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Drug Performance Indicators, Cons and Pros Upon Extended use or Misuse of Proton Pump Inhibitors

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Abstract **Background:** Proton Pump Inhibitors (PPIs) have progressively replaced the traditional therapies for acid-related diseases and are effectively used in treatment and prophylaxis from peptic ulcer disease and Gastro Esophageal Reflux Disease (GERD). **Aim:** Evaluation of the indicators, cons and pros upon extended use or misuse of PPIs among Saudi and Egyptian patients. **Methods:** A cross-sectional survey was distributed throughout Saudi and Egyptian patients who received PPIs, interviewed (Face to Face) and asked questions according to well-designed questionnaire about benefits and adverse effects upon short and long-term use of PPIs. Saudi patients were chosen from university of Ha'il Clinic, KSA and healthcare centers, while Egyptian patients were from different private medical centers, Egypt between October 2024 to December 2024. Data was collected and statistically analyzed using SPSS software (Inc, Chicago, IL, USA, version 25). **Results:** The mean of participant ages in years (35.99±1.46 Saudis vs. 45.65±3.16 Egyptians). About 46.2% of Saudi participants vs. 67.9% of Egyptian are working in the medical field and low percentage of Saudis who used PPI according to medical consultant are 24.3% vs. Egyptians 68.2%. High percentage of Egyptian participants using PPIs for prophylaxis from peptic ulcers mainly due to long term usage of NSAIDs followed treatment of heartburn. While high percentage of Saudi participants using PPI for treatment of GERD more than Egyptians. High percentages of Egyptian patients completed the course of PPI compared to Saudis and the causes of uncompletion in Saudis due to disappearance of symptoms and presence of side effects more than Egyptians (p-value<0.05). Mild side effects due to using PPI was higher percentage among Egyptian vs. Saudi participants (p-value<0.05). The most predominant side effects were bloating followed by headache then nausea, abdominal pain and diarrhea. Severe side effects due to long-term PPIs usage was higher among Egyptian vs. Saudi participants but not significantly different. The most predominant side effect was osteoporosis followed by increased risk of fractures, iron deficiency anemia, then mineral deficiency. On the other hand, Saudi participants suffered more from deterioration of kidney functions, increase risk of gastroenteritis, dementia and gastric cancer than Egyptian. **Conclusion:** The long-term hazards, such as kidney disease, fractures and infections, require careful thought and constant monitoring, even if the short-term side effects are usually modest and controllable. Such risks are further boosted by PPIs misuse and over-prescription, which highlights the importance to follow guidelines based on evidence for its usage. Relatively high number of participants developed severe side effects like osteoporosis and increased risk of fractures which are not common in young age group. This indicates that physicians, pharmacists and patients should be cautious on prescribing or taking PPIs even if the patient within young age. To ensure secure and effective use of these important medications in the future, patients and healthcare professionals need to work together and the risks of using long-term PPI must be weighed against the benefits.

Key Words Proton Pump Inhibitors (PPIs), Benefits, Short-Term & Long-Term Side Effects, Saudia Arabia, Egypt

INTRODUCTION

Since 1989 omeprazole, Proton Pump Inhibitors (PPIs) have progressively replaced the traditional therapies for acid-related diseases. PPIs effectively suppress acid secretion and play an important role in peptic ulcer disease and Gastro Esophageal Reflux Disease (GERD). PPIs also used as protectant agents in stress ulcer disease and along with the use of NSAIDs [1]. Usage of PPIs has grown extremely prevalent among primary care doctors and is now a staple component of the gastroenterologist's repertoire [2].

Numerous studies in Saudi Arabia and other regions worldwide highlighted the irrational recommendation of PPIs by medicine providers without genuine medical indication, which is likely to be associated with iatrogenic problems [3,4].

Adverse effects are either short-term that gives immediate effect or long term that shows effect over an expanded period. In the short-term, PPIs are generally well-tolerated but a variety of mild adverse effects have been reported. These include nausea, headaches, diarrhea, abdominal pain and constipation [1,5]. These risks underscore the importance of evaluating patient tolerance during the initial phases of PPI therapy [6]. According to studies, 40% and 65% of hospitalized patients in the United States and Australia lack a proven ongoing rationale for taking it, implying that continuous use may be harmful [7]. Although PPI usage is still becoming more common in the majority of nations worldwide, other nations, like the USA and Germany, have recently seen a decrease in this prevalence [8,9]. However, this might be a result of more people using over-the-counter PPIs [10].

