

Drug Corner

A Prospective, Cross-sectional, Multicenter, Observational, Questionnaire-based Survey to assess the Knowledge, Awareness, Attitude and Practice of Physicians while Prescribing Proton Pump Inhibitor (PPI) Drugs for Acid Peptic Disease

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Goal : This is a subjective survey to assess the knowledge, awareness, and practices (KAP) of physicians while prescribing Proton pump inhibitors (PPI) in acid peptic disorder (APD) patients in India.

Background : APD represents a variety of gastric anomalies in which PPIs form the mainstay of management. Many of the APD patients are associated with comorbidities, resulting in polypharmacy and increased risk of drug-drug interactions. Therefore, it is essential that physicians be aware of PPI drug interactions while prescribing them to patients with comorbidities. In developing countries like India, studies assessing the KAP of Physicians are limited.

Study Design : This questionnaire-based study consisted of 3 domains: (A) Study objectives and consent; (B) Participants' socio-demographic details; (C) Questions on KAP of Physicians around various aspects of APD management and PPI usage.

Results : A total of 110 Physicians completed the survey. 92% observed stress as the most common risk factor; Obesity (46%), Diabetes Mellitus (41%) and Cardiovascular Disease (33%) as the most frequent comorbidities, in APD. Almost all Physicians (99%) considered patient's comorbidity important while choosing PPI. 84% participants felt that anticoagulants when co-prescribed with PPI have higher chance of drug-drug interactions. 60% ranked Rabeprazole in the top, in terms of safety and tolerability among PPIs.

Conclusion: The present study mapped the awareness of Indian Physicians on APD, PPI usage, their adverse effects, drug-drug interactions; patient compliance and satisfaction with PPIs. These findings can be used to plan future interventions targeting HCPs, to ensure safe and appropriate use of PPIs.

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Key words : Acid peptide disorder, Awareness, Attitude, Knowledge, Proton pump inhibitor.

Acid Peptide Disorder (APD) is a term that represents a vast variety of gastric anomalies including Gastric Esophageal Reflux Disease (GERD), Peptic Ulcer Disease (PUD), Gastritis, Zollinger-Ellison syndrome (ZES), Meckel's diverticulum, and other hyper secretory conditions, which are believed to be caused by gastric acid acting on diminished gastric mucosa¹.

The prevalence of GERD is probably underestimated, as most of the epidemiological studies on GERD are symptom based (heartburn, regurgitation). According to the first consensus on GERD from India by the Indian Society of Gastroenterology Task Force (ASGTS), the prevalence of GERD is approximately 10% among the Indian population². PUD, another major type of APD, has an annual incidence rate between

Editor's Comment :

- In this KAP study almost all physicians felt that stress is the most common risk factor associated with APD. Obesity, Diabetes Mellitus, and CVD were noted as the most common comorbid conditions in APD patients. Efficacy and safety are the most important attributes considered while choosing a PPI and Rabeprazole is rated at the top in terms of safety and tolerability. It is important to choose a PPI with less chance of drug to drug interactions and have a reasonable certainty in providing response in majority of the APD patients.

0.10-0.19% for physician-diagnosed PUD and between 0.03-0.17% from hospitalization data. The 1-year prevalence of PUD on the basis of a medical diagnosis was 0.12-1.50 % and that based on hospitalization data was 0.10-0.19%³.

Since the first Proton-Pump Inhibitor (PPI) Omeprazole was introduced in 1989, PPIs have been proven to be safe and effective agents for the treatment and prophylaxis, in a variety of acid-related disorders affecting the upper gastrointestinal tract⁴. As of 2021,

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6 PPIs have been approved by USFDA namely: Pantoprazole, Rabeprazole, Esomeprazole, Omeprazole, Lansoprazole, and Dexlansoprazole. Adaption of PPI use has dramatically increased among the health care providers (HCPs), and their presence is ubiquitous within the prescriptions of various specialties. The world has seen a substantial, continuing, and unexplained rise in prescription and usage of PPIs.

