



The prevalence of inappropriate use of proton pump inhibitors and its associated side effects among Basrah city population

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ABSTRACT

One of the most often prescribed medications is PPIs (proton pump inhibitors). Because of an increase in proton pump inhibitors that may be purchased without a prescription, their use is probably even higher than previously thought. Regrettably, Proton pump inhibitors are frequently used off-label for prolonged durations of time. In the last two decades, there has been an upsurge in the use of PPIs, raising concerns about their potential side effects. Numerous research have looked into the connection between infection and PPI use, notably pneumonia and *Clostridium difficile*. It is hypothesized that PPI use alters the gastrointestinal microbiota, which creates an environment that is favorable for the growth of these infections. It has been reported by at least one study that dementia risk may be increased by long-term PPI use. When prescribing any medication, drug interactions are a crucial but frequently ignored factor. One of the latest concerns about the use of PPI is its role in progression or development of chronic renal disease.

Thus, This study's aim was to evaluate the prevalence of improper use of proton pump inhibitors and to estimate the link between the use of PPI and its associated severe side effects given growing worries regarding PPI misuse in the general population.

Methodology and Study design: This study is a questionnaire-based descriptive study, carried out from November 2021 to April 2022, the data collected from 406 individuals (83 males and 323 females), average of age (6-58) who were taken any type of PPI or not taken any one in Basrah city, the second questionnaire was specific for pharmacist in Basra (71) which composed (12) questions. The ethics committee of college of pharmacy university of Basrah approved the protocol.

Result: The questionnaire was collect and responses of 406 participant were analyzed 196(48.3%) of them were used PPI, most of them 153(78.1%) were females. Also the large number of PPI user 171(87.2%) were unhealthy with different comorbid illnesses. omeprazole was the most popular choice among the study's participants, took by 110 (56.1%). 77 (39.3%), 21(29.6%) were taken their treatment by Physician prescription as shown on individual and pharmacist questionnaire respectively, and 54 (27.6%), 21(29.6%) treated by pharmacist prescription. In addition the results showed large number of participants were on self-treating without prescription 44 (22.4%), 29(40.8%) as shown on individual and pharmacist questionnaire respectively. Headaches affected about 30 (15.3%) of PPI user participants, and nausea affected about 40 (20.4%). In addition to 27 (13.8%) cases of abdominal pain, 30 (15.3%) cases of constipation, 20 (10.2%) cases of diarrhea, 5 (2.6%) cases of skin rash, and

The prevalence of inappropriate use of proton pump inhibitors and its associated side effects among Basrah city population

13 (6.6%) cases of muscle spasm and arrhythmia. In addition, some participants have kidney illness 10 (5.1%) or hematuria (2, 1%) and (2, 1%) bone fracture however 111 (56.6%), of them do not have any symptoms.

Conclusion: It's necessary to carefully balance the benefits and risks of long-term PPI use, notably in young patients, whose treated with these drugs may continue for many years. Although these medications have a number of known system-related side effects, for most patients with appropriate short-term causes, PPIs' benefits are expected to outweigh their dangers.

Keywords: *Proton pump inhibitors, Inappropriate use, self-treating, adverse effects*

INTRODUCTION

Proton pump inhibitors (PPIs) were first used in clinical practice approximately 30 years ago, revolutionizing the treatment of acid peptic illness. Nowadays, PPIs are one of the drugs that are still most frequently prescribed worldwide. Additionally, the prescription of PPIs as a class of drug is frequently done for unclear reasons or in cases when PPIs have not been proven to be advantageous.^(1,2)

There are a number of PPIs that are available, including Dexlansoprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole. For the short-term therapy of GERD, omeprazole, esomeprazole, and lansoprazole are readily available over-the-counter medications.⁽³⁾

These substances are prodrugs that have an acid-resistant enteric coating to prevent them from being prematurely degraded by gastric acid. In the alkaline duodenum, the covering is peeled off and the prodrug, a weak basic, is absorbed and delivered to the parietal cell. There, it is transformed into the active substance and creates a strong covalent link with the enzyme H⁺/K⁺-ATPase. The enzyme must regenerate for approximately 18 hours, and during this time acid secretion is inhibited.⁽⁴⁾

PPIs are more effective than H₂ antagonists at reducing production of acid and curing ulcers. Therefore, they are the favorable medications for treating and preventing stress ulcers, as well as for treating erosive esophagitis, GERD, active duodenal ulcers, as well as pathologic hypersecretory disorders (for instance, the Zollinger-Ellison syndrome, where a gastrin-

producing tumor results in excessive HCl secretion).