REVIEW OF LITERATURE

The long-term use of PPIs has drawn significant attention due to its association with more serious health risks. Prolonged use, defined as therapy lasting beyond 8-12 weeks, is linked to a range of adverse outcomes, including kidney disease, bone fractures and an increased risk of infections such as Clostridium difficile. Studies have suggested that chronic PPI users are more likely to develop conditions such as acute interstitial nephritis, which can lead to Chronic Kidney Disease (CKD) if left untreated. These findings align with broader research, which indicates that reduced acid secretion can contribute to harmful effects on kidney function over time [5,11]. Some studies highlight the need to carefully consider a patient's medical history, symptoms and current medications before deprescribing [11,12]. Irrational use of PPIs is known to have adverse therapeutic outcomes. Abuse of PPIs may introduce expanded danger of bone fracture, may prompt mineral and nutrient inadequacies. Advancement of dementia, pneumonia, gastric malignancy and chronic kidney diseases are other secondary diseases detailed in patients with long term use of PPIs [10]. Given the potential benefits and adverse effects of PPIs use, it is essential to assess the indicators, cons and pros upon extended use and misuse of PPIs. More studies are needed on the pattern of prescribing PPIs to improve drug safety and highlighted the irrational recommendation of PPIs by physicians and pharmacists which is likely to be associated with any adverse health condition (illness, injury or infection) due to medical treatment or drug interaction with medication or nutrients. Saudi and Egyptian patients are more likely to use PPIs for treatment of different diseases as they have some similarity in their demographic culture. KSA and Egypt have few comparative studies on PPIs indications, the causes of incompletion of the course treatment with these drugs, severe side effects due to long-term duration of treatment and the role of Physicians and Pharmacists to control the hazards due to wrong use of PPIs in terms of wrong doses, duration and timing. This comparison allows us to explore how these differences may affect the pores and cones of PPIs.

Objectives

Primary Objective

This study aims to assess the benefits of uses and pros upon extended use or misuse of PPIs among patients in Saudi Arabia and Egypt who receiving PPIs.

Specific Objectives

- To assess the benefits of PPIs usage among patients in Saudi Arabia and Egypt
- To evaluate the risks and side effects due to misuse or long term-use of PPIs
- To assess the cultural differences and demographic and educational factors among two countries
- To compare between side effects and misuse of PPIs among two countries

METHODS

Study Design and Population

A cross-sectional survey was distributed throughout Saudi and Egyptian patients between October 2024 to December 2024. Saudi patients were chosen from university of Ha'il Clinic, KSA and healthcare centers, while Egyptian patients were from different private medical centers, Egypt. Online questionnaire was distributed among patients who are receiving PPIs for short and long duration in different medical places in Egypt and Saudi Arabia, while other patients were interviewed (Face to Face) in different medical centers and asked questions from well-designed questionnaire.

Sample Size Calculation

The Raosoft sample size calculator was used to calculate the sample size, providing a 5% margin of error and a 95% confidence level. To reach statistical significance, a sample size of at least 200 participants was required.

Data Collection Tool

A well-structure questionnaire was used for data collection. The questionnaire was designed in Arabic for Egyptian and Saudi participants and in English for the research manuscript. participants. The questionnaire was divided into five different sections.

Sociodemographic Information: Age, gender, occupation, working in medical field and education level.

Usage of PPIs: PPI medications were used according to medical consultant and reasons for incompletion of the PPIs course.

Indication for PPIs Treatment

Duration of PPIs Treatment: Short and long-term duration of PPIs.

Side effects of PPIs
Mild and severe side effects due to PPIs usage. Participants were urged to give truthful answers to reduce response bias.

Inclusion Criteria

- All patients from the two countries (Saudi and Egyptian patients Saudi) who received PPIs and their ages 18 years-old and above

Exclusion Criteria

- Patients under 18 years of age and patients who received PPIs

Data Management and Statistical Analysis
Online questionnaire was distributed among patients (received PPIs) in different places in Egypt and Saudi Arabia, while other patients were interviewed (Face to Face) in different medical centers and asked questions from well-designed questionnaire. The informed consent was received from each patient starting after complete explanation of the questions and told the patients that their participation was optional not mandatory and they can withdraw at any time without any problem. Then after explanation we ask the patients if they agree to complete answering the questions or no. Also, we explained that all their personal and historical data will be securely stored and will not use at anything except for this research, also it is the responsibility of the principal investigator on his personal computer and will be deleted after publishing the paper. The questions about the sociodemographic data, PPIs medications, cause for incomplete the doses, PPIs short term and long-term side effects. Any response that does not fulfill inclusion criteria nor answering all questions was deleted. The total number of participants were 618 who are meeting all inclusion criteria; 288 from Saudis Arabia and 330 from Egypt.

