A Study on the Prescription Trend of Proton Pump Inhibitors in Major Divisions of Bangladesh

**Md. Mamunur Rashid[1], Jesmin Sultana[2], Afsana Jahan[1],
Mohammad Saifuddin[3] and Md. Selim Reza[1]**

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka
Dhaka-1000, Bangladesh
[2]Department of Business Administration, University of Asia Pacific
Dhaka-1215, Bangladesh
[3]Department of Mathematics and Statistics, Bangladesh University of Business and Technology
Dhaka-1216, Bangladesh

Abstract

The objective of this study is to investigate the prescription pattern of proton pump inhibitors (PPIs) in association with patients' age, gender and type of hospital visited (government or private), location of the hospital and doctors' specialty in major divisions of Bangladesh. The secondary objective of this study was to analyze the current market size, share and growth of PPIs in the antiulcer drug market. A cross-sectional survey of drug prescriptions was done at hospitals and clinics (private practices) between April 2021 to June 2021 of **7** divisions in Bangladesh. A total of 386 prescriptions, containing 2354 medicines, from 21 districts/areas of 7 divisions in Bangladesh were reviewed to determine the trend of prescribing PPIs. Market data of PPIs were collected from a secondary source (IQVIA). The data collected from the survey were tabulated, analyzed and graphically presented using Microsoft Office Excel 2016. Collected data were entered into the SPSS19.0 statistical software "R" and analyzed. Prescribed antiulcer drugs included Esomeprazole (70.2%), Rabeprazole (7.8%), Omeprazole (4.7%), Dexlansoprazole (4.4%), Pantoprazole (3.1%), and Lansoprazole (0.3%); and 9.3% of collected prescriptions had no anti-ulcerant. There was no association between gender and PPIs prescribed, nor across the type of hospital visited. Only the regression coefficient relating to the patient's age is statistically significant ($\beta=0.01$, $p<0.05$) in overall drug consumption. Along with nonspecific explanations, there were twelve specific reasons for prescribing antiulcer drug generics where the majority of the cases were attributed to NSAID-induced acidity (36%).

Key words: Proton pump inhibitors, prescription trend, regression co-efficient.

Introduction

Proton pump inhibitors (PPIs) are frequently prescribed worldwide as it is the most effective class of drugs to suppress gastric acid secretion (Wolfe *et al.*, 2000; Hálfdánarson *et al.*, 2018). Patients suffering from acid-peptic illnesses such as gastroesophageal reflux disease, peptic ulcer disease and nonsteroidal anti-inflammatory drug-induced gastropathy have all benefited from proton pump inhibitors (Hálfdánarson   *et al.*, 2018). Proton pump inhibitors are generally have few negative effects and few significant medication interactions (Welage *et al.*,

2000). PPIs are considered a major advance in the treatment of acid-peptic diseases and with the ban of Ranitidine the widely prescribed H_2 blocker in 2020, their use is on the rise (Vanderhoff *et al.*, 2002; Dasukil *et al.* 2021).

The National Institute for Health and Clinical Excellence (NICE) published its guidelines on proton pump inhibitors in 2000 where the appropriate use of acute and long-term use of these drugs are relatively selective and limited (Bashford *et al.*, 1998; Forgacs   *et al.*, 2008). Despite the limited prescribing recommendation,

worldwide PPI usage, both prescription and OTC are on the rise due to many contributing factors (Bashford *et al.*, 1998; Fass *et al.*, 2005). The situation is quite similar in Bangladesh as well. It is a country of almost 170 million people with a progressive pharmaceuticals sector that is mostly driven by antiulcer drugs (Arafat *et al.* , 2015; Andalib *et al.*, 2016; Arafat, 2016a; Arafat *et al.*, 2016b, Arafat *et al.*, 2016c, Arafat, 2016d). From June 2020 to June 2021, the pharma market of Bangladesh touched a whopping 276 billion BDT milestone with 18.7% growth, according to IQVIA, a health information technology and clinical research organization (IQVIA 2021, June). 13% share of this pharma market is consists of antiulcer drugs bringing about sales of 37 billion BDT yearly (IQVIA 2021, June). Almost 98% of total antiulcer drug sales come from PPIs (market size 36.36 billion BDT) (IQVIA 2021, June).

