

Drug Corner

Clinical Practice of Prescribing Proton Pump Inhibitors by Physicians : An Indian Perspective

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The proton pump inhibitors (PPIs) are the most widely used category of drugs to reduce gastric acid secretion. The cost of different PPIs vary and could be the deciding factor, especially in India where resources are limited and only a small percent of the population have health insurance. Since no clinical evidence exists to highlight the most effective PPI, the selection of the drug rests with the physician and is usually based on cost and indication. There is need to have systematic assessment of perceptions and practices of health care providers towards the use of this class of drugs. A questionnaire based study was conducted to assess the physician's practice of prescribing PPIs for patients with functional dyspepsia (FD). The aim of the study was to characterize the prescribing patterns so that rationality and cost-effectiveness could be improved in the future. Selection of PPIs depends on indication, lower cost, pharmacokinetics of the drug including rapid onset of maximal acid suppression and less drug-drug interactions.

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Key words : Proton Pump Inhibitors, Acid Peptic Diseases,

The proton pump inhibitors (PPIs) are the most widely used category of drugs to reduce gastric acid secretion. There is rising worldwide burden of acid peptic diseases (APDs) due to changing lifestyles and dietary habits. India has a high prevalence of GERD (39.2%), peptic ulcer disease (PUD, 37.1%) and non-ulcer dyspepsia (25.2%)¹. Available drugs include PPIs, histamine-2 receptor antagonists (H₂RA), antacids, sucralfate and prostaglandin analogues.

The snowballing prevalence continues to increase the global and national demand of acid suppressants. The proton pump inhibitors (only) market in India is estimated to be valued at Rs 2040 Crore (**36.04 Crore units**) in 2020 and PPI in combination is valued at Rs 1585.6 Crore (38.25 Crore units)². PPIs are used to treat peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), erosive esophagitis, Zollinger-Ellison syndrome, Barrett's esophagus and upper gastrointestinal bleeding¹. PPIs have been proven to be superior in the treatment and symptomatic remission of non-erosive reflux disease and erosive esophagitis compared to H₂RAs². They are also used for stress ulcer prophylaxis (SUP) and as gastroprotective agents along with non-steroidal anti-inflammatory drugs (NSAIDs)³.

The PPIs available in India are Rabeprazole, Pantoprazole, Omeprazole, Esomeprazole,

Lansoprazole, Dexlansoprazole, Dexrabeprazole and Ilaprazole. There is currently no convincing RCT evidence that one PPI is preferable to another for the management of GERD or PUD related symptoms. The cost of different PPIs vary and could be the deciding factor, especially in India where resources are limited and only a small percent of the population have health insurance⁴.

There has been dramatic increase in PPI prescribing patterns over the past several years. There is need to have systematic assessment of perceptions and practices of health care providers towards the use of this class of drug. Even though extensive studies have been investigated on the appropriateness of PPIs in Western countries, such data from India are still very limited. Thus, there is an urgent need to characterize the prescribing patterns so that rationality and cost-effectiveness could be improved in the future. In view of this, we carried out a questionnaire based study to assess the physician's practice of prescribing PPIs for patients with functional dyspepsia (FD). To our knowledge, this is the first study on the use of PPIs among practicing physicians in India.

MATERIAL AND METHODS

Study design: The study was carried out using a self-design questionnaire, developed to assess the clinical practice of prescribing PPIs by general physicians across India. Formal sample size calculation was not carried out, but a target of nearly 400 respondents had been planned. The questionnaire was developed after review of previously published

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studies conducted in other clinical settings.

The first part of the questionnaire consisted of questions regarding social-demographic characteristics of patients with functional dyspepsia such as age, gender and symptoms. The second part involved questions pertaining to choice of PPI in different clinical situations such as chronic kidney disease, surgical cases and geriatric patients. The last part had questions about treatment with PPIs including duration and indication. The physicians ticked the answers based on their clinical practice and observations

Statistical Analysis : Data was entered into Microsoft Excel (MS Office 2007) and statistical analyses were conducted using SPSS 17.0. USA and Microsoft Office Excel 2013. Microsoft India.

