

## ORIGINAL RESEARCH

# Patients' Knowledge and Pharmacists' Practice Regarding the Long-Term Side Effects of Proton Pump Inhibitors; a Cross-sectional Study

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**Abstract:** **Introduction:** Proton pump inhibitors (PPI) are a commonly prescribed medication, but recent evidence suggests that their long-term use may lead to several adverse events. To address this issue, our study aims to assess patient awareness and pharmacist practices in educating patients about the potential risks associated with prolonged PPI use. **Methods:** Two questionnaires were developed by researchers and administered in the United Arab Emirates from June to August 2021 to gather insights from patients and pharmacists about the use of PPIs, their knowledge of potential side effects, and their experiences and attitudes toward receiving education about PPI side effects. The patients' knowledge was evaluated based on their cumulative correct answers to questions related to PPI's long-term adverse effects including increased fracture risk and hypocalcemia, vitamin B12 deficiency, hypomagnesemia, and the caution of abrupt withdrawal. All statistical analyses were conducted using SPSS 25.0 software. **Results:** Overall, 348 participants with a median age of 40 years participated in the survey, among them, 91 (26.14%) used various forms of PPI with 38% of users taking PPI as over-the-counter drugs. Patients had low knowledge about PPI side effects and their proper discontinuation with a median knowledge score of 0 (Interquartile range: 0-2) and only 22.2% of patients were familiar with at least three out of five asked harms. Those with lower knowledge were more likely to be Emirati compared to other nations ( $p=0.004$ ) and aged over 30 years compared to their younger counterparts ( $p = 0.016$ ). Few patients have obtained the relevant information from their physicians (25%) or pharmacists (7%). Inquiring 136 pharmacists, it was shown that the most common education was concerning vitamin B12 deficiency (62.5%) followed by fracture risk (58.09%) yet less than half (48%) of pharmacists instructed patients about the potential risk of hypomagnesemia. Almost all pharmacists (99%) agreed that there is a requirement for additional education on the possible harmful consequences of PPIs. **Conclusion:** The present study has established that a considerable proportion of PPI users in the UAE lack the necessary awareness about the potential adverse effects of PPI despite their extensive use in this country. The current pharmacist practice is inefficient for inculcating the potential harms of chronic PPI use and they are required to optimize their efforts to educate patients and bridge the knowledge gaps.

**Keywords:** Proton Pump Inhibitors; Long Term Adverse Effects; Micronutrients; Pharmacists

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## 1. Introduction

Proton pump inhibitors (PPIs) have emerged as one of the most widely used medications globally, with a discernible upward trend in prescription over recent years (1). These drugs act by irreversibly inhibiting H<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase pumps in parietal cells, thereby effectively suppressing gastric acid secretion. Since their debut in 1989, PPIs have significantly transformed the management of gastrointestinal acid-related disorders, including symptomatic gastroesophageal reflux disease (GERD), erosive esophagitis, func-

tional dyspepsia, H.pylori eradication regimen, and prophylaxis against ulcers associated with non-steroidal anti-inflammatory drugs (NSAID) (2).

Historically, PPIs in appropriate dosages have been well tolerated and considered safe, given the rarity and mildness of reported side effects, especially in short-term use (3). As a result, in 2003, this drug category was granted permission for sale as an over-the-counter medication for short-term management of acid-related disorders in the United States. However, emerging literature raised concerns about the long-term administration of PPIs as several potential harms were demonstrated in observational studies (4).

Although no causality could be confirmed, multiple adverse effects were reported in the context of induced hypochlorhydria and hypergastrinemia by chronic use of PPIs, including micronutrient malabsorption, GI microbiome change,

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bacterial overgrowth, and gastrointestinal preneoplastic tumors and cancers (5, 6). Among these adverse effects, electrolyte and vitamin imbalances, including calcium, magnesium, and vitamin B12, have been the subject of numerous studies, which has led to the Food and Drug Administration issuing two drug safety communications regarding the potential increased risk of fracture and hypomagnesemia in patients taking PPIs (7, 8).

