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Research Article

Drug Utilization Evaluation of Proton Pump Inhibitors in General Medicine Department of a Tertiary Care Teaching Hospital

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ABSTRACT

Proton pump inhibitors (PPIs), antagonists of H^+K^+ ATPase, have been found as the most efficacious inhibitors of the gastric acid secretion. Prescribing PPIs is on the rise owing to polypharmacy and multiple co-morbid condition of the patient. This study aims to analyze the drug utilization pattern of PPIs.Methodology: A prospective observational study was conducted in a tertiary care teaching hospital. A total of 98 prescriptions were analyzed as per the inclusion and exclusion criteria for the study. These prescriptions were analysed for the prescribing pattern in accordance with FDA guidelines. Results: In our study 51% were females and 49% were males. The mean age of our study population was 40.87±14.86 years. The most commonly prescribed PPIs in our study was found to be Pantoprazole (59.18%) followed by Rabeprazole (39.80%) and Omeprazole (1.02%). According to the present study, 58 cases were found to have indication for PPIs prescription, 37 prescriptions were found to have possible indications and 3 cases were not having any indications for PPIs prescription. Conclusion: The clinical pharmacists and physicians should keep a constant vigil on the prescriptions to prevent inappropriate prescribing of PPIs with reference to the guidelines available regarding their indication of use which would increase the quality of prescription for individual and community.

Keywords: drug interactions, drug utilization evaluation, prescribing pattern, proton pump inhibitors.

Introduction

Proton pump or H^+K^+ ATPase, present in the parietal cells of stomach is the final common pathway in acid secretion and drugs that inhibit the proton pump could control acid secretion. Proton pump inhibitors (PPIs) are antagonists of H^+K^+ ATPase, chemically benzimidazole derivatives and have been found as the most efficacious inhibitors of the gastric acid secretion. Omeprazole was the first of the PPI family, discovered in 1978 and was approved for its use in 1989. Though omeprazole was the first to be marketed, there are newer PPIs like Lansoprazole, Pantoprazole, Rabeprazole, and Esomeprazole with minor pharmacokinetic variations.[1]

They provide highly effective form of therapy for acid related GI disorders. This also includes healing and maintaining healing of GERD, peptic ulcer disease and *Zollinger-Ellison* syndrome. They are also known to provide treatment and prophylaxis against ulcer related to NSAIDs medications. They have also been approved for eradicating *H.pylori*. Despite the unique and complex pharmacology of PPIs, less information is available by gastroenterologist and primary care physicians[2].

For the inhibition of acid secretion, anti-secretory medications and H_2 receptor antagonists have being used. Recent studies demonstrated the effectiveness of Omeprazole when compared to Ranitidine in the treatment of peptic ulcer disease, upper GI bleeding and GERD. On the other hand, the administration of proton pump inhibitors is more complex as it requires careful attention to food ingestion. [2]

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Good prescribing is sometimes defined as the lack of irrational prescribing. The WHO conference of experts in Nairobi defined the rational use of drugs as one that 'requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and to their community.[3]

Prescribing can be described as irrational for many reasons:[4]

- Poor choice of a medicine
- Polypharmacy or co-prescribing of interacting medicine
- Prescribing for a self-limiting condition
- Continuing to prescribe for a longer period than necessary
- Prescribing too low a dose of a medicine
- Prescribing without taking account of the patient's wishes.

According to the adverse events of clinical significance reported with PPIs (Table 1), it is necessary to analyze the data regarding the adverse effects and safety profile of PPIs which will help us in understanding the magnitude of the problem and also rationalize our approach while prescribing medications to the patients.[5]

Table 1- Adverse events of clinical significance reported with PPIs

S/No	Adverse Events
1	Osteoporosis and fractures
2	Pneumonia
3	Clostridium difficile infection
4	Other enteric infections
5	Adverse perinatal and postnatal events with use in pregnancy
6	Acute interstitial nephritis
7	Vitamin B12 deficiency
8	Hypomagnesaemia
9	Inhibition of Iron absorption

