

*Original Article*

## Uses of Proton Pump Inhibitors and Their Prescribing Pattern among the Patients Attending the Out-Patient Department at a Tertiary Care Hospital in Bangladesh

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Received: January 31, 2019 Accepted: December 25, 2019

doi: <https://doi.org/10.3329/jemc.v10i1.45060>

### *Abstract*

**Background:** Proton pump inhibitors (PPIs) are one of the most frequently prescribed classes of drugs in the world in the treatment of peptic ulcer, dyspepsia and gastro-oesophageal reflux. **Objectives:** To determine demographic, clinical response and practice characteristics of PPIs among the patients attending the out-patient department of a tertiary care hospital. **Materials and Methods:** In this prospective observational study 100 patients attending the out-patient department and taking oral proton pump inhibitors (PPI) for different symptoms and duration were included. Patient's socio-demographic characteristics, PPI-related information (duration, frequency of use, doses and classes of PPIs) and symptomatic responses after taking PPI were noted. Drugs or diseases that influenced the intake of PPI were also recorded. Investigations done before or during PPI use and their findings were also noted. **Results:** Omeprazole (43%) and esomeprazole (35%) were the most frequently prescribed PPIs. Most of the patients (52%) were on PPI therapy for 1–3 months. Majority of the patients (72%) had taken PPIs on daily basis and 19% patients had taken irregularly or occasionally. Dosing frequency of PPIs prescribed were twice daily in most of the patients (77%). Sixty seven percent (67%) patients had taken PPI prescribed by doctors and 33% patients had taken PPI prescribed by non-doctors. Common indications for prescribing PPIs were heart burn (54%), upper abdominal pain/discomfort (38%) and bloating (33%). Symptoms reappeared after stopping the PPI in most of the patients (40%) and 35% patients had satisfactory relief of symptoms with PPI. **Conclusions:** Omeprazole and esomeprazole are the most frequently prescribed PPIs. Majority of the patients had taken PPIs on daily basis. In around one-third of the patients PPIs were prescribed by non-doctors. Common indications for prescribing PPIs were heart burn, upper abdominal pain/discomfort and bloating. Symptomatic responses varied after taking PPI and symptoms reappeared after stopping the PPI in most of the patients.

**Key words:** Proton pump inhibitors; Gastro-oesophageal reflux disease; Out-patient department

J Enam Med Col 2020; 10(1): 10–16

### **Introduction**

Proton pump inhibitors (PPIs) are one of the most frequently prescribed classes of drugs in the world because of their high level of efficacy with low toxicity.<sup>1</sup> Guidelines have been published related

to their use. The guidelines made the following recommendations on indications for prescribing PPIs: Patients with severe gastro-oesophageal reflux disease (GORD) symptoms or those with proven pathology

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(for example, oesophageal ulceration, Barrett's oesophagus) 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 GORD symptoms. Patients with documented duodenal or gastric ulcers should be tested for *H pylori* and treated with PPIs and antibiotics if the test is 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 uninvestigated 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 PPIs, but may be prescribed a short, low dose course provided there is regular review.<sup>2,3</sup>

From our experience, it was evident that many patients attending both out-patient and in-patient departments of the hospital were receiving regular PPI treatment for poorly defined reasons or for conditions where PPIs have not been shown to be useful. Such unapproved or inappropriate indications include nonspecific abdominal symptoms without acid-related features, co-prescription with aspirin, NSAIDs or corticosteroids in asymptomatic patients, but most often receiving a long term repeat prescription for a previous problem which had since resolved. Current evidence suggests PPIs are often overused.<sup>4-6</sup> In a general practice study in 1995, 10% of all patients on long-term acid suppression therapy were on PPIs. Furthermore, up to one-third of them took their drugs on a self-determined regimen rather than regularly.<sup>7</sup> While the use of intermittent H<sub>2</sub> receptor antagonists for symptom relief is considered acceptable, PPIs are prescribed in the expectation that they will be taken as continuous therapy. Although pressure remains on general practitioners (GPs) to prescribe 'appropriately',<sup>8</sup> there remains a lack of clinical data on the use of PPIs in practice.

PPIs are not without their side effects (diarrhoea, headache in up to 10%) and studies have linked the use of PPIs to an increased risk of community-acquired pneumonia, *C difficile* diarrhoea and

*Campylobacter jejuni* gastroenteritis.<sup>7-9</sup> PPIs also have interactions with many drugs and can occasionally cause severe adverse reactions such as hepatic, renal, skin, bone marrow toxicity and anaphylaxis.<sup>9,10</sup> These factors emphasise the importance of following well-constructed, evidence-based guidelines for prescribing PPIs.

