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Research Article

INAPPROPRIATE USE OF PROTON PUMP INHIBITORS, TIME TO REASSESS INDICATIONS

¹Ghulam Fareed, ²Hasham Nawaz, ³Wajid Iqbal, ⁴SM. Nabeel Noor,
⁵Shahab Abid

¹Instructor in Department of Medicine, Section of Gastroenterology, Aga Khan University Hospital Stadium Road Karachi, Pakistan. Email ID: g.faryd@hotmail.com

²Intern, Allied Hospital Faisalabad, Pakistan.

³Chief resident, Department of Medicine, section of Gastroenterology, Aga Khan University Hospital, stadium road Karachi, Pakistan. Email: drwajid1112@gmail.com

⁴Teaching Assistant, Aga Khan Medical College and University Hospital, Stadium Road Karachi, Pakistan., Email: nabeel.noor@outlook.com

⁵ Professor, department of Medicine, Section of Gastroenterology, Aga Khan University Hospital ,Stadium road karachi. E-mail: Shahab.abid@aku.edu

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Abstract:

Introduction: Proton pump inhibitors are one of the most commonly prescribed and most commonly used medications worldwide, both in primary, secondary, and tertiary care settings. In the majority of cases, they are used inappropriately without any clear-cut indication hence leading to lots of unnecessary health related costs both nationally and internationally. Also, misuse is associated with potential complications. Due to the current dearth of available data regarding use and misuse of PPIs in Pakistan, there is an urgent need to assess appropriateness of PPI use both in primary and tertiary care settings to avoid the potentially devastating financial and public health concerns. Materials and Methods: It is a retrospective observational study conducted in department of medicine, Aga Khan University Hospital Karachi, over a period of one year. There was total 13,346 patients admitted in the hospital during the specified period under care of Medicine and allied 6950/13346 (52%), OBGYN 379/13346 (3%) and General surgery and allied 6017/13346 (45%). Estimated sample size was 980 patients and similar percentages of patients were taken from above groups via simple random sampling

Results: Out of 797 patients, 367 (46%) had an FDA-approved indication for PPIs use, 213 (26.7%) had alternate indications as recommended by clinical practice guidelines whereas remaining 217 patients (27.2%) were treated with PPI without any approved indications Conclusion: The results of this study showed that every fourth patient in hospital is getting PPIs without fulfilling indications as per established evidence based clinical practice guidelines.

Key Words: Proton pump inhibitor, PPIs misuse, Financial and health concerns, Approved indications, Inappropriate indications, potential complications

Corresponding author:*Dr Wajid Iqbal,**

Chief Resident, Section of Gastroenterology Department of Medicine,

Aga Khan University Hospital

Karachi, Pakistan.

Email: drwajid1112@gmail.com

QR code



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INTRODUCTION:

Proton pump inhibitors (PPIs) are one of the most widely prescribed classes of drugs worldwide because of their high efficacy as an acid suppression therapy. In 2006 the worldwide expenditure on these drugs was 7 billion pounds (1). More recently in 2012 the annual spending on PPIs in the US alone was \$13.6 billion (2). Despite this, subsequent studies show trends of increasing prescriptions of PPIs in primary, secondary and tertiary care settings (1, 3, 4). There is substantial emerging evidence worldwide from studies conducted in an array of different healthcare settings that a significant proportion (27-80%) of these drugs are prescribed inappropriately (5-8). PPIs success has actually made them victim of their own success, often leading to unnecessary prescriptions without clear indications both as inpatients and outpatients. This corresponds to billions of dollars spent unnecessarily on PPIs worldwide. While there is a dearth of data on pharmaceutical spending in Pakistan it has been anecdotally observed that PPIs are widely prescribed in all clinical settings and a prospective survey from a teaching hospital in a rural setting in 2011 demonstrated that 51% of patients who were prescribed PPIs had no clear indications for them(9). An important detail in the aforementioned study was the definition for 'inappropriate use', which was any PPI taken without prescription so in addition to inappropriately prescribed PPIs there are a significant number of people who are self-medicating with PPIs without any physician input or prescriptions.