But a growing concern of these high values is the inappropriate use of these PPIs. According to a few studies in general care and emergency settings, PPIs are often administered for indications where there are no clear indications or their use provides little benefit (Heidelbaugh *et al.* 2012) . PPIs are commonly prescribed to hospitalized patients, often inappropriately, and these drugs are often continued by primary care physicians after discharge (Sehgal *et al.* 2014). Following both suitable and incorrect prescriptions, the persistence rate of PPI medication is fairly high (62% and 71%, respectively) (Parente *et al.* 2003). Other than that physiological factors of patients, external factors related to the geographical area, national guidelines, promotional focus of the pharmaceutical companies and doctors' profile can influence the choice of PPI prescribed (Cho *et al.* 2010). The attitude of general practitioners toward maintaining or terminating PPIs is influenced by their degree of expertise, opinions of hospital physicians' competence, and the threshold for prescribing in hospitals (Wermeling *et al.* 2014).

In this study, we aimed to statistically analyze the association between the prescription patterns of PPIs with patients' age, gender and type of hospital visited (government or private), location of the hospital and doctors' specialty in major divisions of Bangladesh. The secondary objective of this study was to explore the current market size, share and growth of PPIs in the antiulcer drug market.

Materials and Methods

Study settings: The cross-sectional prospective field survey was conducted directly reviewing the prescription from patients prescribed by physicians between April to June, 2021 in different hospital and private clinics of seven major districts in Bangladesh. The survey mainly employed prescription oriented field study. The information gathered from prescriptions are patients' age, sex, diagnosis, prescribed generic with brand names, prescribers' degree, location of practice, specialty.

Study design: A total of 386 samples of precriptions were selected via random sampling method. Such sampling method was followed to obtain a better and no-biased pattern of prescription as it varies in hospital and private practice. (Inclusion/Exclusion Criteria). All the selected prescription contained 2354 medicines, which were reviewed to determine the prescribed anti-ulcerantants specially PPIs, cause of prescribing PPIs, patient's age and sex. Number of degree, specialty, location and type of chamber practice (outdoor or private practice) of physicians who prescribed those prescriptions were also tabulated against their respective prescriptions.

Statistical analysis: The data collected from the survey was tabulated, analyzed and graphically presented using Microsoft Office Excel 2016. Collected data were entered into the SPSS19.0 statistical software "R" (A language and environment for statistical computing. R Foundation for Statistical Computing) and analyzed (R version 4.0.3) (Team 2013).

Ethical consideration: We obtained physicians & patient's permission before taking required information from the prescriptions of these patients. They were made aware of all of the ethical considerations and were given assurances regarding the confidentiality of their data in the process. The study was exempted from the written informed consent as we did not use name, address or any personal identification information. Moreover the data collected from the prescriptions were de-identified. We also contacted the authority of IQVIA Bangladesh through mailing and received consent to use their data for purly educational purposes.

Results and Discussion

Preferred generics for prescribed proton pump inhibitors: Around 70% of the prescribed PPIs were Esomeprazole (n=271), followed by 7.3% Rabeprazole (n=30), 4.7% Omeprazole (n=18), 4.4% Daxlansoprazole (n=17), 3.1% Pantoprazole and 0.3% Lansoprazole. 9.3% of the prescription didin't have any anti-ulcerant (Table 1).

Table 1. Percentages of prescribed PPIs

Proton pump inhibitors	Percentages (Number of precipiton)
Esomeprazole	70.4% (271)
Rabeprazole	7.8% (30)
Omeprazole	4.7% (18)
Dexlansoprazole	4.4% (17)
Pantoprazole	3.1% (12)
Lansoprazole	0.3% (1)
Without any anti-ulcerants	9.4% (36)
Total	**100%** (385)

Anti-ulcerants prescribed pattern in different divisions: The rate of esomeprazole prescriptions was highest in all anti-ulcerants categories across all divisions. Rabeprazole was the second most commonly prescribed anti-ulcerant generic in most of the divisions. Lansoprazole and Famotidine were the least prescribed anti-ulcerants in Bangladesh (Figure 1).