RESULTS

Data of all 416 physicians was included in the analysis. The respondents reported that the presence of acid peptic syndrome was majorly found in patients in the age group of 20 - 40 years (58.28%) followed by 40 to 60 years (35.90%). Surprisingly, only 3 respondents reported the presence of APS in elderly people. A slight gender predominance was reported in females (37.76%) than males (34.27%) (Figs 1&2).

Peptic syndrome is characterized by different symptoms such as abdominal pain, growling stomach, nausea, vomiting, burning, acidic taste etc. Physician treating these diseases observed that burning in the stomach or upper abdomen (51.28%) was the most common symptom seen in patients followed by bloating (42.42%), belching and gas (35.43%) (Fig 3).

The questionnaire answered by physicians also included grade of dyspepsia associated reflux in patients during treatment. The respondents reported Grade I reflux frequency to be observed in majority of the patients (32.87%) followed by grade II reflux

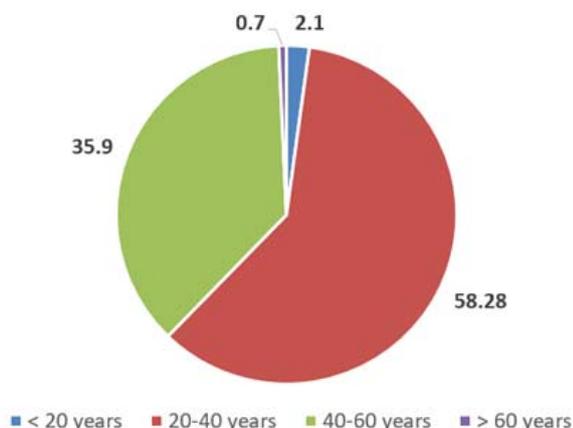


Fig 1 — Age distribution of FD according to respondents

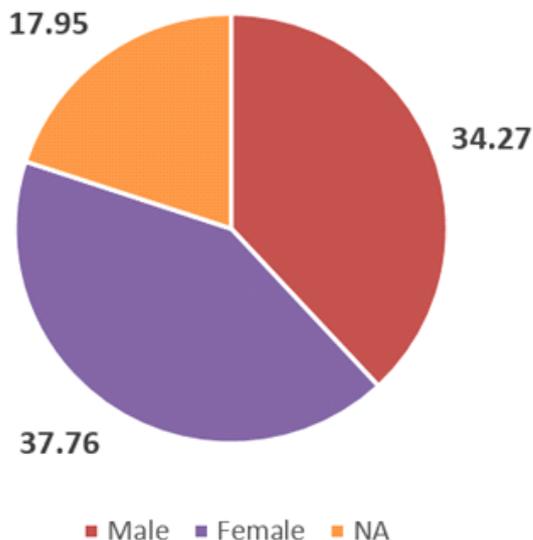


Fig 2 — Gender distribution of FD according to respondents

(28.44%). Respondents reported higher frequency of grade III ulcers than grade II (27.51% versus 20.05%). Similarly according to the physicians, grade II and grade III dysmotility was much more observed in patients (Table 1).

The use of PPI in patient is determined by different associated disease conditions & age of the patient. Patients of CKD often complain about dyspeptic symptoms due to increased production of gastrin. The physicians reported maximum use of Rabeprazole (32.63%) followed by Pantoprazole (25.41%) in patients with chronic kidney disease (CKD). If the patient underwent surgery, most physicians preferred pantoprazole (22.61%) & combination of pantoprazole + Domeperidone (26.81%). In geriatric patients, the respondents preferred combination of Domperidone and Pantoprazole followed by the combination of Rabeprazole and domperidone (Table 2).

Furthermore, the most common choice for GERD treatment by the respondents is combination of Rabeprazole & Domperidone (21.45%) as it has high symptom improvement rate. During answering questionnaire, physician answered the regular use of proton pump inhibitors (PPI) in the treatment of dyspepsia & found that Pantoprazole (13.29%) & combination of pantoprazole with Domperidone (28.44%) was preferred over other PPIs. Also, majority of physicians (38%) recommended use of PPI for the duration of 3-5 weeks in dyspepsia treatment (Fig 4 & Table 3).