Whilst there is no contention on the efficacy of PPIs in treating a number of maladies associated with increased gastric acid secretion (10), there are a number of concerns associated with their use despite their low potential for side effects in the short term. Recent literature has identified a number of potential complications associated with PPI use, including but not limited to an increased incidence of *Clostridium difficile* infection, decreased effectiveness of clopidogrel in patients with acute coronary syndrome, increased risk of community and/or hospital acquired pneumonia and an increased risk of fractures due to decreased calcium absorption (11-13). Furthermore, in 2011, the US Food and Drug Administration (FDA) issued a warning about the potential for PPIs to cause low magnesium level which can lead to muscle spasms, arrhythmias, and convulsions.

This study was based on hypothesis that there is an increasing trend of unnecessary prescription of PPIs during hospital stay and on discharge. There is an urgent need to assess and monitor PPI use in hospital and primary care settings in Pakistan due to the current dearth of available data on the use and misuse of this class of drugs given the potentially devastating financial and public health implications of their misuse.

Our aim was to evaluate appropriateness of PPIs use as per international guidelines, look for departmental differences regarding PPIs use within a tertiary care hospital and extra financial burden on patients due to unnecessary PPIs prescriptions.

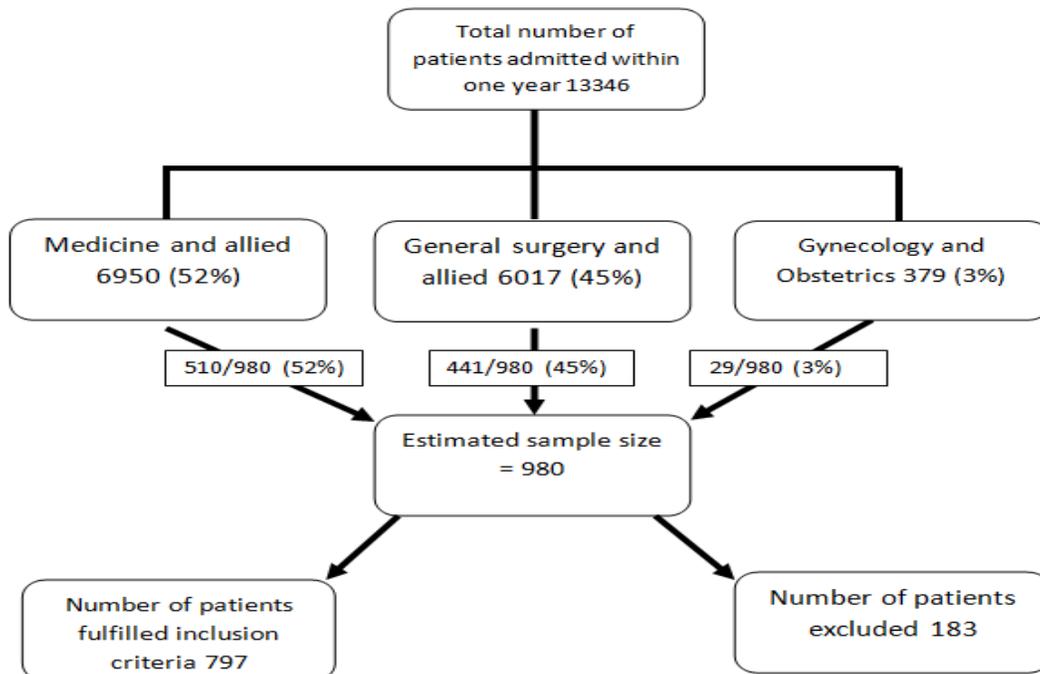


Figure 01

MATERIALS AND METHODS:

After approval by ethical review committee of hospital, we conducted a retrospective observational study on one year data for patient's population who were prescribed PPIs either as inpatients or upon discharge at Aga Khan University Hospital (AKUH), a tertiary care hospital, in Sindh, Karachi. There were total 13,346 patients admitted in the hospital during the specified period under care of Medicine and allied 6950/13346 (52%), OBGYN 379/13346 (3%) and General surgery and allied 6017/13346 (45%). Estimated sample size was 980 patients and similar percentages of patients were taken from above groups via simple random sampling (Figure 01). Data was provided by AKUH Health and Information Management Services (HIMS) and was reviewed on secure hospital computers using AKUH electronic Patient Care Inquiry system. Paper records, when required were requested and reviewed within HIMS department premises.