A recent meta-analysis concluded that the prevalence of comorbid conditions (diabetes mellitus, coronary artery disease, malignancy, arthritis, HIV, respiratory, hepatic, and renal diseases) are high among APD patients⁵. This coexistence of APD and comorbid conditions have resulted in a consistent increase in co-prescription of PPIs along with the drugs used to treat these comorbidities. A recent study which evaluated the drug utilization pattern in cardiovascular diseases reported surprisingly high prescription rates of pantoprazole among patients suffering from cardiovascular disorders. Similarly, various drug utilization studies have reported high prescription rates of PPIs among patients with comorbidities including diabetes^{6,7}, cancer⁸, arthritis⁹, HIV¹⁰, CKD¹¹ and cirrhosis¹². Such a wide usage of polypharmacy (including PPIs) among comorbid patients may potentiate the risk of drug-to-drug interactions and can result in the occurrence of Adverse Drug Reactions (ADRs). This risk is higher especially among hospitalized elderly patients in whom the prevalence of polypharmacy is approximately 31.8%, which increases their susceptibility towards experiencing an ADR^{7,13,14}. Furthermore, there is a growing concern on the usage of PPIs beyond their approved duration^{7,15} and irrational prescribing practices while treating patients with multiple ailments. Various recent epidemiological studies conducted in countries like Jordan, Greece, and China have reported 86%, 81%, and 82% use of PPIs in an inappropriate indication respectively⁷. Therefore, physicians should be made aware of PPIs' drug-drug interactions while prescribing them to a patient who is on treatment for multiple diseases.

In developing countries like India, drug utilization or surveillance studies assessing the knowledge, awareness, and prescribing practices of HCPs are lacking. The main objective of this survey is to access and map the knowledge, awareness, attitude, and practice of physicians while prescribing PPIs for APD in India.

MATERIALS AND METHODS

Questionnaire Design :

A questionnaire was designed on web-based forms and the link generated was shared on WhatsApp or Emails to physicians (doctors treating APD). The purpose of the study was stated in the questionnaire and the participants were asked to fill the questionnaire after giving their consent via the web link by clicking the "Agree to Participate" option. The Participants were assured of the confidentiality of their information, and that it would be used only for the purpose of this study. All the participants were asked to fill the questionnaire only once to avoid duplication of data and that their participation in the study was entirely on voluntary basis. A structured questionnaire was used based on the variables of interest and guided by the study specific objectives. The questionnaire had questions assessing demographics of the Physicians, the knowledge, awareness, and attitude of respondents on APD and associated risk factors and the respondents' knowledge, awareness, attitude and prescribing practices on choice of therapy for APD and factors associated with the choice of therapy.

The questionnaire consisted of mainly 3 domains: (A) Information to the participants about the objectives of the study and their consent for participation; (B) Socio-demographic details of the participants; (C) Questions on the knowledge, awareness, attitude and prescribing practices of respondents on APD, associated risk factors, choice of therapy and factors influencing the choice of therapy. Time spent for the completion of the questionnaire was approximately 10-20 min.

Inclusion Criteria :

- (1) Doctors registered with Medical Council of India and having MBBS Degree and Above
- (2) Doctors having a minimum of 5 years of experience in clinical practice.
- (3) Doctors treating Acid Peptic Disease patients.
- (4) Doctors prescribing Proton Pump Inhibitor (PPI) drugs
- (5) Doctors who are willing to voluntarily participate in the survey and provide the Consent.

Exclusion Criteria :

- (1) Doctors not treating APD patients.
- (2) Doctors not prescribing PPIs
- (3) Doctors not providing the consent for participation.

Dropouts :

Those Participants who have not responded after

providing consent were considered as dropouts. Incomplete questionnaires have not been included in data analysis.

Sample size :

The survey questionnaire was shared to the eligible participants via email or other appropriate means of communication. A total of 110 responses were received from the physicians and included in the analysis.

Statistical Analysis :

All data was cleaned and validated before analysis. Absolute (n) and relative frequencies (%) were presented for qualitative variables and mean (\pm SD) was used for continuous variables. Statistical analysis was performed using STATA v15.0 and Microsoft Office (Excel).

RESULTS

Demographic characteristics of survey participants and APD patient characteristics based on the participants' responses :

A total of 110 respondents from various clinical settings have completed the survey and their responses were considered valid and suitable for analysis. Among these 110 respondents, 95% (105) were male and only 5% (5) were female. The highest responses received were from physicians aged between 31-40 years of age and the mean age of respondents was 45.42 ± 9.82 years old. 55% (60) of respondents were currently practicing in a hospital with a mean clinical experience of 16.73 ± 9.83 years. The demographic characteristics of the respondents are provided in Table 1.