Association between gender and prescribed anti-ulcerant generics: No correlation between gender and the PPIs prescribed was found upon doing Fisher's Exact test. (Figure 2). In both male and female patients, the prescribed anti-ulcerative generic pattern was nearly same. The prescription pattern of PPIs was nearly identical in both male and female patients.
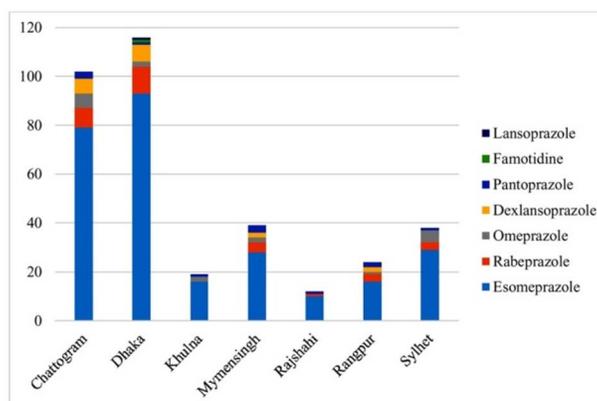

Figure 1. Frequencies and types of anti-ulcerant prescribed in different divisions.
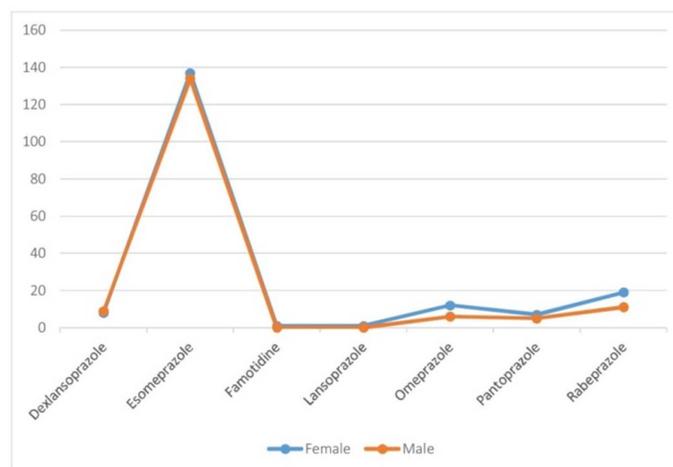

Figure 2. Prescription pattern of anti-ulcerant generics between male and female patients. *Fisher's Exact test: p= 0.7905, n=350, (No association between gender and drug generic).*

Association between hospital types and prescribed anti-ulcerant generic: There is no association between hospital types (clinic/private and government) and the anti-ulcerant generic prescribed, according to data acquired through prescriptions (Figure 3). In both clinics/private and government hospitals, the prescription anti-ulcerative generic pattern was nearly identical. In both types of hospitals (clinic/private and government), Esomeprazole prescriptions were high.

Association between doctors' specialties and percentages of prescribed PPIs: Of the 386 prescriptions, 16 different types of doctors' specializations were identified, with the majority of specialties doctors' first choice being Esomeprazole (77.4%) as an anti-ulcerant (Table 2).
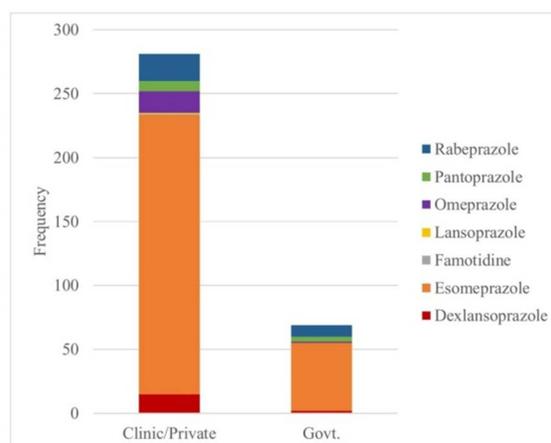

Figure 3. Frequency of the prescribed anti-ulcerant generic in clinics/private and government hospitals. *Fisher's Exact test: p=0. 4424, n=350 (No association between hospital and drug generic).*

Table 2. Doctors specialty wise prescribed anti-ulcerants percentages.