The occurrence of these unfavorable incidents has sparked concerns among both patients and healthcare providers, with some patients attempting to discontinue PPI out of fear of their harmful effects, even though the benefits of PPIs still outweigh their potential drawbacks (9). Moreover, abrupt cessation of PPI after long-term use may cause withdrawal symptoms due to gastric acid secretion beyond pre-PPI levels, a physiological phenomenon named “rebound acid hypersecretion” (10-12). So, while it is generally recommended to stop PPIs when there is no longer an indication for their use, discontinuation should be supervised by physicians or pharmacists.

Over the past two decades, numerous studies with inconsistent findings have been conducted to examine the prevalence of side effects associated with the long-term use of PPIs, as well as patients and healthcare providers’ knowledge and concerns regarding these adverse effects. While many studies have highlighted the role of physicians in disseminating information about PPI use and potential harms, little attention has been paid to pharmacists, given that a notable share of patients acquires PPIs as OTC drugs.

Hence, the current study has been designed with the objective of providing insightful observations into the extent of patients’ knowledge regarding one of the common side effects of PPIs, micronutrient derangements, and considerations on discontinuations in long-term PPI usage.

## 2. Methods

### 2.1. Study design and settings

This prospective observational study was conducted in the United Arab Emirates to assess the knowledge of adult outpatient PPI users and pharmacists’ practice concerning the side effects of long-term use of PPI. Data collection for the current survey was achieved through anonymous electronic questionnaires administered to the target population from June to August 2021.

The study was carried out in accordance with the Declaration of Helsinki. Participation in the study was completely voluntary, and all participants were assured that their responses would remain anonymous, and the data collected would be kept confidential and used solely for research purposes. Before the questionnaire was distributed, the volunteers received a document outlining the study’s goals, the director’s information, and a request for informed consent. Ethical approval was obtained from the Ethics Committee of Dubai Pharmacy College for Girls with the reference number

REC/PG/2021/03.

### 2.2. Participants

Patients were selected randomly from adult outpatients’ cases, who used various forms of PPI and consent to participate in the study. PPI use was defined as taking PPI for more than one week.

The selection of pharmacists for the study was not random but rather involved a purposeful selection of five hospital pharmacies located in Dubai (two hospitals), Sharjah (two hospitals), and Ajman (one hospital), as well as a number of community pharmacies in Dubai. The selection of these hospitals and community pharmacies was made following a thorough review of their respective formularies, with the confirmation that they stocked different products of the PPI category, which could be dispensed on a daily basis.

### 2.3. Data gathering

Two electronic surveys were created to gather insights from patients and pharmacists. The formulation of the survey questions was based on an extensive review of relevant literature and consultation with subject matter experts. To ensure the questionnaire items’ validity and applicability, ten pharmacists working in the UAE and two academic members of pharmacology from different UAE universities reviewed the questionnaire and incorporated their feedback. The survey questions were created in English, with the patient survey also translated into Arabic to cater to a broader audience within the UAE community. The internal consistency of questionnaire items was assessed by Cronbach’s alpha test, which yielded a coefficient of 0.890 for the patient questionnaire and 0.796 for pharmacist questionnaires, indicating acceptable reliability (>0.7).

The ultimate 21-item patient questionnaire encompassed binary yes or no questions and multiple-choice questions inquiring about demographic details, patients’ PPI usage characteristics, level of knowledge regarding the potential side effects and source of information, experience, and attitude regarding receiving education about PPI side effects.

The pharmacist questionnaire included 20 items that asked about demographic details, professional background, experience with dispensing PPI, practice in educating patients about PPI side effects, and perspectives on disseminating knowledge about this matter.

### 2.4. Statistical analysis

Descriptive statistics for quantitative variables were expressed as mean and standard deviation or median and interquartile range.

Qualitative variables were presented as counts and percentages. Normality in the distribution of quantitative variables was investigated through the Shapiro-Wilk test. For each patient, the knowledge score (KS) was calculated by determining the number of correct answers to the five knowledge questions about PPI side effects. The chi-square test

was used to detect significant differences between categorical variables. To investigate the differences in KS between two or more groups, Mann-Whitney and Kruskal-Wallis tests were employed, respectively. A p-value of <0.05 was considered significant. All statistical analyses were performed in SPSS version 26.