Based on the responses received, an average of 306 APD patients visit various clinical settings per month. 88% (97) of the physicians have expressed their opinion that patients commonly experiencing APD symptoms are aged between 25-54 years and approximately 81% physicians opined that male patients experience more symptoms when compared to female APD patients. 55% Physicians responded saying that patients commonly experiencing APD symptoms belonged to "Upper/Upper Middle" socioeconomic class and 64% Physicians opined that they are white collar workers. Physicians' awareness regarding socio-demographic details of APD patients are provided in Table 2.

The Knowledge, Awareness, Attitude and Prescribing practices of participants on APD and Associated Risk Factors :

Among the total respondents, 56% (62) are doing a monthly patient follow-up and prescription review.

Parameters	Participants (N=110)
Gender n (%) :	
Male	105 (95.45%)
Female	5 (4.55%)
Age (years)	45.42 \pm 9.82
21-30	1 (0.91%)
31-40	40 (36.36%)
41-50	39 (35.45%)
51-60	20 (18.18%)
61-70	10 (9.09%)
Highest Medical Qualification n (%) :	
Graduate	20 (18.18%)
Postgraduate	45 (40.90%)
Postgraduate diploma	4 (3.64%)
Doctorate	40 (36.36%)
Data not available	1 (0.91%)
Current clinical practice (type) :	
Hospital	60 (54.55%)
Clinic	49 (44.55%)
Data not available	1 (0.91%)
Clinical Experience (years)	16.73 \pm 9.83

Parameter	Responses (N= 110)
APD patients / month	306.41 \pm 316.82
Age (Years) :	
24 years and below	1 (0.91%)
25-54	97 (88.18%)
55-64	12 (10.91%)
>65	0 (0.00%)
Gender :	
Male	89 (80.91%)
Female	21 (19.09%)
Typical symptoms observed :	
Heart Burn	101 (91.82%)
Dyspepsia	99 (90.00%)
Flatulence/Bloating	84 (76.36%)
Socio-economic class :	
Upper	5 (4.55%)
Upper middle	56 (50.91%)
Lower middle	40 (36.36%)
Upper lower	6 (5.45%)
Lower	3 (2.73%)
Type of employment :	
Blue-collar workers	39 (35.45%)
White-collar workers	71 (64.55%)

92% (101) physicians have observed stress to be the most common risk factor associated with APD patients. 46% (51) perceived obesity as the most common comorbid condition among APD patients followed by Diabetes Mellitus, Cardiovascular Disease (CVD), and arthritis with 41%, 33%, and 31% responses respectively. Among total respondents, 92%, 90%, and 76% selected heartburn, dyspepsia, and flatulence/bloating as the most commonly observed symptom respectively.

The Knowledge, Awareness, Attitude and prescribing practices of participants on the choice of Therapy and Factors associated with the choice :

A total of 63% (70) respondents have mentioned that efficacy is the most important attribute while choosing a PPI and ranked Esomeprazole and Rabeprazole as the most efficacious ones among the PPIs. Further, approximately 60% (66) of respondents ranked Rabeprazole in the top, in terms of safety and tolerability among the PPIs for the treatment of APD.

For questions investigating the dosage regimen and effectiveness, 88% (97) respondents considered "effective acid suppression with once-daily dosing" as the most important attribute in determining the efficacy of a PPI. While 70% (78) of participants opined that Rabeprazole 20 mg and Esomeprazole 40 mg were effective as once-daily dosing regimens, 72% (80) of participants felt that twice-daily regimen has a greater effect on gastric acid suppression.

For the question concerning the usage of the drugs by the APD patients other than the drugs used for APD treatment, 28% (30) of respondents mentioned that NSAIDs are the most commonly used class of drugs. Also, 67% of participants responded that H2 receptor antagonists are the most prescribed class of drugs for APD management, after PPIs.

When asked about the importance of a patient's co-morbidity in deciding the PPI, almost all the Physicians (99%) considered a patient's comorbidity important while choosing a PPI and 88% (97) responded that cardiovascular disease is the most assessed co-morbid condition before prescribing a PPI.

