Assessment of proton-pump inhibitor use at a tertiary teaching hospital in Nigeria

Roland Nnaemeka Okoro¹, Kasim Abdullahi¹ and Dauda Ayuba Dayar²

Abstract
Background: Proton-pump inhibitor (PPI) is a widely used medication class globally. Because of its good safety profile, there is a huge likelihood of inappropriate use.
Objectives: To determine the prevalence of PPI use and indications, describe its pattern of usage, and identify factors associated with inappropriate prescriptions at a federal tertiary teaching hospital in Maiduguri, Nigeria.
Methods: PPI prescriptions were retrospectively assessed in the General Outpatients’ Department (GOPD) and Gastroenterology Unit (GITU) of a teaching hospital. Relevant data for the study were extracted from the patients' medical records. Chi-square or Fisher’s exact tests where appropriate were used to identify factors associated with inappropriate PPI prescriptions. A p < 0.05 was considered to be significant.
Results: PPIs were prescribed to 73.3% (220/300) of patients, while inappropriate prescriptions were noted in 91.4% (201/220) of these patients. Epigastric pain (49.5%) was the most common PPI indication, while omeprazole was the highest prescribed (53.4%). Nearly all inpatients (98.2%), those with epigastric pain (95.7%), and patients who were prescribed intravenous PPIs had more inappropriate PPI prescriptions compared to others.
Conclusion: This study revealed a high prevalence of PPI use and inappropriate prescriptions at the study hospital. As a result, these findings highlight the importance PPI-based stewardship program at the study hospital.

Keywords
Gastric acid–related diseases, guideline-recommended, inappropriate prescription, Nigeria, proton-pump inhibitor

Introduction
Proton-pump inhibitor (PPI) is a class of medication that significantly reduces stomach acid output. It works by binding irreversibly to the parietal cell’s H+/-K+-ATPase pump, which inhibits acid generation in most of the active pumps.¹ It is the most effective class of medication for treating both common and serious upper gastrointestinal problems. For example, peptic ulcer disease (PUD), esophagitis, epigastric pain, dyspepsia, and gastroesophageal reflux disease (GERD) can all be treated with PPI.²⁻⁴ It is also a significant component of the Helicobacter pylori eradication regimen,³ and can also be used to prevent upper gastrointestinal harm caused by non-steroidal anti-inflammatory drugs (NSAIDs).⁵ For most of these conditions, it is only meant to be used for a limited period of time and is rarely needed for more than 4–8 weeks.

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It is noteworthy that PPI has a strong safety track record,7 thus, they are routinely prescribed and used worldwide. Although emerging concerns regarding its long-term adverse effects call for greater caution when prescribing and using this medication class. The adverse effects of PPI therapy include increased risk of Clostridium difficile–associated diarrhea,8 Campylobacter-, Salmonella-, and Shigella-associated enteric infections,9 and fracture,10 deficiencies in iron, and vitamin B12 absorption.11,12 Others are hypomagnesemia,13 acute interstitial nephritis,14 chronic kidney disease,15 sub-acute cutaneous lupus erythematosus,16 and myocardial infarction.17

Despite the growing concerns about these adverse effects, PPI is often reported to be misused in several studies around the world.18–47 In addition, suspected upper gastrointestinal hemorrhage—receiving care at the surgery units, non-emergency room physicians, non-intensive care unit (ICU) admission,46 and the number of medications40—have been reported as significant factors associated with inappropriate PPI prescriptions.

There is an existence of vast international studies on PPI utilization, although, to the best of our knowledge, no such studies have been conducted in Africa, hence the need for this study. The aims of the study were to determine the prevalence of PPI use and indications, describe its pattern of usage, and identify factors associated with inappropriate PPI prescriptions.

Methods

Study design and setting

A retrospective, cross-sectional study was carried out in the General Outpatients’ Department (GOPD) and Gastroenterology Unit (GITU) of a tertiary teaching hospital in Maiduguri, Nigeria.

Inclusion and exclusion criteria

The study included patients aged 18 years and over who received care at the GOPD and GITU of the study hospital from 1 January to 31 December 2019. Conversely, patients who were less than 18 years and those who received care outside the GOPD and GITU of the study hospital during the year under review were excluded from the study.