	Dexlanso-prazole	Esome-prazole	Lansopra-zole	Omepra-zole	Pantopra-zole	Rabepra-zole	Grand total
General physician	58.8%	53.5%	0.0%	44.4%	58.3%	60.0%	54.0%
Medicine	17.6%	17.7%	0.0%	33.3%	0.0%	10.0%	17.2%
Orthopaedic	17.6%	7.0%	0.0%	11.1%	25.0%	6.7%	7.5%
Gynecologist and obstetrics	5.9%	4.4%	100.0%	0.0%	0.0%	10.0%	5.2%
Paramedical	0.0%	4.1%	0.0%	0.0%	0.0%	3.3%	3.4%
Diabetologist	0.0%	3.3%	0.0%	5.6%	0.0%	3.3%	3.2%
Dentist	0.0%	1.5%	0.0%	5.6%	8.3%	3.3%	2.0%
ENT	0.0%	1.1%	0.0%	5.6%	0.0%	0.0%	1.1%
Gastroenterology, medicine	5.9%	1.1%	0.0%	0.0%	0.0%	0.0%	1.1%
Paediatrics	0.0%	1.8%	0.0%	0.0%	0.0%	3.3%	1.7%
Physical medicine	0.0%	0.7%	0.0%	0.0%	8.3%	0.0%	0.9%
Cardiologist	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.6%
Dermatologist	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.6%
Endocrinologist	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.6%
Surgeon	0.0%	0.0%	0.0%	0.0%	0.0%	3.3%	0.3%
Urologist	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.3%
Grand total	4.9%	77.9%	0.3%	5.2%	3.4%	8.6%	100.0%

Association of drug consumption with patients' demographic features: To understand the association of drug consumption with patients' demographic feature a multilevel linear modeling approach was undertaken . In this study, divisions were treated as clusters (J=4 clusters); within each clusters there are n_j patients. Drug consumptions (Drug.con) was measured simply by computing total number of drugs prescribed by physicians and regressed on explanatory variables, like patient sex (0=Female, 1=Male), hospital (0=Private, 1=Govt.) and

patient age. To capture the variance account for division, multilevel model modeling approach was applied. Since, there was no explanatory variable in division level, an intercept-only model was estimated (Model 1).

Model 1:

$$Drug.con_{ij} = \beta_{0j} + e_{ij} = \gamma_{00} + u_{0j} + e_{ij} \; ; \; i = 1,2,\ldots,n_j \; , j = 1,2,\ldots,J$$

With, $u_{0j} \sim N(0, \sigma_{u0}^2)$; $e_{ij} \sim N(0, \sigma_e^2)$

The intra-class correlation (ICC), denoted by ρ is $\frac{\sigma_{u0}^2}{\sigma_{u0}^2 + \sigma_e^2}$.

The model with explanatory variables is expressed as:

Model 2:

$$Drug.con_{ij} = \gamma_{00} + \gamma_{10}(Govt.hopital)_{ij} \\ + \gamma_{20}(Patient\ sex)_{ij} \\ + \gamma_{30}(Patient\ age)_{ij} + u_{0j} + e_{ij}$$

Table 3 presents the parameter estimates, standard errors and p-values for both models. In this table, Model 1 estimates the intercept as 5.11; the average drug consumption across all division and patients. The patient level estimated variance is 1.760 and division level estimated variance is 0.047. The intra-class correlation is 0.0258. Thus only 2.58% of the variance of drug consumption is at the division level, which is low.