PPIs have few immediate and tangible side effects. Achlorhydria is found to be main concern. In short term therapy gastrinemia causes rebound hyper acidity which worsens GERD symptoms and induces dyspepsia. In initial phase trials prior to omeprazole, trials were halted due to oxyntic neoplasia and secondary hyper-gastrinemia can lead to ECL cell hyperplasia. Theory of decades argued against risk of potential carcinoma due to long term PPI therapy. Strong evidence which supports PPI efficacy is due to significant over prescription. Class of anti-secretory therapy falls behind statins in total worldwide expenditure according to IMS Health Report 2008.[6]

A substantial expenditure on PPIs had led many researchers to create cost effective evidence based studies for anti-secretory therapy in treatment of conditions like GERD. However, PPIs use in ICU and General Care floors is inappropriate which leads to useful and controllable expenditure in both hospital setting and after discharge. It was observed that inappropriate prescription pattern have additional significant healthcare costs due to inappropriate prescription patterns in PPIs.[7,8,9,10,11] ICU admitted patients during hospitalisation are prescribed with SUP (Stress Ulcer Prophylaxis) and are being discharged on SUP. The prospective case series study conducted by Wohlt *et al.*, reveals that, the patients prescribed with PPIs have more co-morbid conditions and more risk as compared to patients who were not receiving the same. The potential risks are conditions like enteric infections, community acquired pneumonia, bone fracture and nutritional deficiencies (which includes Vitamin B12, Iron, magnesium). Some studies suggest risk during pregnancy but more studies limited to omeprazole show no significant birth defects. Hence omeprazole is found safe in pregnancy.[12]

Pulmonary micro aspiration of gastric contents during reduced gastric acid secretion led researchers to investigate the development of community acquired pneumonia (CAP). The patients were prescribed PPI therapy which was less than 30 days had an increased risk of CAP. [13]

Long term prospective trials examined the risk of bone fractures with PPI use. They are known to increase risk of bone fracture along with PPI usage as majority of the data comes from retrospective, cross sectional, case controlled and cohort studies. PPIs are known to inhibit intra-gastric secretions of HCl that mediates absorption of calcium from small intestine. The osteoclasts also possess proton pumps and their activity is affected by the use of proton pump inhibitors reducing the

absorption of calcium. Several studies have demonstrated a risk in hip, spine and wrist fractures in both genders who have taken doses of PPIs for longer duration of time.[14]

A study in UK concluded that hip fractures are associated with PPI usage for 1 year of therapy. The duration and usage was observed in both genders and the risk of hip bone fractures was found more in men than women. A case-controlled study determined that these risk factors do not increase unless there are risk factors like alcohol dependence, neurological disease, accidental falls and senility.[15]

A case controlled study conducted in Denmark concluded that the fractures in hip and spine were more likely occurred in patients using PPIs compared to H_2 receptor antagonists. Furthermore, no observations were carried out in dose response yet a slight trend towards decreasing risk of fracture were seen with increasing dose of H_2 receptor antagonists.[16]

The data obtained from Women's Health Initiative also suggests that the use of PPIs in post-menopausal women is not linked with hip fractures but is associated modestly with clinical spine, forearm, wrist and total fractures. The older patients who require long term or high dose therapy should consider increasing their dietary or supplementary calcium intake, Vitamin D intake which aids to minimize risk of bone fractures.[16]
Various trials have evaluated the decrease effect of clopidogrel in patients using concomitant PPI therapy. This effect is observed due to the competitive inhibition of Cytochrome 2C19 by PPIs reducing metabolism of clopidogrel into its active form thus reducing its effect on platelet inhibition.[17]

A double blind study, randomised, placebo-controlled trail in 124 patients with coronary heart disease undergoing implantation where the patients received Aspirin and Clopidogrel were randomised to receive Omeprazole or a placebo. It was found that Omeprazole decreases the effect of platelet activation of Clopidogrel. The major limitation in the study was the absence of defined clinical outcomes.[18]

Another trial had evaluated 300 patients with known Coronary Artery Disease (CAD). They were undergoing coronary intervention and receiving Clopidogrel and Aspirin. They were assigned in the treatment using Pantoprazole or Esomeprazole. The result concluded that the PPI-clopidogrel interactions may not be present to produce effect across all PPIs usage.[19]

US FDA released a warning which recommends avoiding a combined use of Clopidogrel with Omeprazole or CYP2C19 inhibitors.[20]