Sample size calculation

The sample size for the study was calculated based on the formula developed by Yamane48 using a population size of 1000 (N) and a margin of error of 0.05 (e). Thus, the minimum sample size required for the study was 286 patients.

Ethical considerations

The Health Research and Ethics Committee of the study hospital granted approval (UMTH/REC/21/716) prior to data collection. Obtaining written informed consent from the patients whose medical records were selected and reviewed was waived by the Health Research and Ethics Committee of the study hospital. The confidentiality of patients’ information was maintained throughout the study duration.

Sampling

Systematic random sampling with sampling intervals of six and three were utilized to select patients’ medical records in the GOPD and GITU, respectively.

Data collection

Data collection lasted for 4 months (1 March to 30 June 2021). Data extracted from the patients’ medical records included patients’ socio-demographics, chronic diseases, PPI information (indications, route of administration, name, dose, frequency, and duration), and the number of medications per prescription.

Determination of appropriateness of PPI prescription

The latest Nigeria Standard Treatment Guidelines (NSTG)49 and the Essential Medicine Index (EMDEX)50 were used to assess for PPI prescriptions appropriateness. Prescriptions that fell short of guideline recommendations (Appendix 1) were considered inappropriate.

Data analysis

All data were initially entered into Microsoft Excel Spread Sheet 2010, cleaned, coded, and transferred into SPSS for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) for analysis. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean values ± standard deviation (SD). Chi-square or Fischer’s exact tests where appropriate were used to compare groups for categorical variables. A p < 0.05 was considered statistically significant.

Results

Socio-demographic and medical characteristics of the study population

Three hundred patients who received care at the GOPD and GITU of the study hospital were included in the study. The average age of the study population was 36.7 ± 13.8 years. The majority of the patients were females (64.4%), while
most of these patients were between the ages of 30 and 41 years. In addition, married patients (68.0%) and those of the Islamic faith (90.7%) constituted most of the study population, whereas the majority had no chronic diseases (93.0%) as presented in Table 1.

The overall prevalence of PPI use and indications in the study population

Overall, 80 (26.7%) patients did not use PPI, while 220 (73.3%) patients used PPI at different time points during the study period. The analysis of cases requiring PPI prescriptions revealed a total of 279 indications. Note this number is higher than 220 because some patients visited the hospital more than once during the year under review on account of gastric acid–related disorders. However, the analysis of individual indications showed that epigastric pain ranked first with 49.5% (138/279) followed by dyspepsia with 30.5% (85/279). Others were PUD (19.0%, 53/279), gastritis (0.7%, 2/279), and GERD (0.4%, 1/279).

The prescription patterns of PPI during the study period

Of the 1422 medications prescribed with an average of $3.94 \pm 1.76$ medications per patient at the study setting during the study period, 279 were PPIs with omeprazole ranking highest (53.4%) followed by rabeprazole (41.6%) as shown in Figure 1.
was initiated, indication, and route of administration. Significant proportions of inpatients, those who had epigastric pain, and those who received intravenous (IV) PPI had more inappropriate PPI prescriptions compared to their counterparts (Table 2).

Discussion

To the best of our knowledge, this is the first study of African origin to assess PPI use. Therefore, this study adds to the knowledge of the subject in Africa. Second, the inclusion of both outpatients and inpatients data makes this study unique and outstanding. This study revealed that the majority of patients who received care at the GOPD and GITU of the study hospital were prescribed PPI and most of these prescriptions were found to be inappropriate. Epigastric pain was noted as the main indication for PPI prescriptions, while omeprazole was the most common PPI prescribed during the study period. The analysis of the potential factors associated with inappropriate PPI prescriptions among the study population revealed inpatient, epigastric pain, and IV PPI as significant.