Statistical Analysis
Statistical analysis was done using Statistical Package for Social Sciences (version 25 SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as Mean±SD and descriptive statistics such as frequencies (n) and percentages (%) were employed for categorical variables. p-value ≤0.05 was considered statistically significant according to Pearson Chi-Square test.

RESULTS

In this study, the total number of participants were 618; 288 (Saudis) and 330 (Egyptians). Table 1 displayed the demographic features and using of PPI and working in medical field among patients from Saudi Arabia and Egypt. The mean of age in years (35.99±1.46 Saudis vs. 45.65±3.16 Egyptians) which was significantly different from each other (p-value = 0.011) (Figure 1). About 40% of participants their age ranges from 18-24 years (Saudis) and 36.4% from 25-34 years (Egyptians) and most of them from middle and secondary school education levels from two nations (p = 0.390). The number of employees was lower (47.2%) compared with Egyptians (72.7%) which was significantly different at p-value = 0.021. Only 46.2% of

Table 1: The Socio-demographic characteristics of Egyptian & Saudi patients who are receiving Proton Pump Inhibitors (PPIs) (%) [Total n = 618, n = 288 (Saudis), n = 330 (Egyptians)]

Characteristics (%)	Saudis [288]	Egyptians [330]	Total [618]	p-value
Age (Mean±SE)	35.99±1.46	45.65±3.16	618	0.011*
Age (Years)	n (%)	n (%)	n	
18-24	118(41.0)	15(4.5)	133	0.000*
25-34	51(17.7)	120(36.4)	171	
35-44	50(17.3)	45(13.6)	95	
45-54	46(16.0)	75(22.7)	121	
55-65	21(7.3)	45(13.6)	66	
>65	02(0.7)	30(9.1)	32	
Level of Education				
Primary	16(5.6)	30(9.1)	46	0.39
Middel & Secondary	214(74.3)	270(81.8)	484	
University & above	58(20.1)	30(9.1)	88	
Employment				
Yes	136(47.2)	240(72.7)	376	0.021*
No	152(52.8)	90(27.3)	242	
Working in medical field				
None	155(53.8)	95(32.1)	250	0.000*
Yes, Students	4(1.4)	0(0.0)	4	
Yes, Physicians	23(9.1)	45(13.6)	68	
Yes, Pharmacists	8(2.8)	30(9.1)	38	
Yes, Nurses	4(1.4)	15(4.5)	19	
Yes, Technicians	10(3.5)	0(0.0)	10	
Yes, Others	53(18.4)	10(45.5)	63	
Using PPIs according to medical consultant				
Yes	70(24.3)	225(68.2)	295	0.000*
No	192(66.7)	75 (22.7)	267	
Sometimes	26(9.0)	30(9.1)	56	

*Significant difference at p≤0.05

Table 2: Indications and duration of using PPIs among Egyptian & Saudi participants who are receiving Proton Pump Inhibitors (PPIs) (%) [Total n = 618, n = 288 (Saudis), n = 330 (Egyptians)]

Characteristics (%)	Saudis [288]	Egyptians [330]	Total [618]	p-value
Indications for using PPIs				
Prophylaxis with NSAIDs	83(28.8)	150(45.5)	233	0.032*
Heartburn	50(17.3)	105(31.8)	155	
Gastroesophageal reflux disease (GERD)	50(17.3)	16(4.8)	66	
Helicobacter pylori infection	30 (10.5)	44(13.3)	74	
Gastritis	22(7.6)	42(12.7)	64	
Peptic ulcer	16(5.6)	13(3.9)	29	
Esophagitis	5 (1.7)	10(3.0)	15	
Others	70(24.3)	87(26.4)	157	
Short term duration of using PPIs				
As needed not regular	143(49.7%)	82(27.3)	225	0.013*
Regularly less than 2 weeks	47(16.3%)	104(31.5)	151	
Regularly from 2- 4 weeks	12(4.2)	15(4.5)	27	
Regularly from 5- 8 weeks	18(6.3)	30(9.1)	48	
I don't use for short duration	68 (23.6)	99(30.0%)	167	
Long term duration of using PPIs				
Regularly >2 to 6 Months	97(33.7)	115(34.8)	212	0.533
Regularly >6 Months to 1 year	6(2.1)	43(13.0)	49	
Regularly from >1 to 2 years	6(2.1)	15(4.5)	21	
Regularly from >2 to 3 years	4(1.4)	0(0)	4	
Regularly >3 years	14(4.9)	0(0)	14	
I don't use for long duration	161(55.9)	157(47.5)	318	
Appropriate time to take PPIs				
Before meal	113(39.2)	240(72.7%)	353	0.008*
After meal	45(15.6%)	10(3.0%)	55	
With meal	9(3.1)	5(1.6)	14	
Any time	121(42.0)	75(22.7)	196	