Table 3. Intercept only model and model with explanatory variables (hospital types, patients sex and patient age).

	Model 1: intercept only			Model 2: Patient-level variable		
	B	SE	p-value	B	SE	p-value
Fixed effects						
Intercept	5.112	0.1372	0.000	4.789897	0.240204	0.000
Patient-level variable				-0.24239	0.202647	0.233
Hospital type				-0.11093	0.156096	0.478
Patient sex				0.01022	0.004566	0.026*
Patient age						
Random effects						
Division level variance (σ_{u0}^2)	0.04658			0.05578		
Patient-level variance (σ_e^2)	1.76017			1.73393		
Intra-class correlation (ρ)	0.0258					

Model 2 includes patients sex, type of hospital they visited and age. Only the regression coefficient of patients age is significant (β=0.01, p<0.05). This means for each year of age of the patients, the average drug consumption is expected to increase by 0.01; though the magnitude is very low. Neither patient sex nor they visit govt. or private hospital was not associated with drug consumption (p>0.05) (Table 3).

Reasons for prescribing PPIs: PPIs were prescribed in prescriptions for a number of reasons and conditions. There were twelve specific reasons as well as several non-specific causes for prescribing PPIs. After conducting a prescription analysis, we discovered that PPIs are most frequently prescribed for NSAIDs induced acidity (36%), followed by calcium carbonate (11%), iron supplement (10%) and multivitamin (9%) related acidity. A very high number of

prescription (14%) contained PPIs where the cause for prescribing remains unspecified (Figure 4).

Reasons and percentages of prescribed PPIs in different age groups: We split the ages of the 386 patients into three groups: under 20, 20 to below 40 and over 40. NSAIDs induced acidity was the most common reason for prescribing PPIs in different age groups, although iron supplements induced acidity was the major reason for prescribing PPIs in those under the age of 20 (25%). The 20 years to below 40 years -old age group had the highest percentages in the non-specific causes category. Overall, the percentage of people under the age of 20 years was much lower than the percentage of people in the other age groups (Table 4).
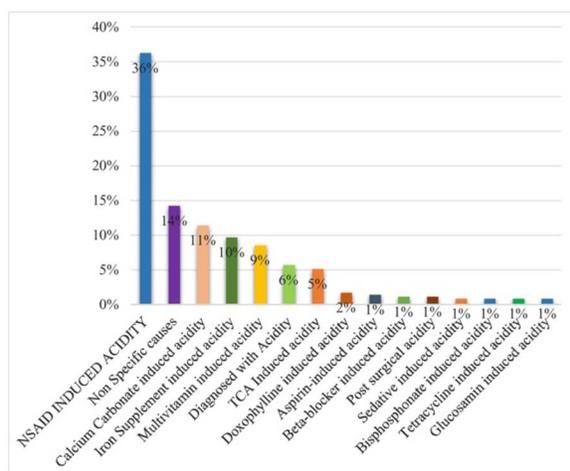
Figure 4. Causes and prescribed anti-ulcerants percentages (higher to lower %).

Frequency and prescription pattern of PPIs in different age group patients: Esomeprazole has been the primary prescribed PPIs among all age group (77%)

followed by Rabeprazole (9%) & Omeprazole (5%). Daxlansoprazole has been prescribed mostly to the patients below 20 years old.

Causes and percentages of prescribed anti-ulcerant in different gender: Comapring the causes of PPIs prescribed male vs. female it was identified that male patients had a higher percentage of NSAID-induced acidity (44% vs. 30%) whereas female patients had a higher percentage of iron-induced acidity (3% vs. 15%). Female patients compared to male also had a higher percentage of multivitamin and mineral-induced acidity (7% vs. 10%) (Table 6).

Market of PPIs in Bangladesh: According to IQVIA data, PPIs sales have been increasing in recent years, with sales of 25059 millions, 26884 millions, 29279 millions, 32361 millions and 36369 millions in 2017, 2018, 2019, 2020, and 2021, respectively (Figure 5).