PPIs can be used to treat or prevent NSAID-induced ulcers and lower the risk of bleeding from ulcers brought on by aspirin and other NSAIDs. Lastly, they are combined with antibiotic protocols to eliminate *H. pylori*.⁽⁴⁾

Due to the stomach's pH being altered by PPIs, they may interact with a wide range of drugs, also due to different PPIs are inhibit CYP2C19 to varying degrees, which may potentially alter the absorption, activation and binding of medicines such as: ketoconazole, itraconazole and iron.⁽⁵⁾ Because of the potential for clopidogrel's effectiveness to be reduced, the FDA strongly cautioned against combining omeprazole and esomeprazole with it.⁽⁶⁾ As a consequence to that, PPIs and clopidogrel shouldn't be used together because there may be an elevated risk of cardiovascular events. Instead, utilize a different PPI with less potent CYP2C19 inhibition, like Pantoprazole.⁽⁶⁾ Also. The overutilization and the improper use of PPIs is linked to adverse results The most common Adverse effects are those result from Short term use like headache, diarrhea, constipation and abdominal pain.⁽⁷⁾

And those associated with long term use like increased incidence of *C difficile*.⁽⁸⁾ Evidence also suggests that PPIs may affect immune cell activity, raising the danger of infectious consequences that could encourage bacterial proliferation and result in pneumonia and tracheal colonization.⁽⁹⁾

The increased use of PPIs for a longer period of time has led to increased concerns about the adverse renal event and the risk of kidney disease.⁽¹⁰⁾

According to a warning the US Food and Drug Administration (FDA) issued in September 2012 regarding osteoporosis and the usage of PPIs stating that “several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine”. Patients who got long-term PPI therapy and high PPI dosage, which is defined as several daily doses, had an elevated risk of fracture (a year or longer). Patients should utilize the smallest dose and shortest course of PPI medication necessary to treat their disease.(11)

The considerable prevalence of PPI prescriptions that are not supported by evidence has been linked to the high rate of acid-related disease, high level of efficacy, PPIs have a comparatively mild toxicity profile, Along with being widely accessible over-the-counter as well as Cheap.(12) The suggested period of PPI treatment is only 2–12 weeks for causes including GERD, Helicobacter pylori infection, and peptic ulcer disease. However, indefinite PPI therapy may be appropriate for some disorders like severe esophagitis and Barrett's esophagus.(13) Patients frequently receive PPI medication indefinitely without being reevaluated for symptom relief or improvement in an ambulatory setting, despite the fact that there are no indications for doing so. This increases the likelihood of polypharmacy, which raises the risk of unpleasant reactions and medication mistakes. Despite the fact that PPI misuse is widespread in the ambulatory setting, a previous report on improper PPI prescription rates showed a rate of 36.1%, highly inconstant cessation success rates (14%–64%) have been reported, demonstrating difficulties in stopping these drugs after starting them.(14-19)

So the aim of this study was to evaluate the prevalence of inappropriate use of proton pump inhibitors and to estimate the link between the use of PPI and its associated severe side effects given increasing concerns about the PPI overuse in the general population.

Methodology and Study design

This is a descriptive study that relies on questionnaires, implemented during the months

of November 2021 through April 2022, a total of 406 people (83 males and 323 females) in the city of Basrah, ranging in age from 16 to 58, were surveyed regarding their use of or lack thereof of PPIs, The second survey, made up of 12 questions, was designed for pharmacists in Basra, where there are 71 of them. The protocol has been authorized by the university of Basrah's college of pharmacy's ethics committee.

Data collection

A validated questionnaire was used to collect data on participants' clinical and demographic characteristics, including age, sex, education level, medical history, current medications, and prior use of proton pump inhibitors (PPIs).

Data on PPI usage, such as the drug name, dose, frequency, duration, and indication; PPI-related adverse effects, such as dizziness, rash, headache and gastrointestinal symptoms like abdominal pain, nausea, flatulence, diarrhea and constipation; and the possibility that PPIs raise the risk of Clostridium difficile infection of the colon. The risk of hip, wrist, or spine fractures due to osteoporosis may be increased with high doses and prolonged use (one year or more). Studies showing that vitamin B12 (cyanocobalamin) absorption is decreased with continued use were also gathered.