In older patients, Vitamin B12 deficiency is found as a common condition which has been linked to PPI usage. Most cases of such deficiency go undetected while the profound ones may present with neuropsychiatric and haematological findings which may herald the underlying disease.[21,22]

It has also been postulated that the use of PPI therapy may lead to iron mal-absorption due to gastric acid hyposecretion and achlorhydria.[23]

Hypermagnesemia which is suspected as secondary to chronic PPI therapy is rare because there is no mechanism to explain such an association. However, the FDA released a warning stating that PPIs may cause hypomagnesia if it is taken longer than a year.[24]

Several guidelines have been published related to appropriate use of PPIs, known as US Food and Drug Administration (USFDA) guideline, American College of Gastroenterological Association (ACG) and the American Gastroenterological Association (AGA) guideline, and National Institute of Clinical Excellence (NICE).[7]

FDA Guideline:

The final result of the appropriateness of PPIs use was classified as indicated, possibly indicated, or not indicated.

Indicated refers to any PPI prescription for a FDA-approved indication which include the maintenance treatment of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease (GERD), eradication of *Helicobacter pylori* infection, healing and maintenance of duodenal ulcers, healing of gastric ulcers, treatment of *Zollinger-Ellison* syndrome, and prevention and treatment of NSAID-induced gastric ulcers. The risk factors in the manner of their importance include history of complicated ulcer disease, concurrent use of more than one NSAID (including Aspirin), use of high NSAID doses, concurrent use of an

anticoagulant, history of uncomplicated peptic ulcer disease, advanced age and concurrent use of steroids.

The term possibly indicated refers to the conditions when there are no physician-documented indications for PPI use but patient was taking an NSAID and an anti-coagulant.

The remaining cases with no documented indication for use where categorized as not indicated.[8]

ACG & AGA Guideline:

Both guidelines include recommendations for the appropriate use of PPIs in the management of dyspepsia and *H. pylori* infection. Guidelines are based on the scientific data and when there is a lack of it recommendations are based upon expert consensus obtained from both the literature and the experience of the authors and the Practice Parameters Committee. Each guideline is evaluated by the committee and the strength of evidence to guide clinical practice is assessed using established criteria.[9, 10]

NICE Guidelines:

The National Institute of Clinical Excellence (NICE) published guidance on the use of PPIs in the treatment of dyspepsia and it include the following recommendations:

Patients with severe gastro-esophageal reflux disease (GERD) symptoms should be treated with a healing dose of a PPI until the symptoms have been controlled. Maintenance treatment with low dose PPIs will prevent recurrent GERD symptoms in 70–80% of such patients.

- Patients with documented duodenal or gastric ulcers should be tested for H. pylori and treated with PPIs and antibiotics if positive. In patients negative for H. pylori or who remain symptomatic despite H pylori eradication therapy, PPI use is appropriate for symptom control and until ulcers heal.
- Patients with documented non-steroidal anti-inflammatory drug (NSAID) or aspirin induced ulcers who must unavoidably continue with NSAID/aspirin treatment should be co-prescribed a PPI.
- Patients with un-investigated dyspepsia may be given full dose PPI for one month to assess response.
- Patients with non-ulcer dyspepsia (NUD) or with mild symptoms of dyspepsia do not generally benefit from a PPI but may be prescribed a short, low dose course provided there is regular review.
- All patients should be reviewed regularly to assess the continuing need for PPIs and to step down to less potent medication where possible.[7]

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- All patients should be reviewed regularly to assess the continuing need for PPIs and to step down to less potent medication where possible.[7]

METHODOLOGY

Study site

This study was conducted at Dr. B. R. Ambedkar Medical College and Hospital which is a 760 bedded multispecialty tertiary care teaching hospital in Bengaluru.
Study duration
The study was conducted over a period of 6 months (September 2015 – February 2016).
Study criteria
All the patients' admitted to General Medicine department of the Hospital, and who met our inclusion criteria were recruited for our study.
Inclusion Criteria

- Patients of either sex aged >18 years of age.
- Patients admitted to the general medicine ward.
- Patient who were willing to give consent.
- Patient who were prescribed with proton pump inhibitors.

Exclusion Criteria

- Patients of either sex aged <18 years.
- Patients who were not willing to give consent.
- Patients who were not prescribed with Proton Pump Inhibitors.