We are lacking in data regarding use of PPIs and their prescribing pattern among our population. So this observational study was designed to find out the use of PPIs by our patients and prescribing pattern of PPIs by our physicians. Aims of our study are to determine demographic, clinical and practice characteristics such as PPI classes, duration of uses, dosing frequency and prescriber information among the patients attending the out-patient department of a tertiary care hospital in Bangladesh and to see the symptomatic response while taking the PPIs.

## Materials and Methods

This prospective observational study was performed in the department of Gastroenterology and Internal Medicine of Enam Medical College & Hospital over a period from June 2017 to February 2018. One hundred patients were included in this study. Patients who attended the out-patient department and were taking oral proton pump inhibitors (PPI) for different symptoms and duration were included in this study. The study was carried out after obtaining the consent from the hospital authority and patients. Patients above 18 years old, prescribed and currently taking oral PPI and patients willing to participate in the study were included. Patients not willing to participate in the study and with insufficiently recorded data were excluded from this study. Patient's socio-demographic characteristics were considered first. PPI-related information including current use, duration and frequency of doses, classes of PPIs, prescriber's information and perceived benefits that is symptomatic responses after taking PPI were noted. Symptoms or disease conditions for which patient was taking PPI were recorded. Associated co-morbid conditions or drugs that influenced PPI intake were also recorded. Upper GI endoscopy, ultrasonogram of abdomen and their findings were also noted for those patients who had done these investigations before or during PPI use.

## Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data were entered into a database and were verified by a second independent person. Quantitative or numerical data were presented as mean±SD and categorical data as percentage and numbers.

## Results

### *Socio-demographic features*

One hundred selected patients were included in this study; among them 54% were male and 46% were female; their mean age was  $44.61 \pm 15.46$  years and 67% were married, 29% single, 3% widows and 1% was divorced. Regarding occupations, 29% were house-wives, 13% farmers, 17% businessmen, 16% service holders, 6% day laborers, 18% students and 1% was from other occupation. They had various educational backgrounds, but mostly graduate (30%)

and HSC level (22%). Regarding monthly family income, in 1% it was <10,000 taka, in 22% 10000 to 20000 taka, in 57% 20001 to 40000 taka and in 20% it was >40,000 taka. Among 100 patients, 58% were non-smokers, 33% were smokers and 9% were ex-smokers. Fifty seven patients drank supplied water and 43 patients tube well water. Majority of the patients (65%) used to take their meals regularly, 22% often ate fried meals from outside and 13% patients often ate fried and spicy meals made at home. Eighty six percent (86%) patients had used pucca latrine and 14% used semi-pucca latrine.

### *Proton pump inhibitors use-related information*

Hundred patients were taking different proton pump inhibitors (PPI) for treatment of various symptoms or conditions. PPI use-related information is shown in Table I. Omeprazole (43%) and esomeprazole (35%) are the most frequently prescribed PPIs class. Most of the patients (52%) were on PPIs therapy for 1–3

Table I: PPI use-related information (N=100)

Features	Description	Frequency	Percentage
Duration of PPI use	<1 month	20	20
	1–3 months	52	52
	4–6 months	10	10
	7–12 months	10	10
	>12 months	8	8
Prescribed classes of PPI	Omeprazole	43	43
	Esomeprazole	35	35
	Rabeprazole	11	11
	Pantoprazole	8	8
	Lansoprazole	3	3
Frequency of PPI use (continuous or non-continuous)	PPI taken on daily basis	72	72
	Two to three times/week	9	9
	Irregularly or occasionally	19	19
Dosing frequency of PPIs prescribed	Once daily	20	20
	Twice daily	77	77
	Thrice daily	3	3
PPI prescribed by	Doctors	67	67
	Non-doctors (pharmacy staff, village doctors or OTC)	33	33
Symptomatic response with PPIs	No change of symptoms	17	17
	Symptoms reappeared after stopping PPI	40	40
	Satisfactory relief of symptoms	35	35
	Feeling of cure	8	8

Table II: Symptoms for which PPIs were prescribed

Description of symptoms or conditions	Frequency	Percentage
Heart burn	54	54
Abdominal pain and discomfort	38	38
Abdominal bloating	33	33
Anorexia	23	23
Nausea	19	19
Vomiting	10	10
Early satiety	10	10
Haematemesis	7	7
Intestinal perforation and surgical repair	3	3
Eradication of <i>H. pylori</i>	10	10

Table III: Findings of upper GI endoscopy and ultrasonography of abdomen

Investigations	Description	Frequency	Percentage
Endoscopy of upper GIT (n=45)	Peptic ulcer disease	14	14
	Gastric erosions	8	8
	Reflux oesophagitis	5	5
	Oesophageal varices	3	3
	Normal findings	15	15
Ultrasonogram of abdomen (n=89)	Normal findings	80	80
	Liver and pancreatico-biliary disease	9	9

months, 20% patients were on less than one month, 10% patients were on 4–6 months, 10% patients were on 7 to 12 months and 8% patients were on more than 12 months. Majority of the patients (72%) had taken PPIs on daily basis and 19% patients had taken irregularly or occasionally. Dosing frequency of PPIs prescribed were once daily in 20% patients and twice daily in 77% patients. Sixty seven percent patients had taken PPI prescribed by doctors and 33% patients had taken PPI prescribed by non-doctors. Symptomatic responses after taking PPI were variable. Symptoms reappeared after stopping the PPI in 40% patients and 35% patients got satisfactory relief.