*Significant difference at p≤0.05

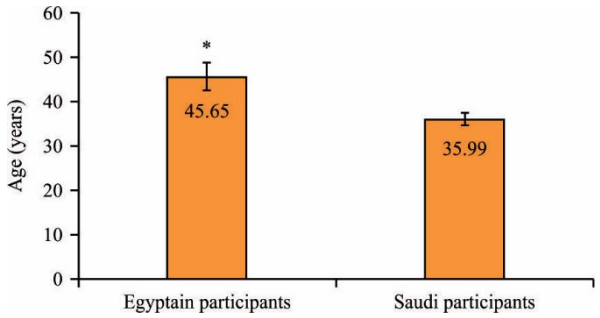

Figure 1: The mean of age of Saudi and Egyptian participants who are receiving Proton Pump Inhibitors (PPIs) (Mean+SE)

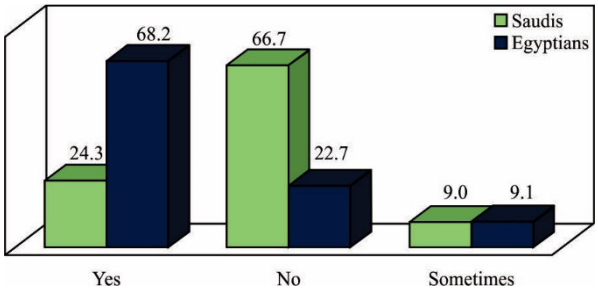

Figure 2: Percentage of participants who are using PPIs according to medical consultant among Saudi and Egyptian

Saudi participants vs. 67.9% are working in the medical field. The number of Saudi participants who used PPI according to medical consultant are 24.3% vs. Egyptians 68.2% (p-value = 0.000) (Figure 2).

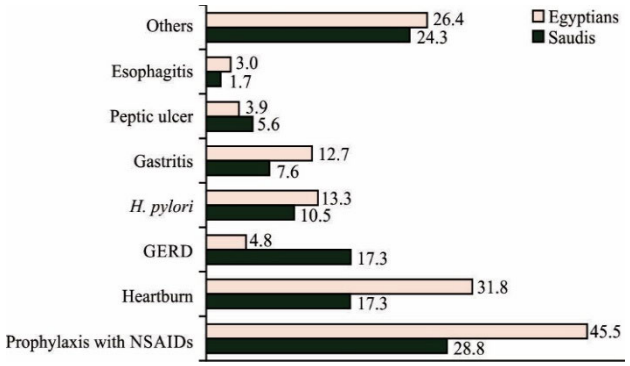

Figure 3: Indications for using PPI among Saudi and Egyptian participants (%)

Table 2 shows the most usage of PPI is for prophylaxis from peptic ulcers mainly due to long term uses of NSAIDs. High percentage of Egyptian participants using PPI for prophylaxis from peptic ulcers mainly due to long term usage of NSAIDs (45.5%) vs. 28.8% (Saudis), followed treatment of heartburn by 31.8% (Egyptians) vs. 17.3% (Saudis). While high percentage of Saudi (17.3%) participants using PPI for treatment of gastroesophageal reflux disease (GERD) more than Egyptians (4.8%). Nealy the same percentage of both nations using PPI for treatment of Helicobacter pylori infection and peptic ulcers (Figure 3).

Regarding short term duration of using PPI, 49.7% (Saudis) used PPIs when needed only vs. 27.3% (Egyptians), while patients who used PPI regularly less than 2 weeks was more among Egyptian (31.5%) than Saudi participants (16.3%), these results were significantly different at

Table 3: Mild and severe side effects of PPIs among Egyptian & Saudi patients who are receiving Proton Pump Inhibitors (PPIs) (%) [Total n = 618, n = 288 (Saudis), n = 330 (Egyptians)]