### 3. Results

#### 3.1. Patients survey

Our study involved a total of 348 participants, out of whom 297 (59.2%) were males with a median age of 40 years old, ranging from 16 to 74 years. The survey revealed that 91 participants (26.14%) reported using PPI, and among them, 27 (29.67%) had been using it for over 2 years. Patients who reported taking PPI were found to be more likely to be male ( $p=0.007$ ), older (Median: 43 vs 38,  $p=0.001$ ), and married ( $p=0.029$ ). Conversely, patients who did not use PPI were more likely to be Emirati ( $p=0.005$ ) and unemployed or housewives ( $p=0.005$ ). Detailed social and demographic characteristics of patients are presented in Table 1. Patients taking PPI were more likely to be prescribed by their physicians (62%). Seventy percent of users stated that they would suspend taking PPI only by orders from their physician or pharmacist. Concerning the reason behind taking PPIs, 40.7% of sampled users took PPIs as they had a constant feeling of acidity, especially after eating or smoking, while 24% of the users were taking PPIs as protection against peptic ulcers when they co-administered other medications such as NSAIDs (Figure 1).

#### 3.2. Patients' knowledge of the side effects

The median knowledge score of respondents was 0 (IQR: 0-2) when answering the five questions related to PPI adverse effects with no difference between those who had a physician's prescription and those obtaining PPI as an OTC medication ( $p = 0.218$ ). Merely 22.2% of the surveyed patients were able to answer more than half of the questions presented, while 31.87% claimed familiarity with PPI side effects.

Individuals who scored higher on knowledge assessments were more likely to be Arab or from other countries except the UAE ( $p = 0.004$ ).

Concerning age, although it was demonstrated to not impact KS, the categorization of patients into two groups of 20-29 and 30 and above demonstrated a significantly higher KS among younger responders (median score 2 vs. 0,  $p = 0.016$ ). Intriguingly, patients' education level and occupation status were not associated with their KS ( $p > 0.05$ ). However, restricting patients to those employed, patients engaged in healthcare-related jobs scored higher than those with office/clerical or police/military positions (Median: 40 vs 0,  $p<0.001$ ).

When patients were asked about their sources of knowledge, nearly half of the patients (49%) reported that they relied on self-reading, followed by information provided by physicians

(25%). Only 7% of responders heard about side effects from their pharmacist (Figure 2).

Delving into the possible explanations for this inadequate knowledge, most patients (90%) declared that they didn't receive any information or warning on this matter from their pharmacists, resulting in almost all patients (93%) expecting more efforts by pharmacists to educate them. According to the results of our survey, 75% of the sample group of patients revealed that heightened awareness of the potential side effects of PPIs would prompt them to discontinue their long-term usage.

#### 3.3. Pharmacists survey

Overall, 118 pharmacists and 18 assistant pharmacists with a median age of 33 years (range: 22-63) took part in our survey, of which 83 (61%) were female. The respondents included pharmacists from different nationalities, with the majority (50.7%) being Arab nationals practicing in the UAE. The majority of the pharmacists (69.1%) had acquired more than 4 years of experience in the field, while 13 respondents (9.6%) had less than 1-year of experience.

Pharmacists were found to dispense PPIs frequently, with all respondents reporting at least one daily dispensation and 23.5% dispensing PPIs more than 20 times per day, indicating a high rate of PPI use in the community. Detailed characteristics of pharmacists is presented in Table 2.

#### 3.4. Pharmacist's practice in educating patients

It was observed that almost all participating pharmacists (93%) exhibited familiarity with the side effects associated with PPIs. 83% of pharmacists reported taking measures to educate their patients to withdraw PPIs if there was no indication for their long-term use. However, nearly all surveyed pharmacists (99%) believed there is a need for further education regarding the potential adverse effects of PPIs.