DISCUSSION

Increasing urbanization and poor eating habits has

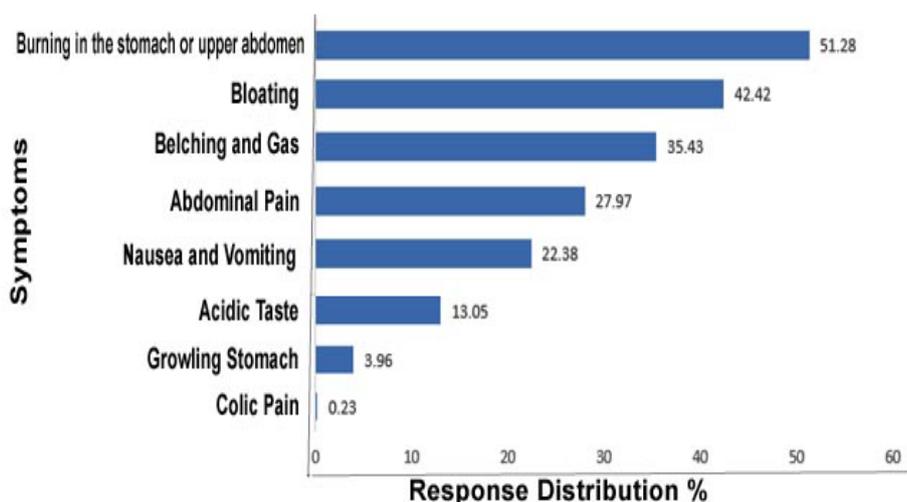


Fig 3 — Symptoms of FD according to respondents

	Response distribution %	
	Reflux	Dysmotility
Grade 1	32.87	15.38
Grade 2	28.44	24.48
Grade 3	16.55	24.71
Grade 4	8.16	11.19
Grade 5	6.29	6.06

Choice of PPI	Response distribution %				
	CKD	Surgery	Geriatric	GERD	Dyspepsia
Acotiamide	2.33	0.23	0.47	1.40	1.86
Esomeprazole	15.15	10.96	17.02	12.59	11.19
LANSOPRAZOLE	0.23	0	0.23	0	0
Omeprazole	9.56	2.80	7.69	5.59	6.76
Pantoprazole	25.41	22.61	18.65	11.42	13.29
Pantoprazole+ Domperidone	12.59	26.81	13.29	31.47	21.91
Pantoprazole+ Levosulpiride	6.29	5.59	6.06	8.16	6.29
Rabeprazole	32.63	21.21	29.60	17.48	23.78
Rabeprazole+ Domperidone	20.75	23.08	22.61	21.45	28.44
Rabeprazole+ Levosulpiride	6.29	7.46	6.29	20.05	12.82

accentuated the global burden of acid peptic syndrome. Physicians often face the difficulty of choosing the PPI since there is no concluding evidence to highlight the most effective PPI for the management of PUD or GERD or for endoscopically confirmed healing of esophagitis⁴. Thus, physicians base their selection of PPI on cost and indication. Thus treatment varies based on both patient and physician. Due to lack of standard guidelines a huge variation exist in selection of PPIs. Our study was conceived in this context to capture data regarding

the clinical practice of prescribing PPIs by general physicians in India. As far as clinical practice is concerned, this study is the first one of its kind in India.

Guidelines from the National Institute of Clinical Excellence (NICE) does not differentiate between PPIs except on the grounds of cost and accepted indications. Furthermore, a review of the pharmacological properties of the four standard PPIs omeprazole, Lansoprazole, pantoprazole and Rabeprazole also concludes that they are

essentially similar in efficacy^{5,6}. Hence, unless one drug is shown to be clinically superior, it seems reasonable to choose the PPI based on cost.

Coming to pharmacological action, Lansoprazole and Rabeprazole have a more rapid onset of maximal acid suppression than the other PPIs. Both Pantoprazole and Rabeprazole, there is a linear relationship between dose and plasma drug concentrations after single and multiple dose administration and there is no reduction in bioavailability of Pantoprazole if concurrently administered with antacids. Rabeprazole has less potential for drug interactions and no interactions of clinical relevance have been reported for Pantoprazole. PPIs share a common mechanism of action but pantoprazole and Rabeprazole show greater selectivity for the cysteine 813/822 sites of the proton pump. Rabeprazole converts rapidly to the activated

sulphenamide form and dissociates more readily from the H⁺K⁺ ATPase than the other drugs, exhibiting a faster rate of inhibition and shorter duration of action⁶.