The high prevalence of PPI use noted in the present study demonstrates that PPI is among the most commonly used medication class in the study settings. This finding calls for caution to ensure both appropriate prescribing and use. This is important because overuse of PPI could cause adverse effects, such as increased COVID-19 severity and mortality, and adverse renal outcomes. Our result is comparable to 60% (33/55) found in a retrospective study of hospitalized patients in Ireland. Conversely, our result is inconsistent with 30.6% (232/758) prevalence reported by a prospective observational study of hospitalized patients in the Netherlands, whereas a retrospective analysis of inpatients records in Singapore showed a prevalence of 46.5% (477/1025). In Switzerland, a review of electronic medical records of adult patients revealed a little above average prevalence of 53.9% (97/180). The plausible reasons for the observed differences between our findings and that of previous studies could be due to differences in gastric acid–related disorder burden, physicians prescribing culture across countries, and variations in the study populations.

The analysis of the reasons for PPI use in our study population showed that epigastric pain and dyspepsia prevailed over others. This finding differed from that of some previous studies that found GERD and prophylaxis of anti-platelet/NSAIDs in Italy, and the prevention of medication-associated complications in the Netherlands. A similar French study reported GERD and dyspepsia as the leading PPI indications, whereas studies conducted in the United States (US) and Australia also reported GERD as the most common indication for PPI use. Also, similar studies conducted in Canada reported gastrointestinal condition and GERD, and receipt of anti-platelet/anticoagulant therapy or NSAIDs combined with two other established risk factors for upper gastrointestinal hemorrhage. The discrepancies observed between the results of these studies and our study could be due to differences in diets and acid-related disease burden across continents.

In the present study, the investigation of the prescribing patterns of PPI showed that omeprazole was the highest prescribed. The cost-effectiveness of omeprazole compared to other PPIs may account for its highest utilization in our study population. This is because the majority of the population in low- and middle-income countries, including Nigeria is poor and the purchase of medications is mainly out-of-pocket due to an abysmal low coverage of health insurance. Nevertheless, our finding is congruent with that of a US retrospective study that showed that most patients were also prescribed omeprazole. A similar study conducted in Shanghai, China also reported omeprazole as the most frequently prescribed PPI. In addition, a 4-year US retrospective review of the medical records and pharmacy prescription database also reported omeprazole as the highest-ranked PPI in 2007 and 2008. In contrast, the same US study reported that pantoprazole ranked highest in 2005 and 2006, while esomeprazole was reported in Ireland and Switzerland as the most frequently prescribed PPI. Differences in the drug formularies and physicians’ prescribing habits could be responsible for these variations in prescription patterns across countries.

The analysis of the present study data for appropriateness of PPI therapy revealed that an overwhelming proportion of patients (91.4%) received inappropriate PPI prescriptions during the study period. This finding is comparable to 60.0% in 162 older patients, 63.0% in 172 hospitalized adult patients, 63.6% in 302 older patients, 70.0% in 55 hospitalized patients, and 80.0% in 58 patients in

![Figure 3. The distribution of inappropriate PPI prescriptions identified during the study period (N=341). Note: Some PPI prescriptions had more than one problem.](image-url)
France,28 the United Arab Emirates (UAE),35 Spain,20 and Ireland,31,32 respectively. In Northern Cyprus, PPI (67.0%) was found as the most common inappropriate medication class prescribed.47 A similar US study reported that 695/876 (79.0%) patients in 2005, 627/763 (82.0%) patients in 2006, 441/562 (78.0%) patients in 2007, and 397/485 (82.0%) patients in 2008, respectively received PPI inappropriately.33 In Greece, an inappropriate PPI use prevalence of 84.0% (195/232 patients) was found.40 In addition, another US study revealed a much higher prevalence rate of inappropriate PPI use of 90.5% (13,589/25,850).39 Differences in countries’ PPI prescription policies and methods of assessing the prevalence of inappropriate PPI use could account for the different results got from these studies conducted in various countries.