Regarding the co-prescription, around 55% of study participants responded saying that co-prescription of a PPI affects the efficacy and safety of other medications prescribed for chronic health conditions. 84% (92) participants felt that anticoagulants when co-prescribed with a PPI have a higher chance of drug-drug interaction. 98% (108) participants felt that NSAIDs require a co-administration of PPI, and 89% agreed that PPIs act as a prophylaxis for NSAID induced peptic ulcers or gastric ulcers.

Regarding the adverse events with PPIs, around 64% (70) of participants considered diarrhea as the most common adverse event observed with the usage of PPIs and 81% (89) felt that there is a significantly increased risk of vitamin-B12 deficiency with long-term usage of PPIs.

For the questions pertaining to the reasons for PPI switching, 40% (44) of study participants considered

"lack of immediate symptom relief" as the most important factor that influenced the switch of one PPI to another and 59% (65) agreed that this factor also influenced the change in the dose of the PPI.

For the questions pertaining to the patient satisfaction with PPIs, 50% of the responders reported that "Immediate relief from symptoms" is the most important factor influencing patient satisfaction and more than 55% (61) of participants responded saying that the patients are "very satisfied" with PPI treatment.

DISCUSSION

APD significantly impacts the Quality Of Life (QOL) of the patients and causes considerable stress on the health services. Several population-based studies have reported poor QOL among patients with APD^{16,17}. QOL worsens if APD is not treated in a rational way and it increases the cost of treatment for the patient, which includes repetitive consultation costs, investigations, medications, and additional complications. Therefore, it is of utmost importance for the physicians to have sound knowledge and awareness regarding the characteristics of APD patients and their management with PPIs. To understand the above-mentioned parameters, this questionnaire-based KAP survey was designed. This was a subjective survey of perception among HCPs on acid peptic disorders and PPI usage.

Our survey evaluated the Physicians' awareness on the demographics of the APD patients and the risk factors associated with APD. As per the Physicians' response, patients commonly experiencing APD symptoms belong to 25-54 age group and male patients experience more symptoms compared to female APD patients. Majority of the physicians opined that the patients commonly experiencing APD symptoms belong to 'Upper/Upper Middle' socioeconomic class and are white collar workers. Coming to the risk factors for APD, more than 90% of the Physicians mentioned stress as the most common risk factor associated with APD. Previous clinical studies have reported stress as a major risk factor for the development of APD, particularly in individuals aged 20's through 50's, who are more susceptible to stress^{18,19}. The individuals in this age group form the major part of active work force and may be more susceptible to work related stress compared to other age groups. Based on this evidence from real world practice through our survey, it appears that 25-54 year old male white collar workers belonging to upper/upper middle socioeconomic class are more prone to stress, probably work related, which can increase their risk of APD.

While evaluating the Physicians' perceptions on

Table 3 — KAP of respondents on associated risk factor with APD

Questions (N= 4)	Responses (N=110)
What are the common risk factors observed in your routine clinical practice for Acid Peptic Diseases?	Stress (91.82%)
What tests do you recommend in order to arrive at a diagnosis of APD?	Upper G.I. Endoscopy 65 (59.09 %)
Which of the following comorbid conditions are seen frequently in APD patients treated by you?	Obesity 51 (46.36 %)
At your clinical practice how often do you follow-up the patient and review their prescription for treatment of APD with PPI?	Monthly - 62 (56.36 %)