Study procedure
All patients' who were admitted to the General Medicine Ward and who met our inclusion criteria were included in the study. The patients' oral consent was obtained. The patients' demographics, past and present medical and medication history, and other relevant data needed for the study was collected in a structured format from the case sheets and from direct patient interview. The medication chart was analysed for appropriate prescribing of PPIs using FDA guidelines. The collected data was then entered in Microsoft Excel and statistical analyses were performed using SPSS V-21.
Statistical analysis
The data were analysed for mean, standard derivation, and percentage calculations.

RESULTS

This prospective observational study which aims to analyze the drug utilization evaluation of Proton

Pump Inhibitor recruited 98 patients' as per the inclusion and exclusion criteria. The distribution of our study patient depicts 48 (51%) were females and 50 (49%) males (Figure 1). The mean age of our study population was found to be 40.87±14.86 and the length of stay was around 5.83 (6 days).

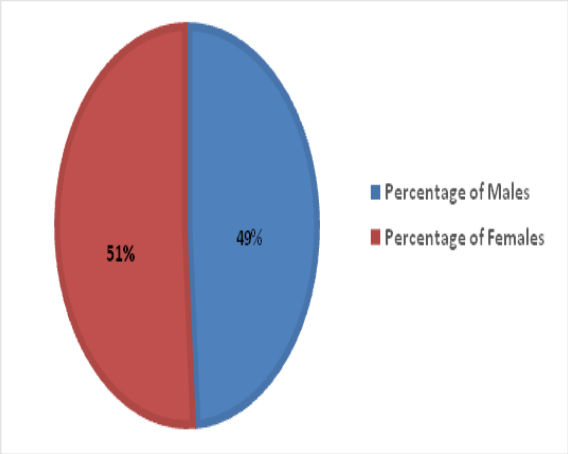

Figure 1: Gender distribution of our study population (n=98)

The most commonly prescribed PPI in our study subjects was found to be Pantoprazole, Rabeprazole, and Omeprazole. Pantoprazole (59.18%) was found to be prescribed the most among others followed by Rabeprazole (39.80%). Omeprazole (1.02%) was found to be the least prescribed drug among the proton pump inhibitors (Figure 2).

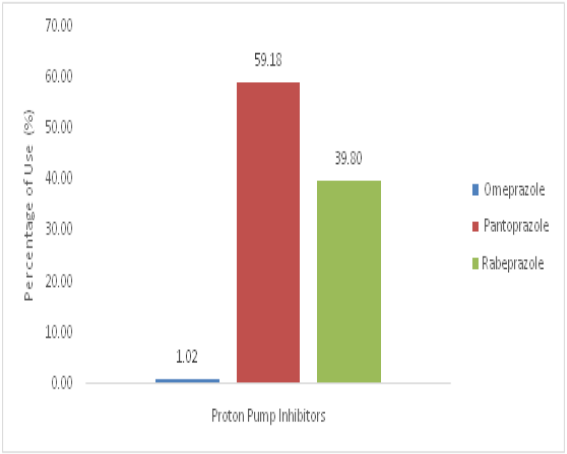

Figure 2: Percentage of use of PPI

In our study, IV route of administration was found to be the most common route of administration which accounts for 85.71 %. Oral route of administration was found to be in 14.29 % patients (Figure 3).

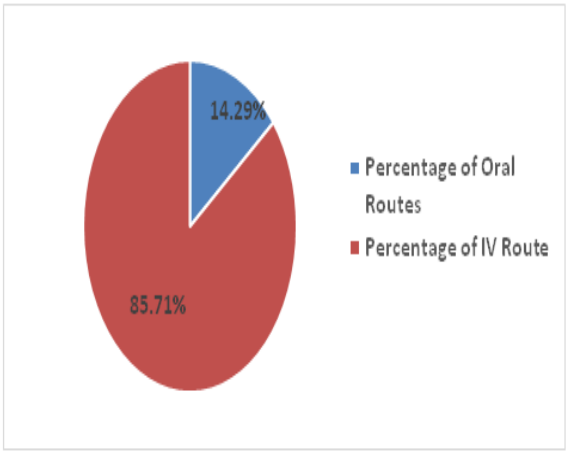

Figure 3: Distribution of Routes of Administration

The further analysis of route of administration for individual drugs shows the following order of Pantoprazole IV (50 %), Rabeprazole IV (36 %), Pantoprazole Oral (8 %) Rabeprazole Oral (5 %), Omeprazole Oral (1 %) and Omeprazole Oral (0 %).