#### *Symptoms analysis*

Symptoms or conditions for which PPI were prescribed are shown in Table II. Most patients (54%) presented with heart burn followed by upper abdominal pain and discomfort (38%), abdominal bloating (33%), anorexia (23%), nausea (19%), vomiting (10%) and early satiety (10%). Most of the patients had multiple presenting complaints.

Drugs taken with PPI were NSAIDs (10 patients), aspirin (9 patients) and steroid (3 patients). Associated co-morbid diseases were ischaemic heart disease (IHD) (9 patients), rheumatic disease (12 patients), chronic liver disease (3 patients), pancreatico-biliary disease (6 patients), bronchial asthma (4 patients) and renal disease (3 patients).

Among 100 patients upper GI endoscopy was done in 45 patients and ultrasonogram of abdomen was done in 89 patients. Findings of upper GI endoscopy and ultrasonography of abdomen are shown in Table III.

#### **Discussion**

PPIs were introduced in the 1980s and rapidly became some of the bestselling medicines of all time. They inhibit gastric acid secretion through blockade of  $H^+/K^+$ -ATPases in parietal cells, and are highly effective for treating peptic ulcer, dyspepsia, gastro-oesophageal reflux and prophylaxis against non-steroidal anti-inflammatory drugs (NSAIDs).<sup>11</sup> For most of the conditions they are only intended for short-term use and are rarely required beyond four to

eight weeks. In a few conditions (for example, severe Barrett's oesophagus, gastrinoma and eosinophilic oesophagitis) protracted courses may be required.<sup>12</sup>

The American College of Gastroenterologists 2013 Guideline recommends PPI therapy for 8 weeks initially after which the PPI should be discontinued in most patients and the need for maintenance therapy should be assessed. If long-term PPI maintenance therapy is required, the lowest effective dose should be used, which can include reducing medication to on-demand or intermittent PPI use.<sup>13</sup> Singh et al<sup>14</sup> showed that majority of patients (48%) were taking PPIs therapy for 1–3 months, 32% patients were on less than one month, 16% patients were on 6 months to one year and only 4% patients were on more than one year. In our study we found that majority of patients (52%) were on PPIs therapy for 1–3 months, 20% patients were on less than one month, 10% patients were on PPIs for 4 months to 6 months, 10% patients were on PPIs for 7 to 12 months and 8% patients were on for more than 12 months.

Five classes of PPIs are currently available worldwide. These are omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole. The clinical efficacy of omeprazole 20 mg was well-studied and efficacy of other PPIs was compared to omeprazole. Generally speaking, omeprazole, lansoprazole, pantoprazole and rabeprazole have similar efficacy for healing the acid-related diseases.<sup>15</sup> All studies related to esomeprazole demonstrated that esomeprazole 40 mg once daily is superior to all other PPIs at standard doses in terms of achieving higher 24-hour median intra-gastric pH and the number of patients achieving intra-gastric pH  $\geq 4.0$  for at least 12 hours per day.<sup>16</sup> Study by Singh et al<sup>14</sup> showed that PPIs are prescribed by physicians in following sequence — omeprazole (48%) > pantoprazole (28%) > rabeprazole (12%) > esomeprazole (8%) > lansoprazole (4%).<sup>14</sup> Our study shows that omeprazole was prescribed in 43% patients followed by esomeprazole in 35% patients, rabeprazole in 11% patients, pantoprazole in 8% patients and lansoprazole in 3% patients.

There are different regimens by which patients may choose to take PPIs that may be grouped broadly into two categories: continuous and noncontinuous. Continuous therapy is the traditional once-daily (or greater) administration that is used to achieve the

initial relief of symptoms and/or healing of erosions and to maintain remission. Noncontinuous therapy encompasses several strategies including on-demand, intermittent, and scheduled non-daily therapy.<sup>17-19</sup> Hungin et al<sup>20</sup> reported survey responses concerning compliance with medication from 175 patients prescribed PPIs for greater than one year. Although 71% of respondents reported taking PPIs on a daily basis, 16% took their medications in “most days” and 13% took them “sometimes”. Our study showed that 72% patients had taken PPI on daily basis, 9% patients had used PPI two to three times in a week and 19% patients had taken PPI irregularly or occasionally.