When inquiring about the education of patients with respect to the common side effects, it was found that over half of the pharmacists took measures to educate patients about vitamin B12 deficiency (62.5%), fracture risk (58.9%), and advised against the abrupt cessation of PPIs (64.7%). However, less emphasis was given to the potential risk of hypomagnesemia due to the long-term use of PPIs (48.3%). While 63% reported success in persuading patients to stop PPIs, only 35.29% of inquired pharmacists admitted that they provided instructions to their patients regarding abrupt cessation of these medications.

### 4. Discussion

The recent mounting evidence linking the use of PPI with multiple adverse effects has instilled concerns among both patients and healthcare providers. To mitigate potential harms, existing literature encourages discontinuing PPIs in cases where their use does not comply with established guidelines and when the risks outweigh the benefits. In this line, multiple initiatives and recommendations have been

proposed to aid physicians in deprescribing PPIs (12, 13). However, ensuring the success of plans aimed at curbing the overuse or misuse of PPIs relies heavily on patients making informed decisions. This, in turn, can be facilitated by creating greater awareness of the potential harms associated with PPIs among users. To this end, pharmacists are believed to be well suited to educating patients by disseminating valuable information about PPI's appropriate use and potential adverse effects, particularly among those who take PPIs without prescriptions as OTC medication (14, 15).

Through our study, we showed the widespread use of PPI among patients in the UAE, with a quarter of sampled patients reporting continuous consumption of this drug category for over a week. This trend can be attributed, in part, to the high prevalence of GERD in our region (16). In 2017, the age-adjusted prevalence of GERD was estimated to be 11760.9 (95% CI: 10364.4 to 13305.7) per 100000 in the UAE, which is approximately 50% higher than the global average of 8818.9 (95% CI: 7780.9 to 9863.1) (17). Despite the widespread use of PPIs, our research indicates that patients in the UAE have limited awareness of the potential risks associated with their use.

Furthermore, while pharmacists maintain that they already inform patients about the possible side effects of PPIs and instruction on their discontinuation, the education provided is reportedly insufficient.

Previous studies have revealed that patients have a low level of awareness regarding the side effects associated with PPI. Our study corroborates these findings, with 68.13% of PPI users being unaware of the adverse events that may arise due to long-term PPI use. A similar study conducted in the United States revealed that over half of the patients were not familiar with PPI side effects, irrespective of their usage. In our survey, we found that more than 20% of patients were aware of the risks of calcium, vitamin B12, and magnesium deficiency in long-term PPI use. Similar to our findings, Kurlander et al. conducted a survey among American PPI users and reported that fewer than 15% and 10% of patients were familiar with the increased fracture risk and vitamin B12 deficiency, respectively, as potential PPI side effects (9). Similarly, Al-jahdi and colleagues conducted a study in Saudi Arabia and demonstrated that only 14.5% and 8.7% of PPI users knew of the mineral deficiency and increased risk of fracture associated with PPI use, respectively (18).

In our study, patients were found to be more likely to seek knowledge about the side effects of PPI from sources other than their physicians and pharmacists, raising concerns regarding the accuracy and reliability of this information. Although all patients had to acquire PPI from pharmacists, a great portion of the patients in our study had physician prescriptions for PPI, highlighting the critical role of physicians, regardless of their specialty, in educating patients. In this line, a survey by Swed et al. demonstrated that only 10.8% of physicians discuss the potential harms of PPI with their patients. Therefore, it is essential to consider the importance

of educating healthcare professionals effectively and providing accurate and up-to-date information to ensure that patients are equipped with the knowledge they need to make informed decisions about their health.