Data was gathered from 416 general physicians was included in the analysis. The respondents reported that the presence of acid peptic syndrome was majorly found in patients in the age group of 20 - 40 years and is similar to a study conducted in Asian patients. Though such an age distribution is seen, many studies suggest that age and ethnicity are not predictive factors for FD¹. The prevalence of peptic ulcer disease has

Table 3 — Preference of PPIs among respondents based on indication and clinical characteristics

	Choice of PPI according to respondents		
	First choice	Second choice	Third choice
CKD	Rabeprazole	Pantoprazole	Rabeprazole +Domperidone
Surgery	Pantoprazole +Domperidone	Rabeprazole +Domperidone	Pantoprazole
Geriatric	Rabeprazole	Rabeprazole +Domperidone	Pantoprazole
GERD	Pantoprazole +Domperidone	Rabeprazole +Domperidone	Rabeprazole + Levosulpiride
Dyspepsia	Rabeprazole +Domperidone	Rabeprazole	Rabeprazole + Levosulpiride

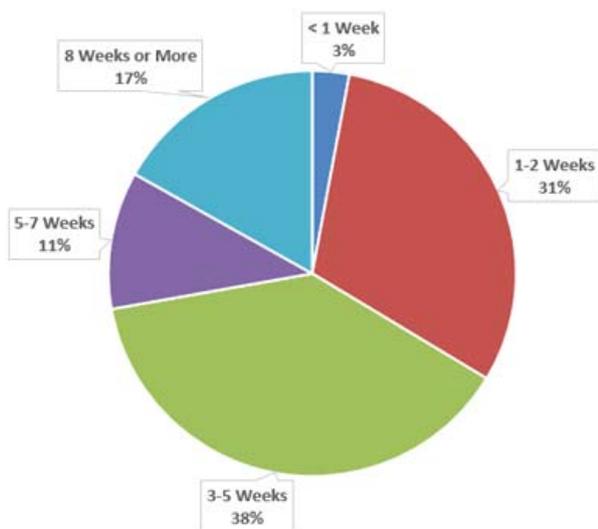


Fig 4 — Duration of PPI in dyspepsia treatment

shifted from predominance in males to similar occurrences in males and females. Our study too reported similar occurrence in men and women. The lifetime prevalence is approximately 11%-14% in men and 8-11% in women⁷.

Rabeprazole was the PPI of choice by the respondents followed by Pantoprazole (25.41%) in patients with chronic kidney disease (CKD). The reason could be that no dosage adjustment of Rabeprazole is required in patients with renal dysfunction. Deprescribing PPIs is important when there is no clear indication for use⁹. There is a strong and consistent association between PPI use and increased risk for incident CKD, CKD progression and kidney failure. Hence, careful monitoring of renal function and cessation of PPI is very important in such patients to reduce the population burden of CKD¹⁰.

If the patient underwent surgery, most respondents preferred pantoprazole alone or in combination with Domeperidone. This may be based on the reason that Pantoprazole has the least drug interactions and patients in the surgical department are generally on many medications. To avoid potential drug-drug interactions, physicians may prefer Pantoprazole as the PPI to prevent stress ulcers. PPIs are used for

stress ulcer prophylaxis in critically ill patients including surgical ICU patients^{11,12}. Furthermore, most PPIs are uniformly effective for reducing gastrointestinal bleeding in ICU patients receiving mechanical ventilation¹³.

Elderly patients are particularly likely to be prescribed acid suppression drugs. In geriatric patients, the respondents preferred combination of Domeperidone and Pantoprazole followed by the combination of Rabeprazole and Domeperidone. PPIs should be used at the lowest dose and for the shortest duration possible in geriatric population. They are still relatively safe drugs but should only be prescribed for proven indications¹⁴. Pantoprazole shows to have minimal interactions with other drugs because of its low affinity for cytochrome P450 than older PPIs. Although, majority of elderly patients have comorbidities and receive other drugs, the efficacy of Pantoprazole may not be adversely affected, attributable to its Pharmacokinetics, which are independent of patient age. Clinical practice suggests that a low dose maintenance of PPIs should be used in older patients with GERD¹⁵.