Characteristics (%)	Saudis [288]	Egyptians [330]	Total [618]	p-value
Completed the course of PPIs				
Yes	137(47.6)	225(68.2)	362	0.033*
No	151 (52.4)	105(31.8)	256	
The cause of uncompleted the course of PPIs				
Complete the course of PPIs	137(47.6)	225(68.2)	362	0.035*
Symptom's disappearance	38(13.2)	27(8.2)	65	
Due to side effects	26(9.0)	13(3.9)	39	
Fear of side effects	12(4.2)	18(5.5)	30	
Expensive for me	6(2.1)	17(5.2)	23	
Not available	8(2.8)	0(0.0)	8	
Others I don't use PPIs	61(21.2)	30(9.1)	91	
Mild side affects you have upon using PPIs				
Bloating	75(26.1)	110(33.3)	185	0.028*
Headache	26(9.0)	85(25.8)	111	
Nausea	35(12.2)	55(16.7)	90	
Abdominal pain	29(10.1)	40(12.1)	69	
Diarrhea	11(3.8)	33(10.0)	44	
Constipation	8(2.8)	12(3.6)	20	
Blockage of heart stent	13(4.5)	15(4.5)	28	
Others	91(3.2)	30(9.1)	121	
Sever side affects you have upon using PPIs				
Osteoporosis	49(17.0))	64(19.4)	113	0.059
Increase risk of fracture	50(17.3)	62(18.7))	112	
Iron deficiency Anemia	37(12.8)	56(17.0)	93	
Mineral deficiency	33(11.5)	40 (12.1)	73	
Increase risk of gastroenteritis	30(10.4)	32(9.7)	62	
Deterioration of kidney function	23(8.0)	21(6.4)	44	
Dementia	20(6.9)	20(6.1)	40	
Gastric cancer	16(5.6)	10(3.0)	26	
Others	60(20.8)	46(13.9)	76	

*Significant difference at p≤0.05

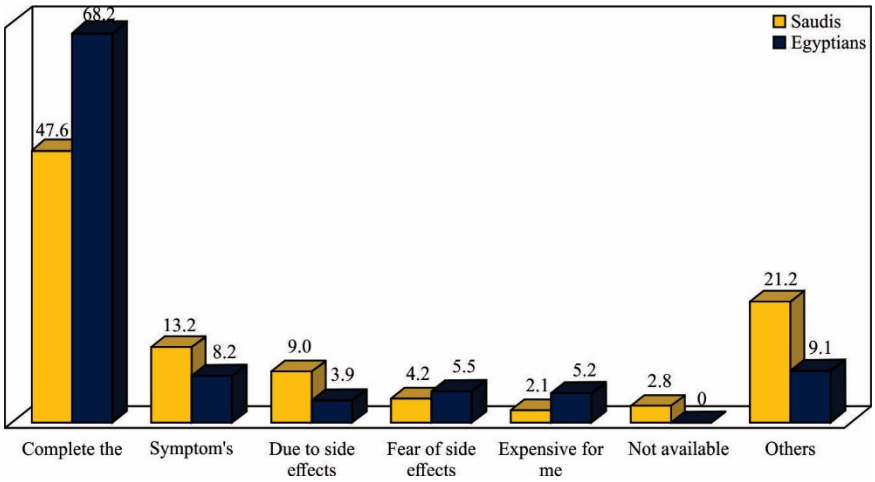

Figure 4: The reasons of incomplete PPIs course among Saudi and Egyptian participants (%)

p-value 0.013. On the other hand, no significant difference was observed among patients in both countries who are using long- term duration of PPI (p-value 0.533). Most of Egyptians received PPIs before meals 72.7% (which is the proper time) compared with 39.2% (Saudis) and about 42.0% received PPIs at any time vs. Egyptians (22.7%) which was significantly different at p-value 0.008.

Table 3 shows the percentages of patients who completed the course of PPI and the causes of uncompletion, also side effects either mild or severe side effects. Concerning the percentages of patients who completed the course of PPIs was high in Egyptian (68.2%) compared with Saudi participants (47.6%) which was significantly different at p-value 0.033.

Table 3 also showed the causes of uncompletion of the PPI course were disappearance of symptom's (13.2% Saudis vs. 8.2% Egyptians) and due to side effects was 9.0% Saudis vs. 3.9% Egyptians which was significantly different at p-value 0.035 (Figure 4).

Regarding the mild side effects that appeared during using PPI was higher percentage among Egyptian compared to Saudi participants which was significantly different at

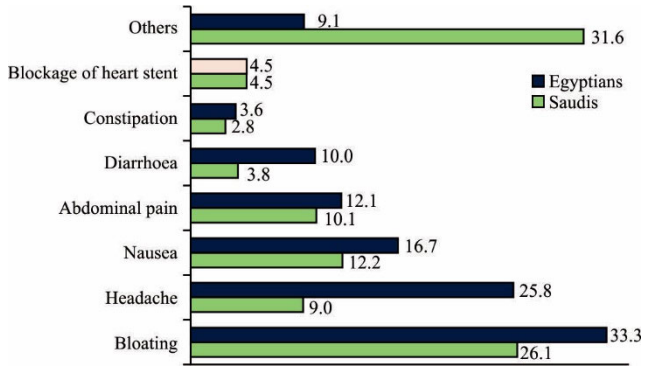

Figure 5: Mild side effects of PPIs among Saudi and Egyptian participants (%)