Table 4 — The respondents KAP on choice of therapy and factors associated

Questions (N = 12)	Responses (N=110)
How important is a patients' comorbidity in deciding a PPI?	Important 109 (99.09 %)
Please rank the proton pump inhibitor according to your perception of its efficacy in treatment of APD?	Esomeprazole (Ranked1) 53 (48.18 %)
Please rank the proton pump inhibitor according to your perception of its safety and tolerability in treatment of APD?	Rabeprazole (Ranked 1)
Which of the following PPIs are effective as once daily dosing?	• Rabeprazole-20 mg - 78 (70.10 %) • Esomeprazole 40 mg - 78 (70.10 %)
Which co-morbid condition do you assess before prescribing a PPI?	Cardiovascular diseases 97 (88.18%)
In your clinical experience which drugs require coadministration of PPI?	NSAIDs 108 (98.18%)
In your clinical experience apart from drugs for APD treatment which other concomitant medications are frequently used by APD patients?	Nonsteroidal Anti-Inflammatory Drugs 30 (27.52 %)
In your clinical experience, which drug may have a higher chance of drug-to-drug interactions when given along with PPI?	Anticoagulants 92 (83.63 %)
Apart from PPI's which other class of drugs do you prescribe during treatment of APD?	H2-receptor antagonists 74 (67.27 %)
Which attributes are important for you in choosing a PPI?	Efficacy 70 (63.63%)
For which conditions do you prescribe PPIs as prophylaxis?	Prevention of peptic ulcers or gastric ulcers induced by NSAIDs - 98 (89.09%)
Which of the following frequency of PPIs has greater effect on gastric acid suppression?	Twice daily (BID) 80 (72.73 %)
Which risks do you observe with long-term use of PPIs?	Vitamin-B12 deficiency 89 (80.90 %)
In your opinion which of the following attributes determine efficacy of a PPI?	Effective acid suppression with once daily dosing. 97 (88.18 %)
Which of the following factors make you switch a PPI with another one?	Lack of immediate symptom relief – 44 (40%)
What are the factors which prompt you to change the dose of PPI?	Lack of immediate symptom relief - 65 (59.09%)
What are the common adverse events observed in your routine clinical practice when PPIs are prescribed?	Diarrhoea 70 (63.64 %)
In your opinion what are the top factors of satisfaction for a patient who is using a PPI?	Immediate relief from symptoms (Ranked-1) 55(50.00 %)
At your clinical practice, what percentage of patients do you think strictly follow and use PPI as per your advice?	71-80% patients- 27 (24.54 %)
How would you rate the overall patient satisfaction with PPI treatment?	Very satisfied 61 (55.45 %)
In your clinical experience, does co-prescription of PPI has an effect on efficacy of other medications prescribed for chronic health conditions ?	Agree 59 (53.64 %)
In your clinical experience, does co-prescription of PPI has an effect on safety and tolerability of other medications prescribed for chronic health conditions?	Agree 60 (54.55 %).

the association of APD with various comorbid conditions, Obesity, Diabetes Mellitus, and CVD were noted by the respondents as the most common comorbid conditions observed in APD patients. Previous studies have reported that PUD is strongly associated with obesity^{20,21}. In 2017, a study has established a correlation of increased weight and high BMI in women with PUD²². Further, some of the researchers have reported that PUD patients have a higher prevalence

of DM and CVD, with increased threat for developing a variety of complications during the course of disease^{23,24}. The current study provides real world evidence of observation of these comorbidities in APD patients, by the physicians.

Majority of the respondents in our survey reported that efficacy and safety are the most important attributes considered while choosing a PPI. As per

the study results, Esomeprazole and Rabeprazole are considered to be the most efficacious PPIs and majority of the respondents ranked Rabeprazole at the top among the PPIs in terms of safety and tolerability, in the management of APD. This adds up to the existing evidence, as Rabeprazole was reported in multiple earlier studies as highly effective PPI compared to other PPIs²⁵⁻²⁷. Another important attribute of PPIs is their once daily dosing. More than two thirds of the respondents reported that Rabeprazole is effective as OD dose. OD dosing is reported to be safer for long-term use of PPIs. Previous studies have also reported the good tolerability profile of Rabeprazole in OD dosing regimen^{28,29}. Our study results have reiterated the existing evidence of Rabeprazole's efficacy, safety and the effectiveness as once daily dosing regimen through this evidence from real world practice.

In terms of safety, the adverse effects associated with PPI long-term use, as observed by more than 50% of the respondents were, vitamin B₁₂ deficiency, risk of fractures and hypomagnesemia. The evidence connecting vitamin B₁₂ levels and PPI use remains controversial. Though multiple studies have reported the possible effect of chronic PPI treatment in vitamin B₁₂ levels^{30,31}, the others have reported no such association^{32,33}. For the risk of fractures, multiple recent studies have reported a positive association of PPIs with an increase in fracture risk which may be due to hypergastrinemia and hypochlorhydria³⁴. The presence of mineral deficiencies, particularly hypomagnesemia, which may be due to the inhibition of active absorption of magnesium, is commonly reported in PPI users^{35,36}. The observation of these adverse effects in the clinical practice by the respondents in our study is in concordance with the available scientific literature.