In addition to patient education, it is imperative for medical practitioners and pharmacists to prioritize evidence-based and judicious prescriptions of PPIs when initiating this category of medications. Moreover, for those who already take PPIs, an ongoing reevaluation of indications is recommended to ensure optimal patient outcomes (12). Although we didn't assess the indications for taking PPI in our survey, studies reported a high rate of inappropriate prescription of PPIs. A study conducted in the Netherlands revealed that only 44% of PPI prescriptions were associated with an appropriate indication (19). Similarly, a Danish study involving 1842 patients found that one in four patients was prescribed a PPI for an inappropriate indication (20). Soubra and colleagues found that over 50% of Lebanese outpatients investigated were prescribed PPIs without an approved indication for gastrointestinal bleeding prophylaxis according to relevant guidelines (21). Despite the absence of a study evaluating the extent of appropriate prescription of PPI in the UAE, it is plausible that a significant proportion of patients may not meet the criteria for taking PPI. Even in cases where acid-related disorders are suspected, complementary measures and alternative management strategies, such as lifestyle modification, weight loss, antacids, alginates, and H2 receptor antagonists, should be discussed with patients to reduce PPI dose (2, 22).

During our study, we did not delve into the medical and drug history of the patients. However, certain comorbidities and medications can put patients at a higher risk of adverse effects associated with prolonged PPI use. For instance, patients taking diuretics along with PPIs are reported to have a higher likelihood of hypomagnesemia compared to those taking PPIs alone (23). Post-menopausal women and those with a risk of osteoporosis are more likely to experience fractures due to impaired calcium intake associated with PPIs (24). Additionally, patients on metformin therapy may have a higher chance of vitamin b12 deficiency if combined with PPI use (25). Therefore, pharmacists are recommended to employ an individualized approach to educating patients about PPI side effects, considering their comorbidities and medication history to reduce the harm in high-risk patients.

Unlike prior studies, we inquired about patients' knowledge of cautions regarding PPI discontinuation. Only a small percentage of patients in our survey had any knowledge regarding the potential dangers of abruptly discontinuing PPIs after a prolonged period. This is particularly important for individuals who take PPIs as OTC medications and those who take PPIs for ambiguously acid-related complaints since abrupt cessation can lead to severe genuine acid-related symptoms in such cases. Additionally, sudden discontinuation and attendant rebound acid hypersecretion could entail lethal consequences in elderly individuals and those who

were taking NSAIDs or antiplatelet medications. So, It is incumbent upon physicians and pharmacists to take the initiative and advise patients about this risk.

Although this is the first study investigating patients' awareness of PPI side effects in the UAE, the strength of our findings is limited by several factors. First, we inquired about a small sample of patients and pharmacists. Second, our threshold for defining long-term PPI consumption was lower than current guidelines identifying short-term PPI use as up to 14 to 8 weeks of usage. Third, side effects investigated in our survey were limited to three electrolyte and micronutrient derangements. However, it's important to bear in mind that the negative effects of chronic PPI use are not limited to just the micronutrient deficiency investigated in our survey. Several systematic reviews and meta-analyses have reported that long-term PPI users are at a higher risk of acute kidney injury, chronic kidney disease (26), GI cancers, community-acquired pneumonia (27), and enteric infections, especially with *Clostridium difficile* (28, 29). However, we disregarded these consequences in our study since there was significant heterogeneity among the studies included in these meta-analyses, and residual confounding could adversely affect the reliability of such associations.

## 5. Conclusions

The presenting survey revealed a high prevalence of PPI use in the general population of UAE yet there is a low knowledge about these side effects among those taking these medications. The current pharmacist practice is inefficient for inculcating the potential harms of chronic PPI use and they are required to optimize their efforts to educate patients and bridge the knowledge gaps.

## 6. Declarations

### 6.1. Acknowledgments

This manuscript is derived from the Aisha Juma AlBlooshi thesis in partial fulfillment of the requirements for the degree of Master of Clinical Pharmacy (ID: 2019002). The thesis entitled has been carried out in the Dubai Pharmacy College, United Arab Emirates under the guidance of Dr. Hanan Anbar. The work is original and has not been submitted in part or full by me for any degree or diploma at any other University. The material obtained from other sources has been duly acknowledged in the thesis.

### 6.2. Competing interest

The authors declare that they have no competing interests.

### 6.3. Availability of data and materials

The data generated and analyzed during the current study are available from the corresponding author upon reasonable request.

### 6.4. Authors' contribution

All the authors met the standard criteria of authorship based on the recommendations of international committee of medical journal editors.

### 6.5. Using artificial intelligence chatbots

None.