Our inclusion criteria included all patients, of either gender, with ages ranging from 18 to 80 years. Patients younger than 18 or older than 80 as well as patients who expired during hospital stay were excluded. We recorded patient's demographic data, their primary and secondary diagnoses and indications for PPIs along with dose and type of PPIs. Patients with appropriate and inappropriate prescription of PPIs were determined by dividing them into three categories. First category received PPIs according to FDA approved indications like healing of erosive esophagitis and maintenance of this healing, GERD with its various clinical manifestations (non-erosive reflux disease, ascertained extra-esophageal symptoms, esophageal strictures and Barrett's esophagus), treatment of *H. pylori* infection in combination with antibiotics short-term treatment of *H. pylori*-negative peptic ulcer and maintenance of healed ulcer, NSAID induced dyspepsia, risk reduction of NSAID associated gastric ulcer, pathologic hyper secretory conditions such as Zollinger-Ellison syndrome (ZES), critically ill patients on prolonged mechanical ventilation, short-term treatment with regular review of patients with functional dyspepsia(14). Second category had alternative indications for PPIs use as recommended by Spanish Clinical Practice Guidelines which are patients taking antiplatelet therapy (aspirin/clopidogrel), patients on anticoagulants (warfarin/rivaroxaban) and patients on oral steroids(15). Third category of patients received PPIs without above mentioned approved indications.

Mean \pm standard was reported for quantitative variables and number (percentages) for qualitative variables. Differences in proportions were assessed by using the Chi-square test or Fisher exact test where appropriate. For contrasts of continuous variables, independent

sample t-test was used to assess the difference of means. Multivariable model was built for the primary outcome of PPI used using forward stepwise selection with criteria for $P = 0.2$. Logistic regression analyses were performed using the Statistical package for social science SPSS (Release 19.0, standard version, copyright © SPSS; 1989-02). All p-values were two sided and considered as statistically significant if < 0.05 .

RESULTS:

Out of 980 patients, 183 were excluded as per exclusion criteria and incomplete data and 797 were analyzed as shown in Figure 01. Mean age was 54.25 years (\pm 18.2 SD) with male predominance (57.2%). Average length of hospital stay was 4.35 days (\pm 4.8 SD) (Table-01). Out of 797 patients, 367 (46%) had an FDA-approved indications for PPIs use, 213 (26.7%) had alternate indications as recommended by clinical practice guidelines whereas remaining 217 patients (27.2%) were treated with PPI without any approved indications (Figure 02).

Most common FDA approved indication in our patients was risk reduction of NSAID induced gastric ulcers and commonest alternate indication was use of antiplatelets (Table 02). We looked for reasons behind inappropriate use of PPIs and in majority of cases PPIs were unnecessary given as gastric protectors in patients on polypharmacy especially elderly population. There was some overlap in patients with more than one indication for PPI use between FDA approved and alternate indications, a total of 89 patients overlapped between the 2 categories as shown in Figure 03.

A subset analysis of various group revealed Medicine had 33.8% FDA approved PPI use, 35 % alternate indications for PPI use and 31.2% use was without approved indications. General surgery had 62.53% FDA approved PPI use, 12.66% had alternate indications and 24.80% had no approved indications. OB/GYN results were 62.5%, 2% and 35.5% respectively (Figure 04).

The average extra cost for inpatient intravenous PPIs prescription was 423 Pakistani Rupees (PKR) and the cost for oral PPIs prescription is around 30 PKR/dose whereas; average hospital stay was 4.35 days. We projected these costs on the study population of 13,346 patients and estimated the wasted capital and financial strain on the patients and the system. We applied our results (27.2% of patients being prescribed PPIs in the absence of any established indications) to the study population and found out that almost 3630 patients were unnecessarily prescribed PPIs. Consequently, the total extra cost incurred due to inappropriate prescription of PPIs would be 71.26 % intravenous use (2586 x 423 x 4.35) and 28.74% per oral use (1044 x 30 x 4.35) which

makes the final number 4,894,611 PKR or almost 4.89 million rupees. This is a conservative estimate of the

added cost of needless prescriptions of PPIs in a single year in one tertiary care hospital of Pakistan.