Another important aspect of PPI safety is the drug-to-drug interactions, particularly with the medications prescribed for longer duration in comorbid conditions like CVD and Diabetes. It should be noted that almost all the respondents in our survey reported that patient's comorbidity is important while choosing PPI for APD. This is crucial since PPIs tend to interact with certain medications used for the management of Diabetes and CVD^{22,37-40}, probably due to the shared enzymatic metabolic pathway of CYP2C19⁴¹. Previous studies have reported an increase (Ex-Digoxin) or decrease (Ex-Ketoconazole) in the absorption of certain drugs, greater number of adverse effects of inactivated drugs (Ex-Citalopram), and reduced therapeutic efficacy due to inhibition in the conversion of prodrug to active metabolite (Ex-Clopidogrel), with concomitant use of

PPI⁴²⁻⁴⁴. However, unlike other PPIs, Rabeprazole gets metabolized predominantly through non-enzymatic pathway and hence, have less chances of DDIs. In a meta-analysis published in 2016 evaluating the risk of Major Adverse Cardiovascular Events (MACE) in patients with coronary artery disease receiving a combination of Clopidogrel and PPIs, all PPIs have shown increased risk of MACE except Rabeprazole⁴⁵. In fact, USFDA has recommended avoiding Omeprazole and Esomeprazole in patients taking Clopidogrel, as these PPIs can interact with Clopidogrel, resulting in adverse clinical outcomes⁴⁶. This highlights the point that all PPIs are not same in terms of safety and drug to drug interactions and physicians should be made aware that co-prescriptions of PPIs can affect the efficacy, safety and tolerability of other medications prescribed for chronic health conditions. In our study, approximately three-fourth of the respondents have reported their awareness on these co-prescription hazards, more than 80% have mentioned that anticoagulants may have higher chance of drug to drug interactions when given along with a PPI and most respondents have ranked Rabeprazole in the top among PPIs in terms of safety and tolerability, reiterating the existing evidence, through this evidence from real world practice.

One of the major issues with PPI treatment is lack of therapeutic response in many patients. For the factors which influence the switching of the PPI or change of the dose of PPI, "lack of immediate symptomatic relief" has come up as the top reason in this survey. As discussed earlier, most of the PPIs get metabolized predominantly through the CYP2C19 enzymatic pathway. Several studies have highlighted the genetic polymorphism which exists in the CYP2C19 enzyme, which results in individuals with multiple CYP2C19 phenotypes and their differential response to the PPIs. In some phenotypes a standard once daily dosing of PPI may be sufficient for adequate acid suppression, whereas in other phenotypes a higher or more frequent dosing may be required. But evaluating these phenotypes in day to day clinical practice and individualizing the PPI dose is practically not possible. This uncertainty in response to PPI can probably be avoided by choosing a PPI like Rabeprazole, which doesn't depend on the CYP2C19 pathway for metabolism and consequently its acid suppressing effect doesn't vary with the enzymatic phenotype. The current survey has highlighted the challenge of patients' variable response to PPI treatment and the need to address this uncertainty.

The introduction of PPIs into the clinical practice

has revolutionized the management of APD^{52,47}. In our survey, the patients' satisfaction with PPI, as reported by the HCPs, was very high, with more than half of the respondents reported that their patients are very satisfied with PPI use. However, Physicians should exercise reasonable caution in prescribing PPIs, particularly in patients with comorbid conditions, where long term use of PPIs can increase the risk of drug to drug interactions. It is important to choose a PPI with less chance of drug to drug interactions and have a reasonable certainty in providing response in majority of the APD patients.

Conclusion :

In conclusion, the present study has mapped the awareness of Indian HCPs on acid peptic disorders, PPI usage, their adverse effects, drug to drug interactions, patient compliance and satisfaction with PPIs. These findings can be used to plan future interventions targeting HCPs, to ensure appropriate prescription of PPIs, according to the risks and benefits in individual patients.

Study Limitations :

Firstly, the assessment of parameters such as knowledge, awareness, attitude, and practice through self-reported instruments may introduce reporting bias which can overestimate positive responses of these parameters. Second, our sample size is relatively small and limited to India which limits generalization of the results. A wider national/international survey with larger sample size may be needed to confirm our findings. Finally, our study only included responses from physicians. Future studies encompassing responses from diverse hospital departments, including nurses and pharmacists, may provide more detailed insights to the prescription practices of PPIs for APD.

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