

# Over-prescription of Proton Pump Inhibitors in elderly Patients at a Tertiary Care Hospital of Khyber Pakhtunkhwa, Pakistan

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**Abstract-** Main objective of the current study was to assess the inappropriate medication prescribing related to Proton Pump Inhibitors (PPIs) by evaluating existing prescribing patterns in tertiary care hospital in KPK. It is descriptive and observational study, in which prescriptions given to elderly patients were analyzed for potentially inappropriate medication (PIM) of PPIs. The appropriateness of prescriptions was assessed following International Classification of Diseases, 9th Revision (ICD-9) codes, while Medscape and Stockley's drug interaction checker was used to find drug interactions. Descriptive statistical analysis was performed using IBM SPSS Statistics 20. The study showed that 49% patient patients received PPIs for unapproved indications and the recommended guidelines were followed in 51% cases only. Moreover, Potential drug interactions were observed in 42.6% cases, the most common drug interactions were omeprazole-ciprofloxacin (i.e., 36.7 %). These findings showed that current prescribing practice of PPIs is prone to overprescription of PPIs for unapproved conditions accompanied with potential drug interactions.

**Index Terms-** Potential drug-drug interaction, Overprescription, Elderly patients, potentially inappropriate medication

## I. INTRODUCTION

Prton pump inhibitors (PPIs) are commonly prescribed drugs worldwide, particularly in elderly patients.<sup>1</sup> PPIs are highly effective to combat gastric acidity as compared to H<sub>2</sub>-receptor antagonists by reducing the gastric acid secretion.<sup>2</sup> US Food and Drug Administration (FDA) recently approved several PPIs for various disease states like gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), dyspepsia, oesophagitis, Helicobacter pylori eradication, prophylactically for stress induced ulcer, Zollinger–Ellison syndrome, prevention of nonsteroidal anti-inflammatory drugs (NSAIDs) induced ulcer and scleroderma oesophagitis.<sup>2,3</sup> Maximum duration of treatment recommended for above indications is four to eight weeks.<sup>4</sup> Regardless of recommended guidelines for treatment, PPIs are used inappropriately in various clinical setting.<sup>5,6</sup>

Although clinical trials have shown that PPIs are largely safe with minor common adverse effects like vomiting, abdominal pain, diarrhea, headache, nausea and flatulence.<sup>6,7</sup> However, overutilization of PPIs can affect the safety profile of the patient if

it is not used according to the recommended guidelines.<sup>8</sup> Overutilization of PPIs can lead to potentially harmful adverse effects like Clostridium difficile infection, osteoporotic fractures, hospital and community acquired pneumonia.<sup>9,10</sup> Serious drug-drug interactions such as adverse cardiac events are observed with clopidogrel and drug-nutrients.<sup>11</sup> It also increases the risk of vitamins and minerals deficiency in body such as magnesium, iron, vitamin B<sup>12,12</sup>

Reportedly, from 25 % to 86 % PPIs are being over prescribed without indications or for unapproved conditions especially in older patients that along with polypharmacy results in high risk of hospitalization, adverse drug reactions, high rate of morbidity and mortality.<sup>13,14</sup>

Despite the recommended guidelines for prescribing PPIs, it is one of the most overused acid-suppressing agents in clinical settings whether the clinical indication persists or resolved those results in a decrease in treatment safety, efficacy and cost effectiveness as well.<sup>15,16</sup>

The present study aims to assess the prescribing pattern of Proton pump inhibitors (PPIs) in geriatric population by evaluating prescription of such medical patients in tertiary care hospital. During this study, potential drug interactions that may occur with PPIs in geriatric patients will also be assessed.

## II. MATERIALS AND METHODS

### Study design, settings and data collection

A cross-sectional descriptive forty days study was conducted on elderly patients receiving treatment in a tertiary care hospital. Age range for the included patients was 50-88 years old. Though, technically people aged  $\geq 60$  years are considered elderly, however, keeping in view the socioeconomic environment of KPK, patients aged  $\geq 50$  years also were included. Data was collected from different hospital wards (ICU patients as well as non-ICU patients and ambulatory patients). Data was collected using patient medication record files and by interviewing them, simultaneously. Patient related information was recorded including, medical history, demographic data, current medications, clinical characteristics, various risk factor that can cause peptic ulcer i.e., ulcer caused by use of NSAIDs, stress and food-induced ulcer. While collecting the data, nonprescription medications and natural products were not considered, as their use

was not registered in the available data collection.

### Inclusion/exclusion criteria

Patients of ages  $\geq 50$  years being prescribed with PPIs as part of their drug regimen were included. Patients having incomplete profile and of age  $< 50$  years, were excluded.

### Ethical approval

Study followed the ethical guidelines of World Medical Association Declaration of Helsinki. The study was approved by ethical committee of department of Pharmacy, Kohat University of Science and Technology and by the hospital.