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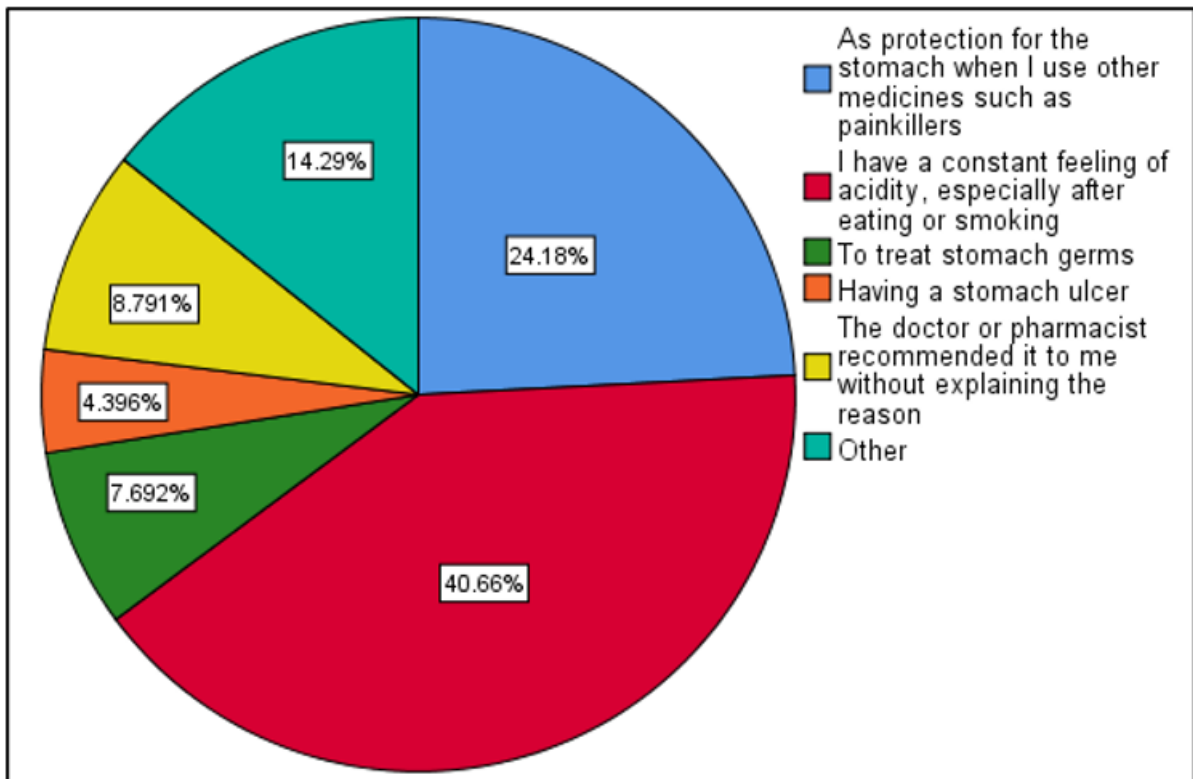


Figure 1: Reasons for taking PPI among patients (91 users).