Members of certain Facebook groups are polled via a link posted in the groups, with responses collected via Google forms. In order to reduce the likelihood of missing data, participants were instructed to complete the entire online questionnaire before moving on to the next section. After answering all of the questions, the participant is instructed to hit the "submit" button, at which point the survey is uploaded to a shared drive. A total of (406 people and 71 pharmacists) are to be studied as samples.

Statistical analysis

In order to analyze the results of the online survey, the collected data will be loaded into Excel and then transferred to SPSS version 28. Measures of output will be presented as frequency and percentages, whereas measures of

The prevalence of inappropriate use of proton pump inhibitors and its associated side effects among Basrah city population

outcomes will be shown as means and standard deviations (SD). To detect the significant difference between the different mean level of PPI used with or without prescription and their disadvantages among patients, chi square test was used; P-value of 0.05 or less is considered statistically significant.

Aim of the study

To estimate the prevalence of inappropriate use of proton pump inhibitors and to report adverse consequences associated with chronic PPI therapy.

RESULTS

Demographic information (such as age, sex, education level, medical history, medications used, and previous PPI use) was gathered and examined through the questionnaire.

Table 1 provides summary demographic information. In total, there were 323 (or 79.6%) female participants and 83 (or 20.4%) male ones. 196(48.3%) of the users reported using PPI while 210 (51.7%) reported not doing so. The current study included 29 (7.1%) smokers and 377 (92.9%) nonsmokers. Approximately 167 (41.1%) of the participants were healthy, while 239 (58.9%) were with multiple comorbidities. (Table 1.).

TABLE 1: Demographic data (n=406)

Variables	Number (%)
Sex	
Male	83(20.4 %)
Female	323 (79.6%)
Smoking	
Non-Smoked	29(7.1%)
Smoked	377(92.9%)
Using PPI	
User	196(48.3%)
Non user	210(51.7%)
Level of education	
Illiterate	1 (0.2%)
Primary school	2 (0.5%)
Intermediate school	27 (6.7%)
Secondary school	114 (28.1%)
BA	247(60.8%)
High Education	15(3.7%)
Health status	
Healthy	167(41.1%)
Un healthy	239(58.9%)

Table (2) compared the demographic data between PPI user and non PPI user between participant groups, there were no statistically significant gender-based differences in PPI usage, smoking, educational status, statistically difference were found between healthy and

unhealthy participants, among the non PPI user there were (142 (67.7%) healthy participants and (68 (32.4%) were unhealthy. While the majority of the PPI user (87.2%) were unhealthy with different comorbid illness the p value of the differences was (0.001).

TABLE 2: Comparisons of demographic data and Health Status of participants

Variable	Not use any PPI (n=210)		Use PPI (n=196)		X ² ; P-value
	N	(%)	N	(%)	
Sex					0.47
Male	40	19%	43	21.9%	
Female	170	81%	153	78.1%	
Smoking					0.247
Non-Smoked	198	94.3	179	91.3	
Smoked	12	5.7	17	8.7	
Educational Status					0.56
Illiterate	0	0%	1	0.5%	
Primary School	1	0.5%	1	0.5%	
Intermediate School	19	9%	8	4%	
Secondary School	68	32.4%	46	23.5%	
Bachelor	114	54.3%	133	67.9%	
High Education	8	3.8%	7	3.6%	
Health Status					0.001
Healthy	142	67.6%	25	12.8%	
Unhealthy	68	32.4%	171	87.2%	

Table(3). Presents the health status and the comorbid illnesses among the PPI user. Among them, there were 39(19.9%), 30(15.3%), 26(13.3%), 23(11.7%), 16(8.2%), 14(7.1%), 7(3.6%), 6(3.1%), 4(2%), 2(1%), 2(1%), and

2(1%) reported having peptic ulcer, joint disease, diabetes, hypertension, Heart Diseases, asthma, Allergy, Irritable Bowel Disease, Osteoporosis, Migrain, Renal Failure, Hyperthyroidism, respectively.