The present study showed that all patients who were prescribed PPI had its guidelines-recommended indications. Nevertheless, the most frequent inappropriate PPI

| Variable                        | Inappropriate prescription | χ² or f | p-value |
|---------------------------------|----------------------------|---------|---------|
| Sex                             |                            |         |         |
| Female                          | 20 (10.6)                  | 169 (89.4) | 1.106  | 0.293  |
| Male                            | 6 (6.7)                    | 84 (93.3)  |        |        |
| Age group (years)               |                            |         |         |
| 18–29                           | 11 (12.5)                  | 77 (87.5)  | 2.237  | 0.684* |
| 30–41                           | 6 (6.6)                    | 85 (93.4)  |        |        |
| 42–53                           | 6 (10.4)                   | 52 (89.6)  |        |        |
| 54–65                           | 2 (6.5)                    | 29 (93.5)  |        |        |
| >65                             | 1 (9.1)                    | 10 (90.9)   |        |        |
| Initiation of PPI               |                            |         |         |
| During ambulatory care          | 25 (11.2)                  | 198 (88.8) | 4.705  | 0.036* |
| During hospitalization          | 1 (1.8)                    | 55 (98.2)   |        |        |
| Indication                      |                            |         |         |
| Epigastric pain                 | 6 (4.3)                    | 132 (95.7) | 16.721 | 0.001* |
| Dyspepsia                       | 7 (8.2)                    | 78 (91.8)   |        |        |
| Peptic ulcer disease            | 13 (24.5)                  | 40 (75.5)   |        |        |
| Gastritis                       | 0 (0.0)                    | 2 (100.0)   |        |        |
| Gastro esophageal disease       | 0 (0.0)                    | 1 (100.0)   |        |        |
| PPI                             |                            |         |         |
| Omeprazole                      | 18 (12.1)                  | 131 (87.9) | 3.124  | 0.305* |
| Rabeprazole                     | 7 (6.0)                    | 109 (94.0)  |        |        |
| Pantoprazole                     | 1 (11.1)                   | 8 (88.9)    |        |        |
| Esomeprazole                    | 0 (0.0)                    | 5 (100.0)   |        |        |
| PPI administration route        |                            |         |         |
| Intravenous                     | 0 (0.0)                    | 43 (100.0)  | 5.224  | 0.019* |
| Per oral                        | 26 (11.0)                  | 210 (89.0)  |        |        |
| Number of medications/prescriptions |                       |         |         |
| <5                              | 18 (9.7)                   | 168 (90.3) | 0.085  | 0.771  |
| ≥5                              | 8 (8.6)                    | 85 (91.4)   |        |        |

PPI: proton–pump inhibitor.
χ²: chi-Square test; f: Fisher’s exact test.
*Significant at 0.05.

France,28 the United Arab Emirates (UAE),35 Spain,20 and Ireland,31,32 respectively. In Northern Cyprus, PPI (67.0%) was found as the most common inappropriate medication class prescribed.67 A similar US study reported that 695/876 (79.0%) patients in 2005, 627/763 (82.0%) patients in 2006, 441/562 (78.0%) patients in 2007, and 397/485 (82.0%) patients in 2008, respectively received PPI inappropriately.33 In Greece, an inappropriate PPI use prevalence of 84.0% (195/232 patients) was found.40 In addition, another US study revealed a much higher prevalence rate of inappropriate PPI use of 90.5% (13,589/25,850) was found.40 These findings demonstrate that widespread use of PPI is associated with a high prevalence of inappropriate use in several countries.54,55 These findings underscore the need for country-specific educational interventions for prescribers as well as the general population to safeguard global health. In contrast, a much lower prevalence rate of 16% in 153 hospitalized adult patients was reported in Malaysia,36 whereas a prevalence of 43.2% (206/477 inpatients) was noted in Singapore.37 In the United Kingdom (UK), audits of medical inpatients revealed inappropriate PPI prescribing rates of 40.7%–54.0%.29,30 In Canada, inappropriate PPI prescriptions were found in 30.7% (267/871) and 46% (70/152) of patients, respectively;21,52 whereas another Canadian study reported a higher prevalence of inappropriate PPI prescriptions of 50% (13,589/25,850).39 Differences in countries’ PPI prescription policies and methods of assessing the prevalence of inappropriate PPI use could account for the different results got from these studies conducted in various countries.