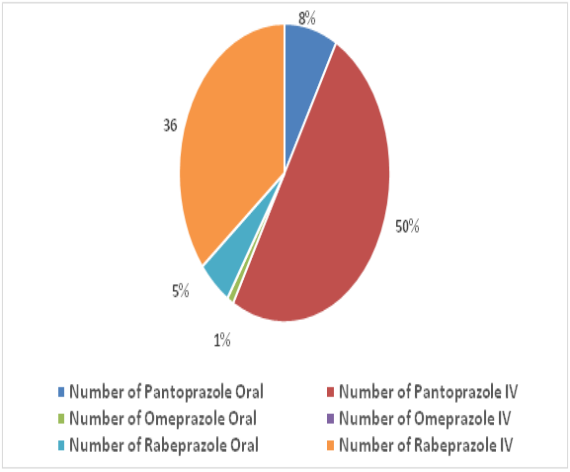

Figure 4: Distribution of drugs and route of administration

Appropriateness of PPI was evaluated by using FDA guidelines and it was categorized into indicated, possibly indicated, and not indicated for the patient condition. This analysis revealed that 58 cases were indicated, 37 cases were possibly indicated and 3 cases were not indicated.

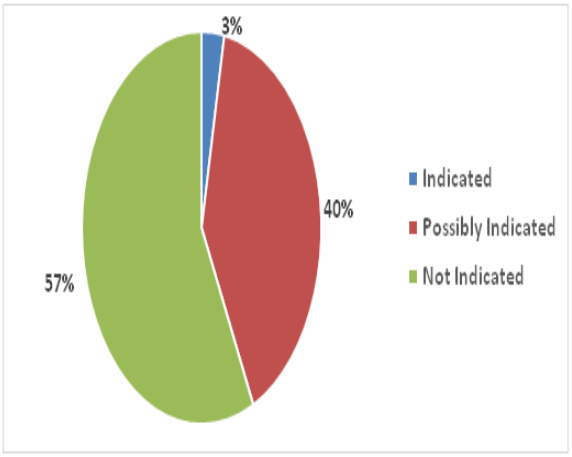

Figure 5: Appropriateness of PPI use

The cases were analyzed for drug interaction out of which 5 were found to be minor drug interaction and one moderate interaction. The remaining cases (90) had nothing significant, no major drug-drug interactions were found in our study.

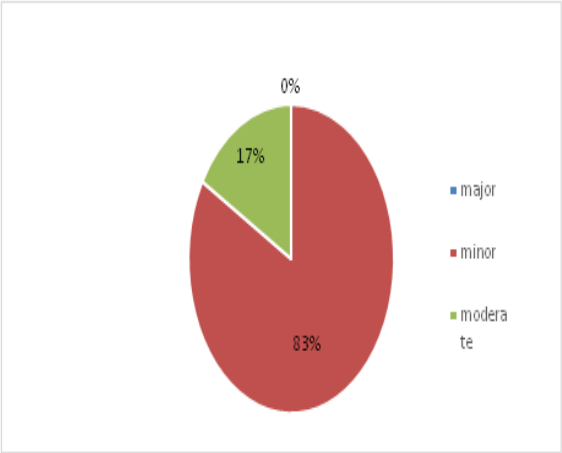

Figure 4: Drug Interactions

DISCUSSION

This study revealed drug utilization evaluation of proton pump inhibitors with particular reference to indication of use, age, gender, length of stay in hospital, diagnosis category, pattern of PPIs use, route of administration, FDA approvals, and drug interactions in general medicine department of a tertiary care teaching hospital.

In our sample of 98 patients in this prospective and observational study, 49% of patients were male and 51% were female. The mean age of the patients was 40.87±14.86 years. The average length of stay of patients in hospital was 5.8±2.4 days.