In this study assessment of dosing frequency of ingested PPIs revealed that 77% patients had taken PPIs twice daily, 20% once daily and 3% patients had taken thrice daily. Velu et al<sup>21</sup> showed that among 144 prescriptions of pantoprazole, 95 prescriptions advised twice daily dosing of pantoprazole and 49 prescriptions advised once daily dosing of pantoprazole. As per FDA guidelines twice daily dosing of PPI is inappropriate, once daily dosing is sufficient to produce desired effects. Thus, twice daily dosing of PPI in the study was changed to once daily dosing through necessary intervention with a physician.

Proton pump inhibitors (PPIs) are available as over-the-counter (OTC) drugs and many patients treat themselves. Of the 1959 patients surveyed by Sheikh et al<sup>22</sup> 61% who obtained over-the-counter PPIs were not using them properly. On the other hand, when the primary care physician prescribed the PPI, proper use went up to 47%. When a GI specialist prescribed the PPI that number increased up to 71%. In our study 67% patients had taken PPI prescribed by doctors and 33% patients had taken PPI prescribed by non-doctors (OTC, pharmacy staff, village doctors). We collected information by interviewing the patients, but did not survey the prescriptions.

This study revealed that 54% patients presented with heart burn followed by upper abdominal pain and discomfort (38%), abdominal bloating (33%), anorexia (23%), nausea (19%), vomiting (10%), and early satiety (10%). After taking PPI, symptomatic responses were variable. No change of symptoms occurred in 17 patients, 40 patients getting some relief of symptoms while on PPI but symptoms reappeared

after stopping PPI; satisfactory relief of symptoms occurred in 35 patients and feeling of cure was reported by 8 patients.

Possible drug contributors to dyspepsia include nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents, calcium channel blockers, nitrates, theophyllines and bisphosphonates.<sup>23</sup> Chronic use of aspirin and other NSAIDs may provoke dyspeptic symptoms in up to 20% cases, but the occurrence of dyspepsia correlates poorly with the presence of an ulcer.<sup>24</sup> This study demonstrates co-prescription of NSAIDs with PPI in 10 patients, aspirin with PPI in 9 patients and steroid with PPI in 3 patients. A review should be conducted to consider whether still these have any indication or could be substituted. Where PPIs are prescribed, the lowest effective dose should be used for the shortest possible duration. The indications and intended durations should be clearly documented and communicated to the patients.<sup>23</sup>

The common rationale for long-term PPI use is prophylaxis when receiving anti-platelet agents or NSAIDs. Most guidelines suggest this is only required for high-risk patients, specifically those aged over 65 years, with a history of peptic ulcer disease or upper gastrointestinal haemorrhage or taking multiple medicines that augment gastrointestinal adverse effects.<sup>25</sup> In this study, 10% patients were taking PPIs for 4 months to 6 months, 10% patients for 7 to 12 months and 8% patients for more than 12 months. Reason for long-term PPI use was prophylaxis with antiplatelet agents or NSAIDs or maintenance therapy for GORD. Patients on long-term therapy should be reviewed at least annually. Substitution of PPIs with antacid or alginate therapy or H<sub>2</sub> receptor antagonists can also be considered.

Endoscopy before any therapy is still considered as the diagnostic gold standard for patients with an upper gastrointestinal disorder. Endoscopy allows direct recognition of organic causes of dyspepsia such as peptic ulcer, erosive oesophagitis, or malignancy.<sup>26</sup> Abdominal ultrasonography can be used to rule out liver and pancreatico-biliary disease. In this study, upper GI endoscopy was done only in 45 patients. Among them 14 patients had peptic ulcer disease, 8 patients had gastric erosions, five patients had reflux oesophagitis, 3 patients had varices and 15 patients had normal endoscopic finding. Ultrasonogram of

abdomen was done in 89 patients. Eighty patients had normal finding and nine patients had evidence of liver and pancreatico-biliary disease.

Omeprazole and esomeprazole were the most frequently prescribed PPIs in this study. Majority of the patients had taken PPIs on daily basis with twice daily dosing for 1 to 3 months. PPIs were usually prescribed by doctors, but 33% prescribers were non-doctors. Indications for prescribing PPIs were heart burn, upper abdominal pain/discomfort and bloating. Symptomatic responses varied after taking PPI and symptoms reappeared after stopping the PPI in most of the patients.

Prescribing of PPIs has skyrocketed over the past decade. These drugs can be effective and are principally intended for short-term use but these are often not discontinued. There is clear and consistent evidence of overprescribing as clinicians overestimate benefits and underestimate harms associated with substantial costs. Measures should be taken to educate prescribers on appropriate indications and durations for PPI use, provide a degree of stewardship, and facilitate long-term users in de-escalating therapy.

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