Table-01

Characteristics	PPIs during hospital stay (n=797)
Age (mean \pm SD)	52.53 (\pm 18.69)
Sex	
Male	455 (57.09%)
Female	342 (42.91%)
Length of hospital stay in days (Mean \pm SD)	4.35 (\pm 4.8)
Types of PPI (Route of administration)	
Omeprazole (Intravenous)	568 (71.27%)
Esomeprazole (Oral)	161 (20.20%)
Pantoprazole (Oral)	68 (8.53 %)

Figure 02

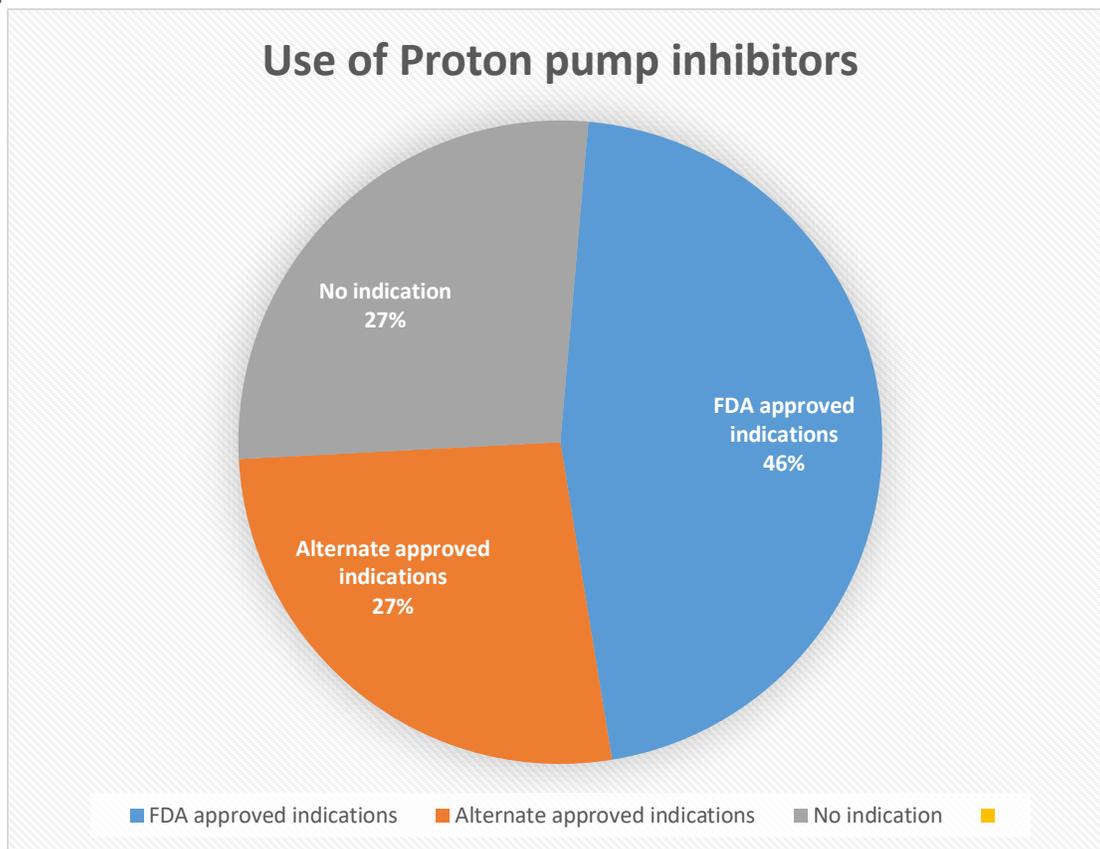


Table 02

Indication	N (%)
Erosive gastritis	22 (2.76)
GERD	18 (2.25)
H. pylori infection	12 (1.50)
H. pylori –ve gastric ulcer	06 (0.75)
NSAID induced dyspepsia	14 (1.75)
Healing of NSAID induced dyspepsia	06 (0.75)
Risk reduction of NSAID induced gastric ulcer	230 (28.85)
Zollinger-Ellison Syndrome	0 (0.0)
Critically ill patients on prolonged mechanical ventilation	59 (7.40)
Antiplatelet use	162 (20.32)
Anticoagulant use	37 (4.64)
Oral steroids	14 (1.75)
No indication	217 (27.22)
Total	797 (100)