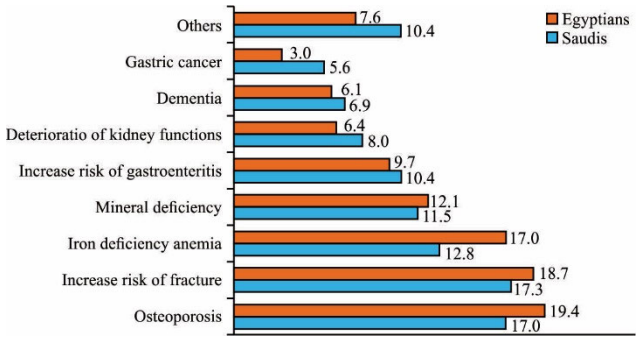

Figure 6: Severe side effects of PPIs among Saudi and Egyptian participants (%)

p-value 0.028. The most predominant side effect was bloating (33.3% vs. 26.1%) followed by headache (25.8% vs. 9.0%), then nausea (16.7% vs. 12.2%), abdominal pain (12.1% vs. 10.1%) and diarrhea (10.0% vs. 3.8%) respectively (Figure 5).

Concerning the severe side effects that appeared during using PPI was slightly higher among Egyptian compared to Saudi participants which was not significantly different at p-value 0.051. The most predominant side effect was Osteoporosis (19.4% vs. 17.0%) followed by increased risk of fractures (18.7% vs. 17.3%), Iron deficiency anemia (17.0% vs. 12.8%), then mineral deficiency (12.1% vs. 11.5%). On the other hand, Saudi participants suffered more from deterioration of kidney functions (8.0% vs. 6.4%), increase risk of gastroenteritis (10.4% vs. 9.7%), dementia and gastric cancer than Egyptian which was not significantly different at p-value 0.051 (Figure 6).

DISCUSSION

The usage of PPIs became extremely prevalent among primary care physicians and now they are chief element of the gastroenterologist's selection either in Saudia Arabia or in Egypt. In this study, about 40% of Saudi participants (18-24 years) and 36.4% from 25-34 years (Egyptians) who used PPIs, this results in accordance with studies done in Saudia Arabia and Egypt [3,10,13].

About half of Saudi participants and more than two thirds of Egyptians are working in the medical field which reflect the results that 68.2% of Egyptian participants completed the PPIs course and received the drug according to medical consultants. Other study in KSA agree with us, they found that only 26% of participant works in medical field such as physicians, pharmacist, administrators and students [13]. Low number of Saudi participants who used PPIs according to medical consultant are 24.3% vs. Egyptians 68.2%. These results were in agree with study done in Saudi Arabia [13,14]. Others in medical ward of King Abdulaziz University Hospital (Jeddah, KSA) revealed that a large number of patients received incorrect PPI prescriptions (not in line with clinical guidance) [15]. Others said that patients may use these medications for extended periods of time without seeking medical assistance. Low percentages of participants in Al Qassim, KSA about dosing, proper time and side effects of PPIs [16,17]. The proper time to use PPIs and compliance with prescriptions were strongly impacted by educational level and working in the medical fields [17]. Others found that physicians, pharmacists and nurses from various public and commercial institutions discovered that people with more professional experience and those with higher education levels knew more. Compared to doctors, pharmacists and nurses were less likely to use PPIs. The study also found that Saudi Arabian healthcare professionals' views, knowledge and Behavior regarding the use of PPIs were positively correlated [6].

The widespread of PPIs misuse led to poor health outcomes was observed in different countries worldwide such as Irish [18], Qatar [19] and Danish [20]. A significant number of PPIs were prescribed improperly, so, they need a review or adjustment of PPI usage by Lebanese doctors [21]. Others said that only 30% used PPIs prescriptions was in line with guidelines [22]. Others stated that the adverse health effects and financial burden was recognized upon overprescribing too many PPIs [23]. On the other hand, about 70% of Egyptian participants followed the guidelines for the use of PPIs, avoiding self-medication, taking PPIs in right dosage & proper time as prescribed by a physician which was agreed with the other study done in Makka, KSA [3]. Despite PPIs' known effectiveness, it contributed to the widespread occurrence of improper PPI use [24].