TABLE 3: Comorbid illnesses among PPI user

Disease	Number (196)	%
peptic ulcer	39	19.9%
joint disease	30	15.3%
Diabetes	26	13.3%
Hypertension	23	11.7%
Heart Diseases	16	8.2%
Asthma	14	7.1%
Allergy	7	3.6%
Irritable Bowel Disease	6	3.1%
Osteoporosis	4	2%
Migrain	2	1%
Renal Failure	2	1%
Hyperthyroidism	2	1%
Healthy	25	12.8

Figure 1 displays the respondents' prevalence of PPI use. According to the data, omeprazole was the most popular choice among the study's participants, with 110 (56.1%), followed by

lansoprazole (23 (11.7%)), and rabeprazole (23 (11.7%)). Dexlansoprazole 15 and Pantoprazole 18 account for 7.7% and 9.2%, respectively. 7(3.6%) esomeprazole.

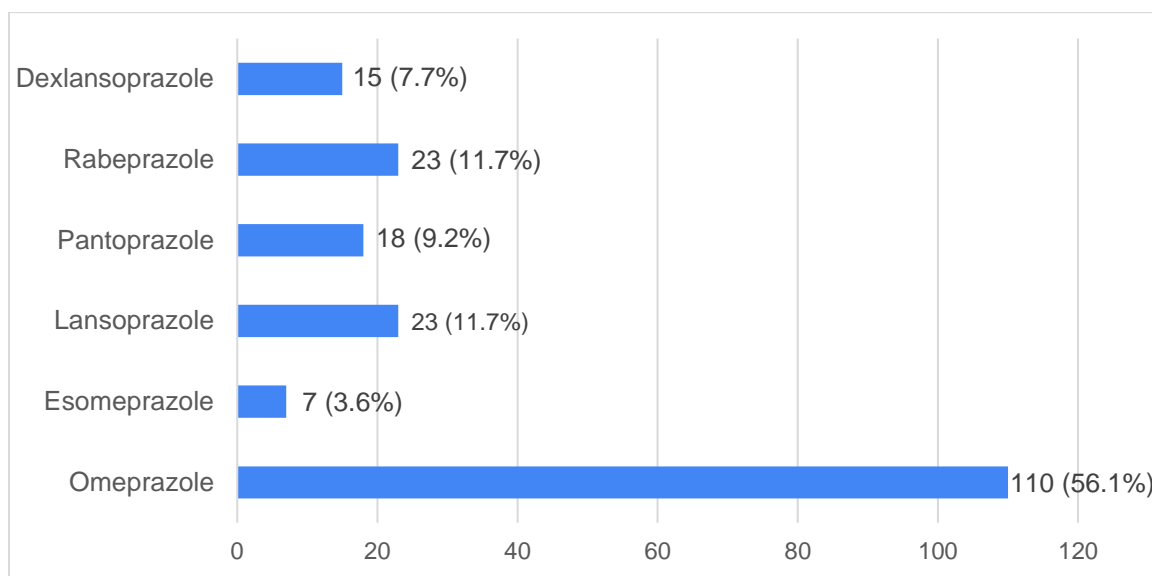


FIGURE 1: The common used PPI among the participants.

Figure 2 and Figure 3: According to the results of the individual and pharmacist questionnaires, the majority of study's respondents (77 or 39.3%) were treated by a physician's prescription, while a smaller percentage (54 or 27.6%) were treated by a pharmacist's prescription (44 or 22.4%). In addition, the data showed that a sizable proportion of participants were engaging in self-treating without a prescription, with 44 (22.4%) of individuals and 63 (26.1%) of pharmacists reporting such behavior.

The study resulted that large number of participants 77 (39.3%), 21 (29.6%) were taken their treatment by Physician prescription as shown on individual and pharmacist questionnaire respectively, and 54 (27.6%), 21 (29.6%) treated by pharmacist prescription. In addition the results showed large number of participants were on self-treating without prescription 44 (22.4%), 29 (40.8%) as shown on individual and pharmacist questionnaire respectively