The present study showed that all patients who were prescribed PPI had its guidelines-recommended indications. Nevertheless, the most frequent inappropriate PPI
prescription identified in this study was shorter than the guideline-recommended duration. Conversely, the most common cause of inappropriate PPI prescription reported in the UK, Ireland, the US, Italy, Jordan, the Netherlands, and France was no clear indication for PPI prescription, whereas dose higher than the guideline-recommended dose was reported in the Netherlands and untreated guideline-recommended indication was reported by other studies conducted in the Netherlands and Greece.

Furthermore, the analysis of factors that were associated with inappropriate PPI prescription in this study population revealed that a higher proportion of inpatients, those who had epigastric pain, and those that received IV PPI had more inappropriate prescriptions with significant differences. This result could be due to the majority of the inpatients and cases of epigastric pain being treated at a shorter than guideline-recommended duration. It is surprising that many inpatients included in this study did not continue their PPI medications with oral preparation after receiving the IV form. Despite hospitalization presenting a unique opportunity to address issues of inappropriate medication use, inappropriate PPI use observed during patients’ hospitalization continued on discharge even in the presence of guideline-recommended indications. These findings highlight the need for hospital ward-based pharmacists and frequent educational interventions among physicians attending to inpatients with gastric acid-related diseases at the study hospital to ensure appropriate prescriptions. In contrast, other similar studies identified the number of medications, suspected upper gastrointestinal hemorrhage, receiving care at the surgery units, non-emergency room physicians, and non-ICU admission as significant factors associated with inappropriate PPI prescriptions. Variations in the study settings and populations could be responsible for the observed disparities.

**Limitation**

The main limitation of this study was that the study was conducted in two units of a teaching hospital, therefore, our results might not be generalizable to other units of the study hospital, as well as other categories of hospitals, such as primary, secondary, non-teaching tertiary, and private hospitals. Another limitation was the retrospective design which may not reflect the current use of PPI at the study hospital.

**Conclusion**

This study found both a high prevalence of PPI use and inappropriate prescriptions in the study settings. The most frequent indication for PPI use was epigastric pain, while omeprazole was the highest utilized PPI. The significant factors associated with inappropriate PPI prescriptions were inpatients, epigastric pain, and IV PPI prescriptions. Thus, there is a need for the institution of a PPI-based stewardship program at the study hospital. Consequently, the clinical services of ward-based pharmacists are critical for its successful implementation. In addition, pharmacist-led educational interventions focusing on the identified significant factors of PPI misuse are also paramount to ensure appropriate prescriptions, thereby improving the quality of patient care at the study hospital.

**Author contributions**

R.N.O. has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Acquisition of data was done by K.A. Interpretation of the data was performed by D.A.D. Supervision was performed by R.N.O. and D.A.D. Drafting of the manuscript was performed by R.N.O. Study concept, design, and critical revision of the manuscript for important intellectual content were performed by all authors. All authors read and approved the final manuscript.

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**Availability of data and materials**

The data set generated and/or analyzed during this study is available from the corresponding author upon reasonable request.

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**Appendix 1**

**Recommended indications for PPI use and their dosage regimen.**

| Indications | Proton-pump inhibitor recommended dosage regimen |
|-------------|-------------------------------------------------|
|             | Esomeprazole | Omeprazole | Pantoprazole | Rabeprazole |
| 1. Gastroesophageal reflux disease (GERD) | 20 mg once daily × 4 weeks | 20 mg once daily × 4 weeks | 20–80 mg once daily × 4–8 weeks | 20 mg once daily × 4–8 weeks |
| 2. *H. pylori* eradication | 20 mg twice daily × 7 days (triple therapy regimen) | 20 mg twice daily × 7 days (triple therapy regimen) | 40 mg twice daily × 7 days (triple therapy regimen) | 20 mg twice daily × 7 days (triple therapy regimen) |
| 3. Epigastric pain/ dyspepsia | 20 mg once daily × 4 weeks | 20 mg once daily × 4 weeks | 20–80 mg once daily × 4–8 weeks | 20 mg once daily × 4–8 weeks |
| 4. Peptic ulcer disease | 20 mg once daily × 2–8 weeks | 40–80 mg once daily × 2–8 weeks | 40–80 mg once daily × 2–8 weeks | 10–20 mg once daily × 4 weeks |
| 5. Gastritis | 20 mg once daily as required | – | – | – |