xi'an of Northwest China. *World J Gastroenterol* 2004; 10:1647-1651.
23. Hatlebakk JG, Katz PO, Camacho-Lobato L, Castell DO. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. *Aliment Pharmacol Ther* 2000; 14:1267-72.
24. Nimish V, Sander V, Kahrilas P, Dent J, Jones R, Global Consensus Group. The montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006; 101:1900-20.
25. Dent J, El Serag H, Wallender M, Johansson S. Epidemiology of gastroesophageal reflux disease: a systematic review. *Gut*.2005; 54:710-7.
26. Chey WD, Inadomi JM, Boohar AM, et al. Primary-care physicians' perceptions and practices on the management of GERD: results of a national survey. *Am J Gastroenterol* 2005; 100:1237- 42.
27. Yuan Y, Hunt RH. Evolving Issues in the Management of Reflux Disease? *Curr Opin Gastroenterol*. 2009; 25(4):342-351.

28. Dean BB, Gano AD Jr, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004; 2:656–64.
29. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: Protonpump inhibitor failure in gastro-oesophageal reflux disease – where next? *Aliment Pharmacol Ther* 2005; 22:79–94.
30. Yuan Y, Wang CC, Yuan Y, Hunt RH. The proportion of patients who are free of reflux symptoms during the initial days of treatment with proton pump inhibitors (PPIs) in GERD trials: a meta-analysis. *Gastroenterology* 2008; 134(4):A174.
31. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. *J Clin Gastroenterol* 2007; 41:131–137.
32. Gardner JD, Gallo-Torres H, Sloan S, Robinson M, Miner PB. The basis for the decreased response to proton pump inhibitors in gastro-oesophageal reflux disease patients without erosive oesophagitis. *Aliment Pharmacol Ther* 2003; 18:891–905.
33. El-Serag HB. Epidemiology of Non-Erosive Reflux Disease. *Digestion* 2008; 78(1):6-10.
34. Pace F, Pallotta S, Manes G, et al. Outcome of nonerosive gastro-esophageal reflux disease patients with pathological acid exposure. *World J Gastroenterol* 2009; 15(45):5700-5705.
35. Caviglia R, Ribolsi M, Gentile M, et al. Dilated intercellular spaces and acid reflux at the distal and proximal oesophagus in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2007; 25(5):629-36.
36. Orlando LA, Orlando RC. Dilated intercellular spaces as a marker of GERD. *Curr Gastroenterol Rep.* 2009; 11(3):190-4.
37. Hershcovici T, Fass R. Nonerosive Reflux Disease (NERD) - An Update. *J Neurogastroenterol Motil* 2010; 16(1).

38. Fass R, Chey WD, Zakko SF, et al. Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2009; 29:1261-1272.
39. Yuan Y, Vinh B, Hunt RH. Nonhealed rate of moderate-severe (LA Classification Grade C and D) erosive esophagitis after 4-8 weeks proton pump inhibitors (PPIs): evidence of an unmet need. *Gastroenterology* 2009; 136 (Abstract #M1893.).
40. Fass R, Sampliner RE. Barrett's oesophagus: optimal strategies for prevention and treatment. *Drugs* 2003; 63:555–64.
41. Garud SS, Keilin S, Cai Q, Willingham FF. Diagnosis and management of Barrett's esophagus for the endoscopist. *Therap Adv Gastroenterol*. 2010; 3(4):227-38.
42. Moore JM, Vaezi MF. Extraesophageal Manifestations of Gastroesophageal Reflux Disease: Real or Imagined? *Curr Opin Gastroenterol*. 2010;26(4):389-394
43. Peghini PL, Katz PO, Bracy NA, Castell DO. Nocturnal recovery of gastric acid secretion with twice-daily dosing of proton pump inhibitors. *Am J Gastroenterol* 1998; 93:763–7.
44. Chey WD, Mody R, Chen L, et al. Nighttime symptoms and sleep impairment among patients with gastro-esophageal reflux disease (GERD) receiving prescription (Rx) proton pump inhibitors (PPIs). *Gastroenterology* 2008; 134(4 Suppl 1):A323–A324;Abstract #M1033.
45. Chey WD, Mody R, Kothari S, et al. Are proton pump inhibitors (PPIs) sufficient in controlling symptoms of gastro-esophageal reflux disease (GERD)? A community-based US survey study. *Gastroenterology* 2008; 134(Suppl 1):A-325;Abstract #M1041.
46. Galmiche JP, Zerbib F, Bruley des Varannes S. Review article: respiratory manifestations of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2008; 27:449–464.