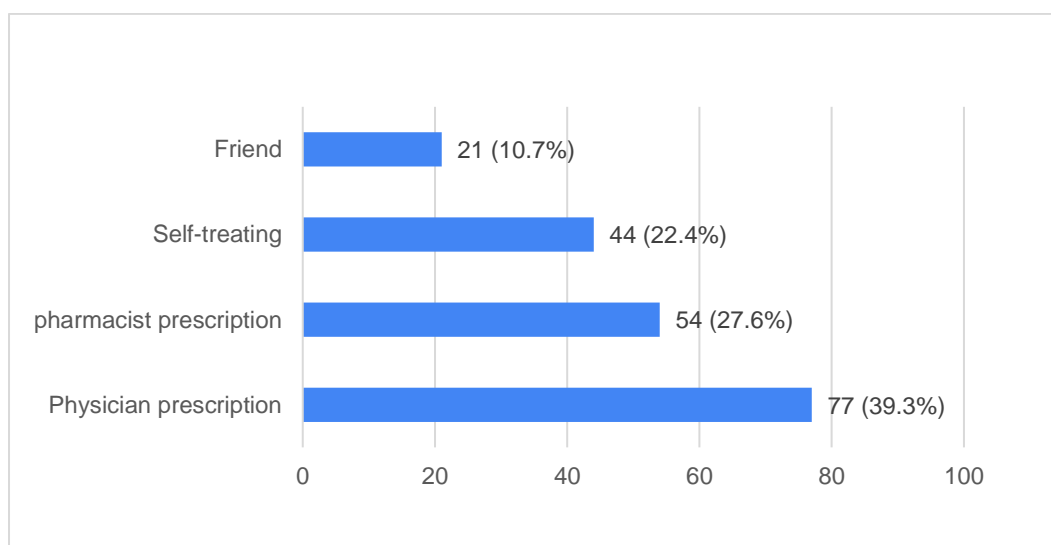


FIGURE 2: Non-prescription proton-pump inhibitors for self-treating from individual questionnaires

The prevalence of inappropriate use of proton pump inhibitors and its associated side effects among Basrah city population

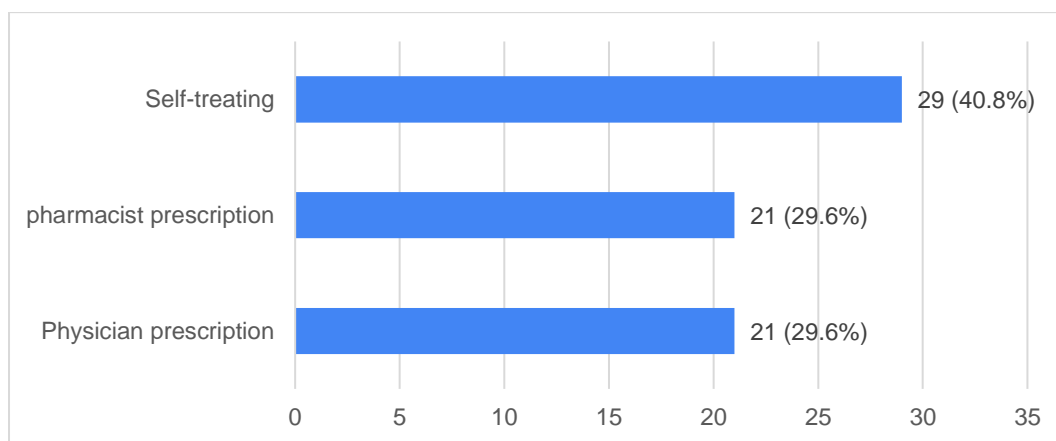


FIGURE 3: Non-prescription proton-pump inhibitors for self-treating from pharmacist questionnaires