Furthermore, the most common choice for GERD treatment by the respondents is combination of Pantoprazole & Domeperidone. During answering questionnaire, physician answered the regular use of proton pump inhibitors (PPI) in the treatment of dyspepsia & found that Pantoprazole (13.29%) & combination of Pantoprazole with Domeperidone (28.44%) was preferred over other drugs. No solid evidence is available to point out the most effective PPI for GERD, thus selection depends on cost and indication¹⁶. In India, the prevalence of GERD ranges between 7.6 - 30%¹⁷.

Most of the physician recommended use of PPI for the duration of 3 to five week in dyspepsia treatment. Authors of a Cochrane review concluded the duration of the PPI treatment for functional dyspepsia (FD) is at least two weeks¹⁸. There is no standard for duration since it depends on the patient's improvement, cost and indication. An expert review provided key recommendations for decision making in order to

minimize the irrational use of PPIs. Those patients with GERD and acid-related complications must take a PPI for at least 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. Those patients at high risk for ulcer-related bleeding from NSAIDs must take a PPI if they continue to take NSAIDs¹. These recommendations would assist the physicians in taking treatment related decisions.

Drug-induced gastrointestinal (GI) symptoms with NSAIDs, metformin, antibiotics and anti hypertensives are commonly encountered in clinical practice. Given the common use of these drugs in clinical practice and the rising burden of chronic diseases including cardiovascular disease and diabetes, it is not at all recommended to discontinue these drugs. Furthermore, failure to recognize and prevent drug-related symptoms may lead to unnecessary investigations and treatment. It seems reasonable that co-prescription of a PPI be considered when there is a risk of drug-induced gastritis¹⁹.

Gastric mucosal injury and adverse reaction caused by NSAIDs is clinically problematic. About 25% of patients using NSAIDs develop peptic ulcer. In one study, treatment efficacy (endoscopic cure rate) of Rabeprazole for NSAID-induced ulcer under continuous NSAID administration was 71.1%²⁰. In another study it was seen that PPIs significantly reduced gastric and duodenal ulcers and their complications in patients taking NSAIDs or COX-2 inhibitors²¹. Low-dose Aspirin (LDA) also reduced cardiovascular events by about 25% in comparison to non-use but increase gastrointestinal events two- to five-fold. The use of long-term Rabeprazole 10-mg and 5-mg once daily prevented the recurrence of peptic ulcers in subjects on low-dose aspirin therapy, and both were well-tolerated²². Thus, these two studies confirm that the proton pump inhibitor (PPI), Rabeprazole is highly effective in preventing upper GI ulcers or bleeding in patients taking low-dose aspirin or NSAIDs.

The 2017 joint American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG) guidelines recommended standard-dose PPIs as first-line treatment in patients with H. pylori-negative functional dyspepsia. Those patients with H pylori-positive dyspepsia, must take PPI if eradication is unsuccessful at reducing symptoms. The guidelines also pointed out that low dose therapy is as effective as standard-dose therapy¹⁸.

Despite the useful information learnt from this study, several limitations require mention. First, our

findings about clinical practice of prescribing PPI for functional dyspepsia among physicians are based on a self-reported instrument. Secondly, the small number of respondents cannot account for all the physicians in the country.

CONCLUSION

Our study is one of its kind to gather data on clinical practice of prescribing PPIs among physicians in India. The snowballing rise of acid peptic diseases have given rise to a variety of PPIs. Since no clinical evidence exists to highlight the most effective PPI, the selection of the drug rests with the physician and is usually based on cost and indication. The data from our study indicates that the majority of the respondents prefer Rabeprazole and Pantoprazole for functional dyspepsia in most clinical situations including surgery, CKD and elderly. Rapid onset of maximal acid suppression, drug-plasma linear relationship, less drug-drug interactions and low cost may be attributable factors. PPIs have a huge economic burden on the patient as well as the country. Hence, understanding the prescribing preference of PPIs is important in developing countries, such as India, to improve rationality and cost-effectiveness of PPIs.

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