Table 4. Causes wise prescribed anti-ulcerants percentages in different age groups.

Age group	NSAID induced acidity	Calcium carbonate induced acidity	Iron supplement induced acidity	TCA induced acidity	Multivitamin & minerals induced acidity	Diagnosed with acidity	Doxophylline induced acidity	Aspirin induced acidity	Sedative induced acidity	Beta-blocker induced acidity	Bisphosphonate induced acidity	Tetracycline induced acidity	Post-surgical acidity	Glucosamine induced acidity	Non specific causes	**Total**
Below 20	20%	5%	25%	0%	30%	10%	0%	0%	0%	0%	0%	0%	0%	0%	10%	**6%**
20 to below 40	33%	11%	14%	6%	8%	7%	0%	1%	0%	0%	1%	1%	1%	1%	17%	**46%**
40 or above	42%	13%	4%	5%	7%	4%	4%	2%	2%	1%	1%	1%	2%	1%	12%	**48%**
All age groups	36%	11%	10%	5%	9%	6%	2%	1%	1%	1%	1%	1%	1%	1%	14%	**100%**

5. Percentages of prescribed PPIs in different age groups.

Different age group	Esomeprazole	Rabeprazole	Omeprazole	Dexlansoprazole	Pantoprazole	Famotidine	Lansoprazole	Grand Total
Below 20	77%	8%	5%	**6%**	4%	0%	0%	8%
20 to below 40	77%	9%	6%	4%	3%	1%	1%	44%
40 or above	81%	7%	4%	4%	4%	0%	0%	49%
All age group	77%	9%	5%	5%	3%	0.3%	0.3%	100%

Table 6. Cause wise prescribed anti-ulcerants percentages in male and female.

Gender	NSAID induced acidity	Calcium carbonate induced acidity	Iron supplement induced acidity	TCA induced acidity	Multivitamin & minerals induced acidity	Diagnosed with acidity	Doxophylline induced acidity	Aspirin induced acidity	Sedative induced acidity	Beta-blocker induced acidity	Bisphosphonate induced acidity	Tetracycline induced acidity	Post-surgical acidity	Glucosamine induced acidity	Non specific causes	Total
Female	30%	11%	15%	5%	10%	7%	1%	1%	1%	1%	2%	2%	1%	1%	15%	57%
Male	44%	12%	3%	6%	7%	4%	3%	3%	1%	1%	0%	0%	2%	1%	14%	43%
Total	36%	11%	10%	5%	9%	6%	2%	1%	1%	1%	1%	1%	1%	1%	14%	100%

The PPIs market was positive in growth in recent years and the highest growth molecule was Dexlansoprazole and the Esomeprazole market growth was very much positive. On the other hand the Omeprazole molecule growth was negative in 2021 (Table 7).

Table 7. Proton pump inhibitors market analysis (IQVIA data June 2021).

Therapeutic class/molecule	Market size (Cr)_2021	Growth (%)
Proton pump inhibitors	3636	12
Esomeprazole	1958	20
Omeprazole	652	-9
Rabeprazole	458	9
Pantoprazole	403	16
Dexlansoprazole	143	38
Lansoprazole	22	10

Market trends of PPIs from 2017 to 2021: In recent years, the market trend of PPIs has been extremely obvious to say that the whole PPI market has been increasing very fast, with Esomeprazole playing a significant part with favourable growth (Figures 6 and 7).

Except for omeprazole, all of the PPIs (Esomeprazole, $(\beta = 0.01, p < 0.05)$ Rabeprazole, Pantoprazole, Lansoprazole, Dexlansoprazole) showed considerable positive growth. Omeprazole had a negative growth rate of 8.6%.
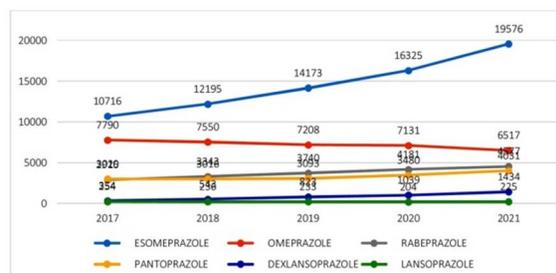

Figure 6. Market trend of PPIs in recent years (IQVIA data June 2021).