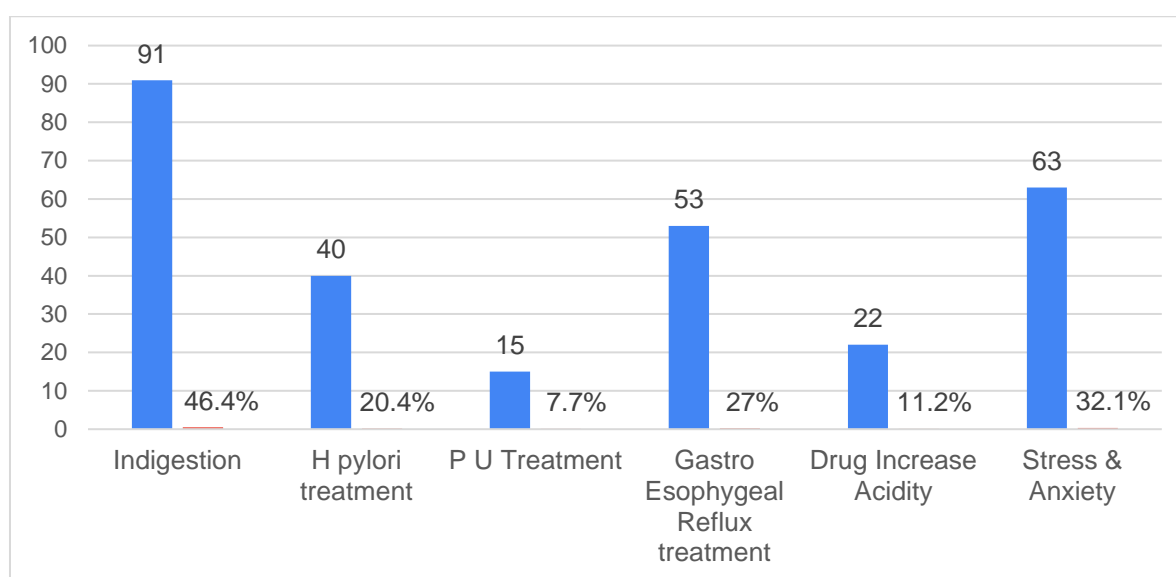


FIGURE 4: Indication for using PPI

*One patient can use the drug for more than one indication

**Percentage among PPI users

Figure (4). Large numbers of participants using PPI for a variety of indications were revealed by the individual questionnaire data, with 91 (46.4%) of participants using PPI for indigestion, 63 (32.1%) using PPI to relieve stress and anxiety, 53 (27%) having gastro esophageal reflux diseases, and only 15 (7.7%) using PPI for ulcer. In addition, 22 (11.2%) of participants taking PPIs were doing so because they were taking other medications known to raise stomach acidity, and 40 (20.4%) were taking PPIs for treatment of H. pylori.

Table 4 displays the demographic information. Headaches affected about 30 (15.3%) of PPI user participants, and nausea affected about 40 (20.4%). In addition to 27 (13.8%) cases of abdominal pain, 30 (15.3%) cases of constipation, 20 (10.2%) cases of diarrhea, 5 (2.6%) cases of skin rash, and 13 (6.6%) cases of muscle spasm and arrhythmia. In addition, some participants have kidney illness (10, 5.1%) or hematuria (2, 1%) and (2, 1%) bone fracture however (111, 56.6%), of them do not have any symptoms.

TABLE 4: Adverse effects associated with PPI use.

Adverse effect of PPI	Number (%)
Headache	30 (15.3%)
Nausea	40(20.4%)
Abdominal pain	27(13.8%)
Constipation	30(15.3%)
Diarrhea	20(10.2%)
Rash	5(2.6%)
Muscle spasms	13(6.6%)
arrhythmia	13(6.6%)
Pneumonia	0(0.0%)
Kidney disease	10(5.1%)
Hematemesis	2(1%)
Bone Fractures	2(1%)
Without symptom	

*one participant could suffer from more than one side effect

**Percentage among PPI users

Fig. 5. According to the study's pharmacist questionnaire, an overwhelming majority of the participants (58, or 81.7% of the total) were either self-treating without a prescription or using

PPIs incorrectly. Thirteen patients (18.3 percent) followed their doctor's orders and used PPI as directed. Incorrect dosage and timing were also identified as causes of poor outcomes.

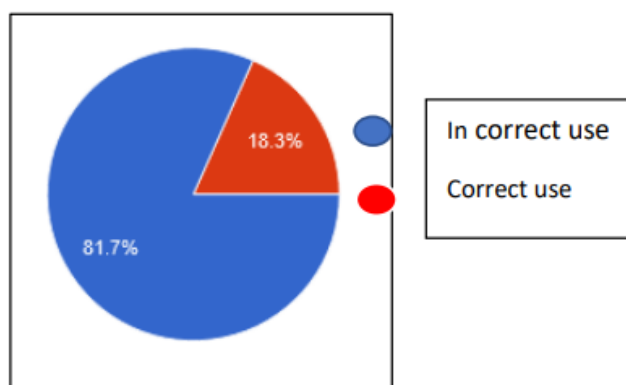


FIGURE 5: The rate of inappropriate Use of Proton Pump Inhibitors

DISCUSSION

Acid-related diseases can be treated well with proton pump inhibitors (PPIs); however, these drugs are sometimes prescribed inappropriately and might have unwanted side effects.(20) This study's purpose was to determine how commonplace PPI usage is in the urban population of Basrah. In this study, PPI use was detected in 48.3% of the sample population, most

of them were women. (Table1, 2). Women were shown to be substantially more likely to receive a prescription for a proton pump inhibitor (PPI) than males, despite the fact that men are more prone to be diagnosed with gastric ulcer disease Somewhat related commentary has been made before Reasonable hypotheses include Women tend to visit doctors more frequently, and overprescribing is a possibility.(21)