### Criteria

The International Classification of Diseases, 9th Revision (ICD-9) codes guidelines was used to determine the appropriateness of PPI's prescribed, as shown in Table 4. The drug interactions were found using Medscape and Stockley drug interaction checker.

## III. RESULTS AND DISCUSSION

Total 300 prescriptions covering the patients in the age range of 50-88 years and with a mean age of 62.1 years were collected (Table 1).

**Table 1.** Patients' Demographics

Reimbursed Prescriptions	
Total number of Prescriptions	300
Number of medications	1440 (1.6 %)
Number of PPIs	310 (0.2 %)
Number of diagnosed conditions	419
Old Patients	
Age ( Mean $\pm$ SD, years)	62.1 $\pm$ 8.4
Age (Range)	
% Men	147 (49 %)
% Women	153 (51 %)
Age groups	
1 <sup>st</sup>	46-60 years
2 <sup>nd</sup>	61-75 years
3 <sup>rd</sup>	76-90 years

Among 300 prescriptions, 147 (49 %) to men while 153 (51 %) were prescribed to women. Frequently prescribed PPIs in the hospital were rabeprazole, pantoprazole, lansoprazole and omeprazole. Esomeprazole was the most commonly prescribed (administered to 221 patients, 71.3 %), followed by omeprazole as the second most prescribed PPI (administered to 70 patients, 22.6 %) and then pantoprazole (administered to 17 patients, 5.7 %), lansoprazole (administered to 1 patient, 0.3 %) and rabeprazole (given to 1 patient, 0.3 %) as shown in Table 2.

**Table 2.** Frequency of various PPIs Prescribed

Prescribed PPI	Number of cases = n (%)
Lansoprazole	1 (0.32%)
Pantoprazole	17 (5.6%)
Rabeprazole	1 (0.3%)
Esomeprazole	271 (21%)
Omeprazole	70 (22.6%)

Elderly patients suffered mostly from cardiovascular (CVS) disorder (n = 100, (23.7 %), followed by rheumatologic (n = 93, 22.2 %), neuropsychiatric (n = 32, 7.6 %), gastrointestinal (GIT) (n = 31, 7.4 %), respiratory (n = 27, 6.4 %), diabetic (n = 21, 4.01 %), urologic (n = 16, 3.8 %) and then Ophthalmologic (n = 02, 0.5 %) disorders as shown in Table 3.

**Table 3:** Prevalence rate of various diagnosis

Type of diagnosis	Prevalence = n (%)
Cardiovascular (CVS)	100 (23.9 %)
Neuropsychiatric	32 (7.6 %)
Rheumatologic	93 (22.2 %)
Diabetes	21 (4.0%)
Gastrointestinal (GIT)	31 (7.4 %)
Respiratory	27 (6.4 %)
Urologic	16 (3.8 %)
Ophthalmologic	2 (0.5%)
Other	41 (9.3%)

Only 51 % (n = 153) patients received PPIs for approved conditions. Patients number who received PPIs for unapproved indications was 147, thus prevalence of overprescribing for PPIs was 49 %. Approved conditions for which PPIs were prescribed included NSAID induced peptic ulcer; n = 107 (35.6 %), Stress induced ulcer with minor risk factors; n = 15 (5 %), Stress induced ulcer with major risk factors; n = 9 (6.3 %), H. Pylori eradication and active duodenal and gastric ulcer; n = 5 (1.66 %), GERD; n = 4 (1.3 %) and for stomach acidity and dyspepsia; n = 2 (0.6 %), displayed in Table 4.

**Table 4.** The Most Common Indications for prescribing PPIs

Common Indications	Number of cases = n (%)
International Classification of Diseases (ICD-9)	Approved Indications
Helicobacter pylori.	5 (1.7 %)
Duodenal or gastric ulcer	5(1.7 %)
Prophylactically along with NSAIDs for preventing ulcer caused by NSAIDs	4 (1.3 %)
Stress induced ulcers	4 (1.3 %)
GERD (Gastroesophageal reflux disease)	4 (1.3 %)
Stomach acidity	9 (6.3 %)
PPIs for one month to assess response	15 (5 %)
Stress induced ulcer with one major risk factors	107 (35.6 %)
Stress induced ulcer with two minor risk factors	15 (5 %)
NSAID induced peptic ulcer	107 (35.6 %)

Drug interactions among 300 prescriptions, n = 128 were assessed using Medscape and Stockley's drug interaction checker as shown in Table 5. Most common drug interactions were Omeprazole + ciprofloxacin; (n = 47, 36.7 %), followed by esomeprazole + Clopidogrel; (n = 34, 26.6 %), esomeprazole+ alprazolam; n = 15, 11.7 %, esomeprazole + escitalopram (n = 12, 9.4 %), dexamethasone + omeprazole; (n = 5, 3.9 %), esomeprazole + digoxin; n = (4, 3.1 %), esomeprazole + duloxetine; (n = 3, 2.3 %), fluconazole + esomeprazole; (n = 3, 2.3 %), omeprazole + tizanidine; (n = 2, 1.1 %), carbamazepine + pantoprazole; (n = 1, 0.8 %), esomeprazole + midazolam; (n = 1, 0.8 %), and esomeprazole + clonazepam; (n = 1, 0.8 %). Table 5 shows details of drug interactions.