Figure 03: Overlap of Indications for PPI use

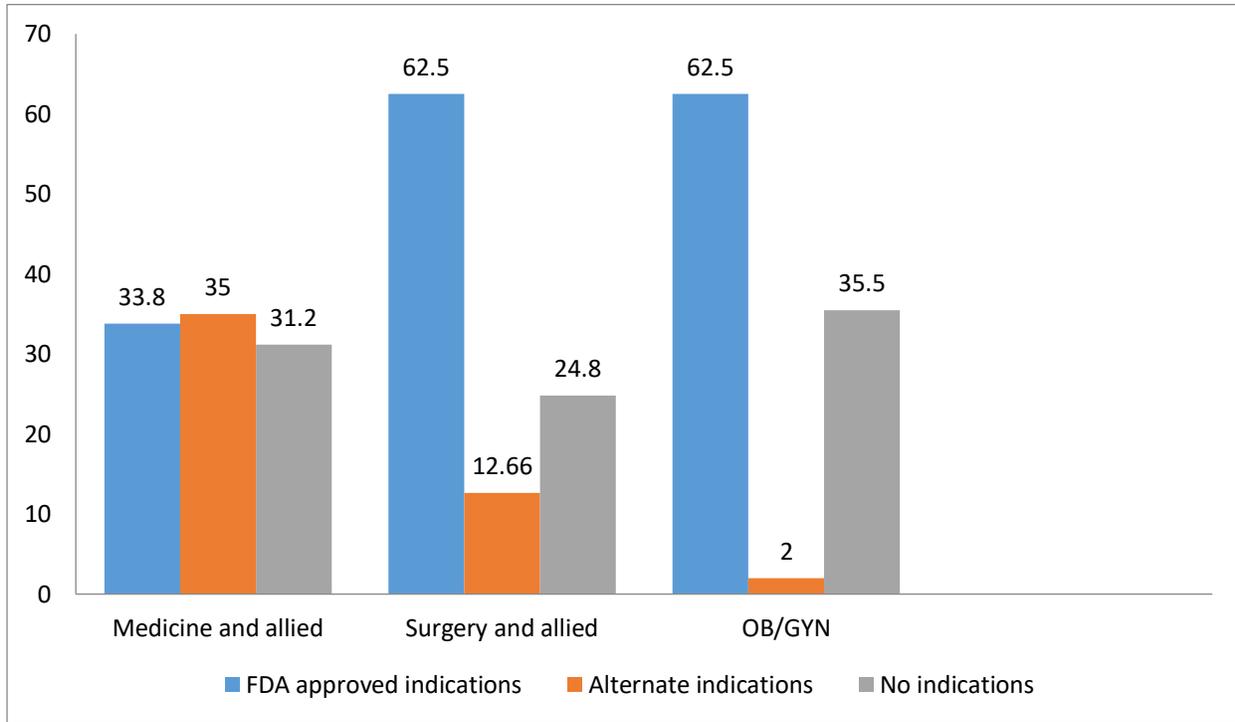


Figure 04: Departmental review for PPI indications (%).