The most common category of diagnosis was Viral Fever with Acute Gastro Enteritis (11 cases; 11.22%) followed by Acute Febrile Illness (9 cases, 9.18%), the moderate diagnosis belonged to Alcoholic liver disease (6 cases; 6.12%) followed by Fever, UTI, Type II DM (4 cases; 4.08%), and the least common category of diagnosis was Tuberculosis (1 case; 1.02%). A retrospective chart review by Marsha Dangler *et al.,* in a general medical and surgical hospital, titled as "Assessing the appropriate use of proton pump inhibitors in a veteran outpatient population" revealed that the most common indication for PPI use documented in patient charts was GERD (55%), the moderate indication belonged to duodenal ulcer, dyspepsia, heartburn, gastritis, GI bleed, abdominal pain, etc. (4%), and the least indication belonged to gastric ulcer (1%).[11]

Among all the PPIs prescribed, Pantoprazole was the most common PPI used (n=58; 59.18%), followed by Rabeprazole (n=39; 39.8%) and Omeprazole (n=1; 1.02%). The PPIs administered were found to be either Oral (14.29%) or IV (85.71%). This results were not in coherence with a retrospective chart review which was conducted by Marsha Dangler *et al.,* in a general medical and surgical hospital, titled as "Assessing the appropriate use of proton pump inhibitors in a veteran outpatient population" showed that of the 199 charts most patients were initially prescribed Omeprazole therapy (66%), Rabeprazole (24%), Lansoprazole (9%), and Pantoprazole (2%).[11]

Similar results were also found in another study conducted by Mat saad AZ *et al.,* titled as "Proton pump inhibitors: a survey of prescribing in an Irish general hospital" revealed of the 157 inpatients, 48 (30.6%) were on PPI therapy and omeprazole was the most widely prescribed PPI. Rabeprazole was the least prescribed.[12]

In current study 59% of PPI uses were found to be indicated, 38% possibly indicated, and 3% had no indication of for PPI use. These results of our study was found to be similar to a retrospective study at a geriatric ambulatory care practice within an urban medical centre done by C. J. George *et al.,* about the "Appropriate Proton Pump Inhibitor Use Among Older Adults: A Retrospective Chart

Review" states that Out of ~2500 patients in the geriatric practice, 702 (~28%) were identified as having a current prescription for a PPI. From these, 110 charts were randomly selected for review, of which 10 were excluded based on predefined criteria. In this study, PPI use was indicated in 64% of these patients, possibly indicated in 7%, and not indicated in 29%.[8]

Another 1-day survey by Mat saad AZ *et al.,* titled as "Proton pump inhibitors: a survey of prescribing in an Irish general hospital" revealed similar results as that our study. In their Prescription of PPI therapy was for an approved indication in 66.6% of the patients, 18.8% possibly indicated, and 14.6% not indicated.[12]

The pattern of drug interactions between the PPIs and the other medications in the prescriptions were found to be 5.10% as moderate drug interactions. 1.02% as moderate drug interactions and 93.87% no interactions. It is a challenge to determine the pattern of PPIs use within the confines of a study and in this study the FDA-approved indication guideline was employed to study the appropriateness of the PPIs prescribed to the patients.

CONCLUSION

Due to the increased utility of healthcare, the patient's longevity of life has increased which ultimately leads to increased number of people living with multiple disease conditions. The changes in the lifestyle and food habits leads to the increased incidence and prevalence of GI diseases in which the proton pump inhibitor treatments are rendered mandatory. The use of PPI according to FDA is indicated as in cases of evident GI diseases include maintenance treatment of erosive esophagitis, treatment of symptomatic gastroesophageal reflux disease (GERD), eradication of Helicobacter pylori infection, healing and maintenance of duodenal ulcers, healing of gastric ulcers, treatment of Zollinger-Ellison syndrome, prevention and treatment of NSAID-induced gastric ulcers. Possibly indicated use of PPIs were examined for the presence of risk factors for NSAID-induced ulcer complications, which included history of complicated ulcer disease, concurrent use of >1 NSAID (including aspirin), use of high NSAID doses, concurrent use of an anticoagulant, history of uncomplicated peptic ulcer disease, advanced age, and concurrent use of steroids. The remaining cases with no documented indication for use were categorized as not indicated.

The clinical pharmacists and physicians should keep a constant vigil on the prescriptions to prevent inappropriate prescribing pattern which would consequently increase the quality of prescription for individual and community.

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