There were 2354 generics and 246 distinct kinds of prescribers out of 386 prescriptions. The biggest percentage of generics were different types of vitamin supplements (16.95%), Esomeprazole (10.54%), calcium carbonate (9.47%) and so on.
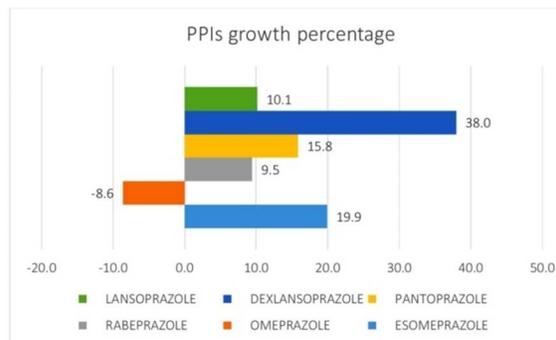

Figure 7. Growth percentages of PPIs in 2021 (IQVIA data June 2021).

The parameter estimates, standard errors and p-values for both models are presented in the table. Model 1 calculates the intercept as 5.11 in table 3.8, which is the average drug consumption across all divisions and patients. The estimated variance at the patient level is 1.760, while the estimated variance at the division level is 0.047. 0.0258 is the intra-class correlation. As a result, just 2.58 percent of the variation in drug consumption is seen at the division level, which is a small percentage. Patients' sex, the type of hospital they visited, and their age are all included in Model 2. Only the regression coefficient of patient age is significant. This suggests that for every year the patients get older, their average drug use is predicted to rise by 0.01; nonetheless, the magnitude is relatively small. Patient sex, as well as whether they visited a government or private hospital, had no effect on drug intake (p>0.05).

Only a few of the 386 cases had people under the age of 20 years who had been administered anti-ulcerants. Anti-ulcerants had been prescribed to the majority of the patients, who were above the age of 20 years. According to the collected prescriptions, approximately 8% of patients under the age of 20 years had gastrointestinal issues, while 44% of patients aged 20 years to under 40 years and 49% of patients over 40 years had gastrointestinal issues.

The majority of the cases were attributable to medication-induced acidity. The reason for NSAID-induced acidity (36%) was the most frequently recommended anti-ulcerant reason across all of the reasons investigated in this study, according to the findings. Anti-ulcerant prescription reasons such as 'Non Specific Causes' (14%) ranked second on the list of most often prescribed reasons.

In addition to the acidity caused by multivitamins and minerals, acidity has been identified as a problem. Acidity-inducing drugs, such as doxophylline and aspirin, as well as sedatives and beta-blockers, were discovered in the prescriptions. Acidity-inducing drugs, such as bisphosphonates and tetracyclines, as well as post-surgical acidity and glucosamine-inducing acidity, were also discovered in the prescriptions.

According to IQVIA data (June 2021), Esomeprazole accounted for 54% share of the total PPI market. Omeprazole came in second place, accounting for 18% share of the PPI market. Rabeprazole, Dexlansoprazole, Pantoprazole, and Lansoprazole each held 12%, 11%, 4%, and 1% share of the PPI market.

Conclusions

PPIs are widely prescribed especially over the age of 40 years mostly for drug induced acidity. However, they are also being used for disorders that do not usually require PPIs. The findings obtained from this small sample size, we were unable to conclude the differences in prescribing patterns between rural and urban areas. So, there is a scope for such comparative study in the future.

References

Andalib, A. and Arafat, S.M.Y. 2016. Practicing pattern of physicians in Bangladesh. *Int. J. Perceptions Public Health* **1**(1), 9-13.

Arafat, S.M.Y. 2016a. Doctor patient relationship: an untouched issue in Bangladesh. *Int. J. Psychiatry* **1**(1), 2.