47. Miehlike S, Madisch A, Kirsch C, et al. Intra-gastric acidity during treatment with esomeprazole 40mg twice daily or pantoprazole 40mg twice daily – a randomized, two-way crossover study. *Aliment Pharmacol Ther* 2005; 21:963–967.
48. El-Omar E, Banerjee S, Wirz A, et al. Marked rebound acid hypersecretion after treatment with ranitidine. *Am J Gastroenterol* 1996; 91:355–9.
49. Hunfeld NG, Geus WP, Kuipers EJ. Systematic review: Rebound acid hypersecretion after therapy with proton pump inhibitors. *Aliment Pharmacol Ther* 2007; 25:39–46.
50. Jensen RT. Consequences of long-term proton pump blockade: Highlighting insights from studies of patients with gastrinomas. *Basic Clin Pharmacol Toxicol* 2006; 98:4–19.
51. Qvigstad G, Waldum H. Rebound hypersecretion after inhibition of gastric acid secretion. *Basic Clin Pharmacol Toxicol* 2004; 94:202–208.
52. Gillen D, Wirz AA, Ardill JE, et al. Rebound hypersecretion after omeprazole and its relation to on-treatment acid suppression and *Helicobacter pylori* status. *Gastroenterology* 1999; 116: 239–47.
53. Gillen D, Wirz AA, McColl KE. *Helicobacter pylori* eradication releases prolonged increased acid secretion following omeprazole treatment. *Gastroenterology* 2004; 126: 980–8.
54. Waldum HL, Arnestad JS, Brenna E, et al. Marked increase in gastric acid secretory capacity after omeprazole treatment. *Gut* 1996; 39: 649–53.
55. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R: The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101(8):1900-1920.
56. Flook NW, Wiklund I: Accounting for the effect of GERD symptoms on patients' health-related quality of life: supporting optimal disease management by primary care physicians. *Int J Clin Pract* 2007; 61(12):2071-2078.

57. Gisbert JP, Cooper A, Karagiannis D, et al. Impact of gastroesophageal reflux disease on patients' daily lives: a European observational study in the primary care setting. *Health and Quality of Life Outcomes* 2009;7:60
58. Wiklund I: Review of the quality of life and burden of illness in gastroesophageal reflux disease. *Dig Dis* 2004; 22(2):108-114.
59. M. Kulig, A. Leodolter, M. Vieth, et al. Quality of Life in Relation to Symptoms in Patients With Gastro-Oesophageal Reflux Disease - An Analysis Based on The ProGERD Initiative. *Alimentary Pharmacology & Therapeutics* 2003; 18(8).
60. Ronkainen J, Aro P, Storskrubbet T, al. Gastro-oesophageal reflux symptoms and health-related quality of life in the adult general population-The Kalixanda study. *Aliment Pharmacol Ther* 2006;15(23):1725-33.
61. Jung-Hwan Oh, Tae-Suk Kim, Myung-Gyu Choi, et al. Relationship between Psychological Factors and Quality of Life in Subtypes of Gastroesophageal Reflux Disease. *Gut and Liver* 2009; 3:259-265.
62. Johnson DA, Levy III BH. Evolving drugs in GERD: pharmacologic treatment beyond PPI. *Expert Opin Pharmacother* 2010; 11:1541-1548.
63. Kaywood C, Wakefield M, Tack J. A proof-of-concept-study evaluating the effect of ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, on acid exposure and symptoms in GERD. *Gut* 2009; 58:1192-9.
64. Falk GV, Fennerty MB, Rothstein RI: AGA Institute technical review on the use of endoscopic therapy for gastrointestinal reflux disease. *Gastroenterology* 2006; 131:1351-66.