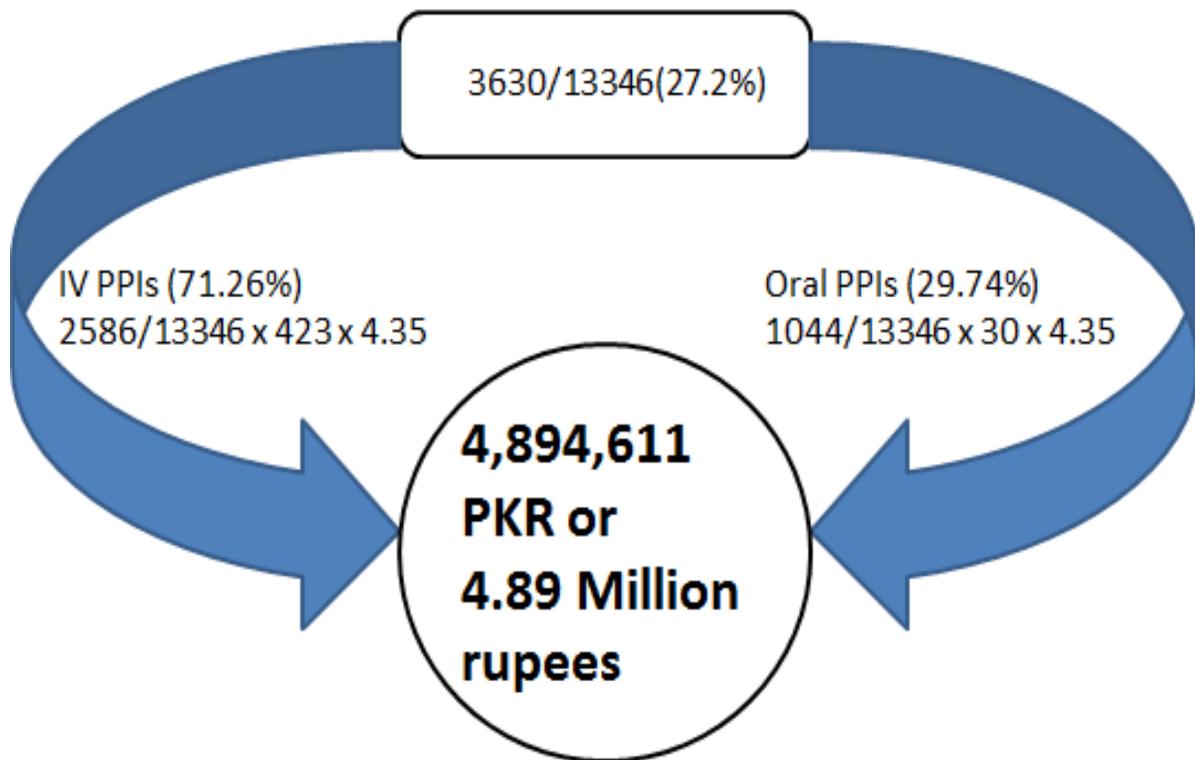


Figure 05: Inappropriate PPI use and total estimated cost.

DISCUSSION:

The results of our study showed that every fourth patient in hospital is getting PPIs without fulfilling indications as per established evidence based clinical practice guidelines; this is in accordance with the studies conducted in various part of the world including France, Switzerland and Lebanon (16-18). Recently published data from China including 45 hospitals has shown similar results regarding PPIs misuse(19). This inappropriate use of PPIs is leading to unnecessary exposure to multiple side effects (11-13). Prolong use of PPIs also effect gut microbiota which can further enhance potential risks for adverse effects including hypomagnesaemia and even hepatic encephalopathy in patients with decompensated chronic liver disease (20-22).

In our study we highlighted misuse was not uncommon in different departments of hospital. This sort of study is actually an initial step in order to find out amplitude of the problem, there is an urgent need for development and implementation of local guidelines in order to reduce misuse of PPIs (23). Hongli luo et al from China supported this fact that medical staffs are usually unaware of appropriate use and potentials side effects of these drugs(24). Residents driven quality improvement interventions and various educational programs targeting hospital physicians and general practitioners would also be beneficial(7, 24).

Considering the fact that majority of the patients in this part of the world are not medically insured and consequently paying their bills out of their own pockets. Unnecessary use of PPIs is not only exposing them to aforementioned potential adverse effects but also causing financial strain on these patients. In our study ,we tried to estimate an extra cost of PPIs misuse and this has been supported by various studies in literature including one from our neighboring country India(25). To ascertain overall extra cost further studies are needed from different hospitals and healthcare settings in order to obtain figures that will very likely be of importance to healthcare policy.

Even though our study was relatively comprehensive when considering the dearth of available data on pharmacology and community healthcare practices in Pakistan it was not without limitations. The study was limited to a single, tertiary care teaching hospital and results in other healthcare settings may be very different however it is safe to assume that the proportion of inappropriate prescriptions would be higher as illustrated by a previous study which demonstrated that 51% of patients who were prescribed PPIs had no clear indications. The definition for 'appropriate' indications in the aforementioned study was a lot less rigorous since they considered anything prescribed by a licensed

physician as appropriate. In addition, ours was a retrospective study and therefore it was impossible to evaluate decision making process behind prescriptions or establish temporality of indications or symptoms with the prescriptions. Although we tried our best to make the list of approved indications as comprehensive as possible but it was not possible to include some indications since they are still new areas of investigation and not part of any published guidelines. Moreover most studies investigating PPIs use only consider FDA indications as appropriate. We were unable to establish and examine correlations with side effects of PPIs however considerable evidence already exists linking PPIs use to the aforementioned side effects and this study was not aimed at to evaluate PPI side effects

CONCLUSION:

In conclusion, results of our study suggest widespread PPIs use in all specialties which are not always in accordance with evidence-based guidelines. There is a need for further evaluation of this trend and measures to limit PPIs use which could potentially cause serious complications especially in older patients and during prolonged use.

CONFLICT OF INTEREST: Authors declared no conflict of interest

FUNDING: There is no funding for this study.

PATIENT'S CONSENT: All patients signed a document of informed consent

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