Concerning the indication of PPIs, in this research high percentage of Egyptian participants using PPIs for prophylaxis from peptic ulcers mainly due to long term usage of NSAIDs somewhat high than Saudis, followed treatment of heartburn and others such as GERD, *H. pylori* eradication (in addition to some antibiotics), gastritis, peptic ulcer and esophagitis. Some studies were in line with our results, they found that PPIs were used with long term duration of treatment of NSAIDs for ulcer avoidance in patients with history of peptic ulcer diseases [2,20,22]. Also, PPIs are frequently used to prevent GIT bleeding in patients receiving aspirin and clopidogrel as part of a dual antiplatelet regimen after myocardial infarction and percutaneous

coronary intervention [25]. Others stated that PPIs were used for short duration in intensive care units to protect from stress ulcer for patients with high risk of GIT bleeding [26]. In our research, high percentage of Saudi participants using PPIs for treatment of GERD more than Egyptians. Nealy the same percentage of both nations using PPI for treatment of *H. pylori* infection and peptic ulcers. Recent study in 2024 revealed that PPIs have a good efficacy in eradication of *H. Pylori* in triple therapy regimen in many governorates in Egypt in addition to other antibiotics [27]. Other study stated the uses of PPIs in treatment of esophagitis, peptic ulcer, GERD, part of the triple therapy regimen for *H. pylori* infections [2]. Others advise an 8 week trial of PPIs once daily, 30 to 60 minutes before a meal, preferably in the morning before breakfast rather than at sleep, for patients with classic GERD symptoms of heartburn and regurgitation who do not exhibit alarm signs [28].

In the current research, half of Saudi participants used PPIs when needed, while one third of Egyptians used PPI regularly less than 2 weeks which was significantly difference between two groups. On the other hand, no significant difference was found between both countries in using long-term duration of PPI. Study done in 2018 revealed that PPIs may now be purchased freely in many countries as over-the-counter medications, so, patients may use these potent medications for extended periods of time without seeking medical assistance. It should be noted that excessive PPI prescriptions, especially for older patients, can result in several adverse effects [16]. Most of Egyptians received PPIs before meals which is the proper time, compared to Saudis. This result was in agree with study in USA said that, if all USA patients received PPIs before breakfast with 20-30 min, the patients become more satisfied and USA could save about 4 billion Dollars/year [29]. Minimizing the widespread PPI usage by advising the proper prescription, dose, time and duration to treat hurt burns and GERD [3,30]. One of the key issues associated with the adverse effects of PPIs is their widespread misuse. Studies have found that many patients continue taking PPIs beyond the recommended treatment duration or time without proper medical supervision. In many cases, this continued use stems from a combination of patient habits and physician inertia, rather than a clear medical necessity. One of the important factors lead to the misuse of PPIs is that primary care providers frequently prescribe them considering that they are harmless easy solution for any gastric symptom; in addition to their availability over the counter; and the availability of generic drugs with low cost [31].

This study also showed that most of the Egyptian participants completed the course of PPIs (more than two thirds) while about half of the Saudis participants did, this results similar to that done in 2022 which revealed that about two thirds of participants completed the PPIs course 13 [13]. For both Saudis and Egyptians, the more common cause for uncompletion of PPIs course is the subsidence of symptoms but there are significant differences in other causes; more Saudis participants stopped the course due to side effects than Egyptian, while more Egyptians stopped due to financial difficulties ($p<0.05$). These results are agreed to other studies done regarding the same issue and revealed that about half of the patients were not compliant with appropriate PPI usage, this is also found for many long-term medications [32].

Regarding the mild side effects of using PPIs also there is significant difference between the rates of occurrence of most of the side effects although they follow the same sequence of frequency for both groups. The Egyptian group showed significantly higher rate of mild side effects; bloating, headache, nausea, abdominal pain, diarrhea and constipation compared to Saudis group ($p<0.05$). This results about mild side effects were agreed with other studied who stated that PPIs are usually well tolerated, they have little side effects. Short-term PPI use has caused a little mild adverse effect in patients, including headache, rash, dizziness and gastrointestinal symptoms such diarrhoea, constipation, flatulence, nausea and stomach discomfort. Physicians are not worried about severe adverse effects from PPIs while taking them at the recommended dosage for a two-week treatment period. However, as the number of people using these medications rises, more people are reporting side problems, especially after long-term usage [33]. According to current studies, PPIs should be used for the shortest amount of time at the lowest effective dose [34]. On the other hand, there is no significant difference in the frequency of severe side effects between Saudi and Egyptian groups ($p>0.05$). The most common in both groups are osteoporosis and increased risk of fractures, others include iron deficiency anemia, mineral deficiency, increase risk of gastroenteritis, deterioration of kidney function, dementia and gastric cancer. Many studies have shown the link between PPI use for long term duration and the risk of osteoporosis and increased susceptibility to bone fractures after long term. This may be due to reduction of calcium absorption. No appreciable changes in fracture risk or bone mineral density among PPI users during a relatively short to moderate period duration. But hypochlorhydria, which affects calcium absorption, is one of the hypothesized mechanisms that explain the link between prolonged PPI therapy and decreasing bone mineral density [35]. This link is usually clearer with the presence of other factors specially advanced age [5,36]. Presence of iron deficiency anemia after long-term treatment with PPIs as a result of reduced non hem iron absorption due to reduction of stomach acidity [28]. Significant deficiency in vitamins (C & B12) and mineral such as iron, calcium and magnesium may be due to long-term PPI usage. These minerals require stomach acid for absorption. Pregnant women who received PPIs for an extended period exposed to a risk of developing congenital defects [35].