Arafat, S.M.Y. and Ahmed, Z. 2016b. Medical representative in Bangladesh: a job with different pattern. *Int. J. Acad. Res. Manag. Business* **1**(1), 47-51.

Arafat, S.M.Y, Asad, S.M.H.A , Hasan, M.J., Ahmed, Z., Halder, K. and Rahman M.I. 2016c. Prescription modifying marketing factors: a survey among the clinicians in Bangladesh. *Int. J. Business Manag. Inv.* **5** (1), 46-48.

Arafat, S.M.Y. , Hussain, F., Alam, M.S., Rahman, M.I. and Asad, S.M.H.A. 2015. Job satisfaction among the medical representatives in Bangladesh. *Austral. J. Business Manag. Res.* **5**(1), 22-28.

Arafat, S.M.Y. 2016d. Anti-ulcerants: The driving force of the pharma market of Bangladesh. *Int. J. Percep. Public Health* 1(1), 1-2.

Bashford, J.N., Norwood, J. and Chapman, S.R. 1998. Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the general practice research database. *BMJ.* **317** (7156), 452-456.

Cho, Y. K., Choi, M.G., Lim, C.H., Nam, K.W., Chang, J.H., Park, J.M., Lee, I.S., Kim, S.W., Choi, K.Y. and Chung, I.S. 2010. Diagnostic value of the PPI test for detection of GERD in Korean patients and factors associated with PPI responsiveness. *Scand. J. Gastroenterol.* 45 (5), 533-539.

Dasukil, S., Verma, S., Routray, S., Arora, G. and Boyina, K.K. 2021. Ranitidine: Is its injunction a warning bell? *Indian J. Pharmacol.* **53** (1), 80-81.

Fass, R., Shapiro, M., Dekel, R. and Sewell, J. 2005. Systematic review: proton pump inhibitor failure in gastro oesophageal reflux disease–where next? *Aliment Pharmacol. Ther.* **22** (2), 79-94.

Forgacs, I. and Loganayagam, A. 2008. Overprescribing proton pump inhibitors. *BMJ.* **336,** 2-3.

Hálfdánarson, Ó. Ö., A. Pottegård, E. S. Björnsson, S. H. Lund, M. H. Ogmundsdottir, E. Steingrímsson, H. M. Ogmundsdottir and H. J. T. a. i. g. Zoega. 2018. Proton-pump inhibitors among adults: a nationwide drug-utilization study. *Ther. Adv. Gastroenterol.* **11**, 1–11.

Heidelbaugh, J. J., Kim, A.H., Chang, R. and Walker, P.C. 2012. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Ther. Adv. Gastroenterol.* **5** (4), 219-232.

IQVIA. 2021, June. IQVIA Pharmaceutical research data. *https://www.iqvia.com/.*

Parente, F., Cucino, C. and Porro, G.B. 2003. Treatment options for patients with Helicobacter pylori infection resistant to one or more eradication attempts. *Dig. Liver Dis.* **35** (8), 523-528.

Sehgal, V., Bajwa, S.J.S. and Bajaj, A. 2014. Clinical conundrums in management of hypothyroidism in critically ill geriatric patients. *Int. J. Endocr. Met.* **12**(1), e13759.

Vanderhoff, B. T. and Tahboub, R.M. 2002. Proton pump inhibitors: an update. *Am. Fam. Physician* **66** (2), 273-281.

Welage, L.S. and Berardi, R.R. 2000. Evaluation of omeprazole, lansoprazole, pantoprazole and rabeprazole in the treatment of acid-related diseases. *J. Am. Pharm. Assoc.* **40**(1), 52-62.

Wermeling, M., Himmel, W., Behrens, G. and Ahrens, D. 2014. Why do GPs continue inappropriate hospital prescriptions of proton pump inhibitors? A qualitative study. *Eur. J. Gen. Pract.* **20** (3), 174-180.

Wolfe, M. M. and G. J. G. Sachs. 2000. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease and stress-related erosive syndrome. *Gastroenterology* **118**(2), S9-31.