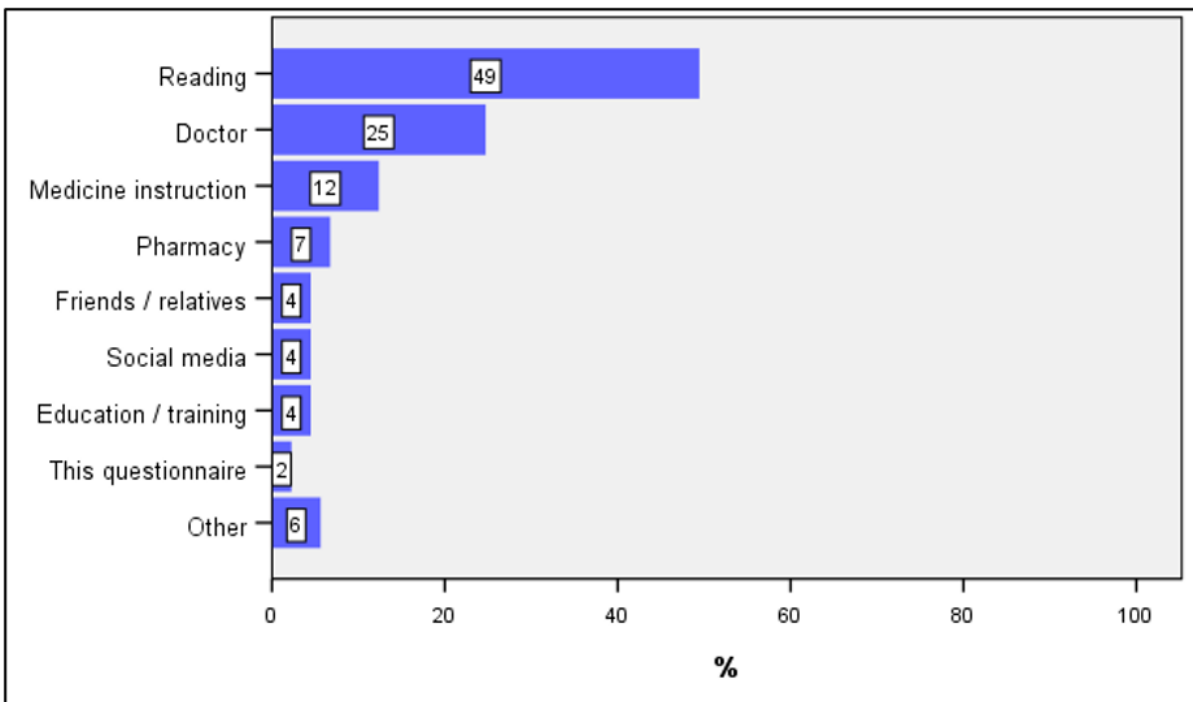


Figure 2: PPI users' source of knowledge regarding its side effects.

**Table 1:** Demographic characteristics and knowledge score (KS) of participants in the patient survey

Variables	PPI users		KS (IQR)	P-value
	Yes (n=91)	No (n=257)		
<b>Gender</b>				
Male	65 (71.4)	142 (55.3)	0 (0–2.5)	0.804
Female	26 (28.6)	115 (81.6)	0 (0–2)	
<b>Age (year)</b>				
20 - 29	14 (16.1)	63 (25.4)	2 (1–5)	0.105
30 - 39	15 (17.2)	70 (28.2)	0 (0–1)	
40 - 49	34 (39.1)	63 (25.4)	0 (0–1)	
50 - 59	16 (18.4)	39 (15.7)	0.5 (0–3)	
≥ 60	8 (9.2)	13 (5.2)	0 (0–0.5)	
<b>Marital status</b>				
Single	11 (12.1)	62 (24.7)	1 (0–2)	0.658
Married	78 (85.7)	180 (75.4)	0 (0–2)	
Divorced	2 (2.2)	9 (3.2)	0.5 (0–1)	
<b>Education</b>				
Below high school	2 (2.2)	10 (3.9)	0 (0–0)	0.749
High school	19 (20.9)	71 (27.6)	0 (0–1)	
Diploma	10 (11)	36 (14)	1 (0–5)	
Bachelor	45 (49.5)	109 (42.4)	0 (0–2)	
Higher education	15 (16.5)	31 (12.1)	0 (0–1.5)	
<b>Nationality</b>				
Emirati	59 (64.8)	201 (78.2)	0 (0–1)	0.004
Other	32 (35.2)	56 (21.8)	0 (0–0)	
<b>Employment</b>				
Employed	66 (83.5)	132 (64.1)	0 (0–2)	0.865
Retired	7 (8.9)	14 (6.8)	0 (0–2)	
Student	2 (2.5)	25 (12.1)	2 (0–4)	
Housewife	3 (3.8)	23 (11.2)	0 (0–2.5)	
Unemployed	1 (1.3)	12 (5.8)	0 (0–0)	

Data are presented as number (%). Knowledge score is presented as median (IQR: interquartile range).