In this research, most of our participants were from secondary school and university students (not elderly) from two nations but they suffered from severe side effects such as osteoporosis, tendency to easy bone fracture and iron deficiency anima which explain the harms that happen because of long period of treatment. A review article

included a huge number of studies on the adverse effects of PPIs concluded that common adverse effects are osteoporotic-related fractures, vitamin B12 deficiency, kidney disease and dementia, demonstrated by a number of case-control, cohort studies and meta-analyses. In addition, in most of these studies found that the occurrence of side effects is related to the age of the patient, the dose and the duration of the PPIs use. Also, some studies revealed a significant relation between PPIs adverse effects and the presence of other comorbidities; kidney diseases [37,38], cardiac and hepatic diseases [39,40,41].

It is apparent in this study that most of the participants used PPIs for short duration; about 73% used it for <8 weeks and only 10.5 used it for more than 6 months (long duration). Even though a considerable number of participants developed PPI adverse effects, this might not be in complete agreement with many studies which relate the adverse events to the prolonged use of the PPIs medication and it indicates that other factors also contribute to the occurrence of PPIs adverse effects. Certainly, it is a fact documented by much research that elderly patients are more vulnerable to the side effects of PPIs [38,39]. In this study, the majority of the participants are below 55 years which is not considered as elderly patients, even though a relatively high number of participants developed severe side effects like osteoporosis and increased risk of fractures (each about 18%) which are not common in this young-age group. This indicates that physicians, pharmacists and patients should be cautious on prescribing or taking PPIs even if the patient is not elderly. Others said firstly that patient's primary care physician should be aware about patient current indications for a PPI usage reviewed and documented on a frequent basis. Secondly, all patients who do not have a clear sign for a chronic PPI should be given the opportunity to try deprescribing. Thirdly, patients who take twice-daily PPIs and have a chronic rationale for their usage should be evaluated for a step-down to once-daily PPIs [42].

CONCLUSIONS

PPIs are completely changed the way that acid-related gastrointestinal illnesses are treated, so extensive use has brought up serious safety concerns. The long-term hazards, such as kidney disease, fractures and infections, require careful thought and constant monitoring, even if the short-term side effects are usually modest and controllable. Such risks are further boosted by PPI misuse and over-prescription, which highlights the importance to follow guidelines based on evidence for its usage. Relatively high number of participants developed severe side effects like osteoporosis and increased risk of fractures which are not common in young age group. This indicates that physician and patients should be cautious on prescribing or taking PPIs even if the patient within young age. To ensure secure and effective utilization of these strong medications in the future, patients and healthcare professionals need to work together and the risks of using long-term PPI must be weighed against the benefits. Educational programs about PPIs from Ministry of Health should be held in KSA and Egypt due to their immense importance.

Limitations

Limitations of this study were somewhat limited number of participants from limited locations, whether in Egypt or Saudi Arabia.

Recommendations

We recommended applying the study in several locations either in Saudi Arabia or in Egypt with large number of patients used PPIs. Also, trying to use participants with age more than 54 years old and with higher education university degrees for more clarification of the results about indications and side effects mainly due to long-term duration of drug treatment, also clarifying the role of physicians and pharmacists to help patients for proper doses, timing and duration.

Conflicts of Interest

The authors declare no conflict of interest. No financial, professional or personal interests influenced the study's design, data collecting, analysis or results; the research was carried out freely.

Ethical Considerations

This study followed the guidelines proved by the University of Ha'il Research Ethics Standing Committee (REC). On October 2024, the research protocol and instrument (Study ID: (H-2024-453) were examined and authorized. The goals of the study, the confidentiality of their answers and their right to voluntary participation were all explained to the participants. Prior to administering the questionnaire, informed consent was received from each participant. Patients' information and their data were anonymised to protect participant privacy.

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