High rates of PPI using were found among unhealthy participants with chronic diseases in the present study 171 (87%), p value was 0.001.(Table2) Analysis revealed a link between the high comorbid burden of chronic conditions and PPI misuse, which are indicators of gastrointestinal disorders.(22) so that required the concomitant use of other drugs. Long-term administration of non-steroidal anti-inflammatory medicines (NSAIDs), anti-platelet therapies, anticoagulants, and *Helicobacter pylori* infection are all recognized causes of peptic ulcer bleeding.(23) Therefore PPIs are frequently prescribed as gastroprotective medications.(24, 25, 26, 27, 28) However, controlling for concomitant diseases and assessing the clinical condition of the patient is more efficient ways to manage the polypharmacy side effects on the stomach as well as give the patient an ideal and affordable plan of therapy than long-term PPI use.(29)

As can be seen in figure(4), several of the people who took part in a recent study had been given a prescription for an antacid to treat indigestion, symptoms of GERD and PPI use for *H. pylori* infection.As PPIs are typically prescribed for patients suffering with acid reflux, GERD, or a peptic ulcer.(1,30)

Proton pumps on stomach parietal cells are inhibited by proton pump inhibitors.(30) Thus, it is more effective than histamine receptor-2 (H2) blockers in lowering acid production.(31)

As evidenced by the most recent meta-analyses, 32.1% of participants in this study also reported using PPI for stress and anxiety,(32, 33) which favors using SUP with PPI or H2RA for stress ulcer prophylaxis. 22 (11.2%) of the PPI user reported using PPI to treat side effects of drug increased acidity.Figure (4).as most PPI user participants had a history of chronic disease, like joint disease, asthma, heart diseases.Table(3).This might be connected to medications like analgesics ,steroids and other drugs which are linked to stomach ulcers, PPIs are frequently recommended as gastro protective drugs, which may help to explain this.(34, 35)

According to other researches (1, 36, 37) Omeprazole is one of the most commonly used

PPIs. The present study's findings, omeprazole (used by 110 people, or 56.1%) was most frequently, then lansoprazole (23) 11.7% and rabeprazole (23) 11.7% were utilized. Along with Dexlansoprazole 15 (7.7%), Pantoprazole 18 (9.2%) and 7(3.6%) Esomeprazole, (figure 1).

The participants most frequently complained of headaches and nausea, which were both reported by 30 (15.3%) and 40 (20.4%) of the participants, respectively. Along with diarrhea 20 (10.2%), skin rash 5 (2.6%), muscle spasms 27 (13.8%), constipation 30 (15.3%), and arrhythmia 13 (6.6%). Additionally, some participants experience hematemesis 2 (1%), bone fractures 2 (1%), and kidney illness 10 (5.1%) Table 4. But alarmingly, the results of the current study revealed that a significant portion of individuals who use PPIs rely on their information or guidance from their family members (figures 2, 3) While there is growing evidence linking the use of PPIs for longer than one year to a considerably higher risk of pelvic fracture as well as another osteoporotic fractures, in addition to the majority of studies demonstrating a clear dose and period of response connection.(31)

Additionally, improper PPI use is linked to major adverse health effects, such as pneumonia, osteoporosis, colon cancer, and a vitamin B-12 shortage.(7) Additionally, there are worries that their judicial usage can postpone the diagnosis of stomach malignancy.(38)

The pharmacist may be a great help by asking pertinent questions regarding the patient's symptoms, determining the best course of therapy, and spotting any alarm features or uncommon symptoms that would call for further medical evaluation. After deciding on a course of therapy, the pharmacist can give detailed advice on how to take the medication safely. The pharmacist's responsibilities also include checking in to see if the problem has returned, fielding inquiries regarding side effects, establishing monitoring parameters, and advising on when medical attention is necessary. Patients with heartburn can rely heavily on their local pharmacist for guidance in self-care decision making and education on how to utilize medications safely and effectively.

CONCLUSIONS

Particular attention should be paid to weighing the hazards and advantages of PPI use for a prolonged period in young patients, whose therapy with these medicines may last for many years. While PPIs have several system-related adverse effects, for most patients with valid short-term reasons, the benefits are likely to exceed the risks.

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