This study was conducted at a tertiary care hospital in KPK, Pakistan to determine the risk of overutilization of PPIs in geriatric pharmacotherapy. Moreover, potential drug interactions of PPIs with drugs co-prescribed were also determined out of 300 prescriptions, the number of medications prescribed for various diagnosis were 1440 (1.6 %) and number of PPIs prescribed were 310 (0.2 %). It was also found that patients prescribed with acid-suppressing agents for unapproved indications, continued taking PPIs for longer period (three months) after getting discharged from the hospital. Frequent and prolonged overuse of PPIs may lead to severe adverse effects like clostridium-difficile infections, GIT infections, increased risk of fractures and pneumonia.<sup>17</sup>

Present study targeted old age patients as they constitute a group at a higher risk of both mortality and morbidity. Prevalence of overprescribing of PPIs was 49%. Potential drug-drug interactions of PPIs being co-prescribed with omeprazole, esomeprazole and to a lesser extent with pantoprazole were also found. Patients diagnosed with cardiovascular diseases (n = 100, 23.9 %) were being prescribed with omeprazole and clopidogrel, concomitantly (both the drugs are substrate for CYP2C19). PPIs cause the inhibition of CYP2C19 which is required for activation of clopidogrel which results in reduction in platelet inhibition effect. Most commonly prescribed PPIs among the study patients was esomeprazole.<sup>18</sup> Although all PPIs were found to be equally effective at recommended doses, however, lesser drug interactions were observed with lansoprazole and rabeprazole as compared to omeprazole and esomeprazole. Studies conducted in various countries also concluded the overuse of PPIs at both primary and tertiary level.<sup>19</sup> According to a study conducted in United Kingdom, PPIs were prescribed inappropriately up to 60.4 %. A similar study conducted at a tertiary care hospital in Mexico found that 35.5 % patients received PPIs inappropriately.<sup>20</sup> Few studies also suggest that PPIs are the most overprescribed acid suppressing agents in health care settings.<sup>21,22</sup> Moreover, several other studies conducted on PPIs showed varied results for inappropriate use and overutilization of PPIs (40 % - 81 %) with a mean of 63 % targeting different age groups.<sup>23,24</sup>

### Limitations

Current study focused on only one hospital. A multi centered, metaphase study would show better results. It would add valuable data, if it is also evaluated that how many errors were intercepted before their occurring. Prescribing PPIs was equally prevalent hospitalized and ambulatory patients and used for prolonged periods (for 2 to 3 months) therefore, considering such patients for follow up and observing adverse effects in them, if any, would provide profound insight about over prescription and over utilization of PPIs. Therapeutic efficacy, safety and cost effectiveness of PPIs may be significantly increased by following the recommended guidelines and approved conditions.<sup>25,26</sup>

**Table 5.** Most Common Potential Drug-Drug Interactions Observed in Prescribed PPIs

Potentially interacting drug combinations prescribed	Number of cases, n (%)
Omeprazole + ciprofloxacin	47 (36.7 %)

Esomeprazole + clopidogrel	34 (26.6 %)
Esomeprazole + alprazolam	15 (11.7 %)
Esomeprazole + escitalopram	12 (3.9 %)
Dexamethasone + omeprazole	5 (3.1%)
Esomeprazole + digoxin	4 (3.1 %)
Esomeprazole + duloxetine	3 (2.3 %)
Fluconazole + esomeprazole	3 (2.3 %)
Omeprazole + tizanidine	2 (1.6 %)
Carbamazepine + pantoprazole	1 (0.8 %)
esomeprazole + midazolam	1 (0.8 %)
esomeprazole + clonazepam	1 (0.8 %)

### IV. CONCLUSION

Current study showed over prescription of PPIs in hospitalized and ambulatory patients leading to adverse effects and drug interactions. Apparently, Standard protocols for PPIs prescription were not properly followed. Our findings reflect the need for Interventions at health care settings to address those factors which cause PIM. An effective drug utilization review and reporting of prescription/medication errors is crucial intervention to be introduced and followed by hospitals. Efficient contribution of pharmacists is also required at various stages of therapeutic monitoring including prescriptions review for possible drug interactions and unapproved indications.

### ACKNOWLEDGMENT

This work was supported by the Department of Pharmacy, Kohat University of Science and Technology, Pakistan.

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