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INVESTIGATION OF AWARENESS OF PROTON PUMP INHIBITOR THERAPY IN ADULTS USING PROTON PUMP INHIBITORS ADMITTED TO PRIMARY CARE

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Abstract

Objectives: Because proton pump inhibitors are effective and well tolerated, their use without an appropriate indication is increasing. This raises concerns about long-term side effects.

Materials and Methods: This cross-sectional survey study was conducted among patients using proton pump inhibitors for any reason in 4 primary care centers in Hatay province. The study included 451 participants. The statistical significance level of the data obtained was interpreted with the "p" value. $p<0.05$ values were considered statistically significant.

Results: In this study, 39.9% of patients were using proton pump inhibitors inappropriately. 38.4% of the patients had been using proton pump inhibitors for more than 2 years. There was also a significant association between use for more than 2 years and the occurrence of side effects ($p=0.001$). 75.4% of the patients stated that they were not informed about the side effects of the drug. In addition, in patient-physician communication, there was a significant correlation between the physician's mention of side effects and inappropriate use of proton pump inhibitors ($p=0.009$).

Conclusion: Inappropriate proton pump inhibitors can be prevented by starting the appropriate dose of proton pump inhibitor in the patient with the necessary indication, informing the patient at the first prescription, creating a physician's plan about when to terminate proton pump inhibitors, and raising awareness of the patient about this issue.

Keywords: Proton pump inhibitors, primary care, inappropriate use.

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Introduction

Proton pump inhibitors (PPIs) are the most effective agents for inhibiting hydrochloric acid secretion and are widely used in the treatment and prophylaxis of upper gastrointestinal disorders such as gastroesophageal reflux disease (GERD), Helicobacter pylori (HP) eradication therapy, drug-induced ulcers, and other hypersecretory conditions.[1]

Proton pump inhibitors (PPIs) are the third most widely used drugs in the world after antibiotics and statins.[2] It is also at the forefront of the list of safe medicines prepared by the World Health Organization. It is rare for a patient to discontinue these drugs due to side effects.[2, 3] Therefore, long-term use without an appropriate indication is increasing. According to current literature, inappropriate use of proton pump inhibitors (PPIs) is defined as prescribing omeprazole or esomeprazole in patients receiving clopidogrel, using PPIs in cases of uncomplicated gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux, in the treatment of uncomplicated peptic ulcer, in patients diagnosed solely with gastritis or functional dyspepsia, continuing PPI therapy after completion of Helicobacter pylori eradication, using PPIs as a diagnostic tool, and prolonged use (beyond eight weeks) for stress ulcer prophylaxis in non–intensive care unit (ICU) patients.[4-7]

Looking at the PPI prescription rate in Turkey in general, while the total number of 1-month treatments administered was 13.767.477 in 2006, it increased by approximately 255% in 2011 and reached 35.152.889.[8] In 2012, a total of 31.342.307 PPI prescriptions were written in 1 year, 2.576.080 in 1 month, and 85.869 in 1 day.[2] In addition, it was observed that 25-75% of those who used PPIs for a long time used them without indication.[3] All these cause negative feedback to the health system and the economy.

Therefore, it has become important to draw attention to the inappropriate use of PPIs in primary care, which is the most common referral point of patients and where PPIs are most commonly prescribed, and to increase the awareness of patients on this issue. For this reason, this study aimed to determine the inappropriate use of PPIs and related factors, as well as the side effects associated with the inappropriate use of PPIs.

Materials and Methods

Survey Design

This cross-sectional study was conducted by applying a questionnaire, and the 'PPI use and awareness' questionnaire, which was prepared according to the existing literature, was applied. The questionnaire included 34 questions in total, the first 3 questions were designed to measure demographic information(age, gender, education level), 3 questions were designed to measure patient-physician communication during PPI

use(mentioning side effects, warning about the duration of use of the drug, warning about unconscious use of the drug), 5 questions were designed to measure patients' lifestyle habits(Smoking, alcohol, tea, coffee consumption status and frequency, meal plan), 3 questions were designed to measure the incidence of side effects due to PPI use(if you experience any side effects and what side effects you experience), and the other 20 questions were designed to measure physician and patient attitudes and behaviors regarding PPI use.

Sample Selection and Data Collection

This study was approved by the Ethics Committee for Non-Interventional Clinical Research of Hatay Mustafa Kemal University on November 29, 2021, under decision number 01. All participants signed a consent form that was prepared following the principles of the Declaration of Helsinki. The sample size of the study was determined to be 384 using the online Raosoft sample size calculator, with a 95% confidence level and a 5% margin of error. Adults using PPIs were included in the study voluntarily, and a questionnaire was considered valid for analysis only when 100% of the questions were answered.

The participants of this study were selected voluntarily among patients who used PPIs for any reason (presenting with gastrointestinal complaints, presenting for PPI prescription) who applied to 4 primary care centers in Hatay province. After verbal and written informed consent was obtained, the questionnaire was administered face-to-face. Data were collected by us between December 1, 2021, and February 28, 2022. This cross-sectional study included individuals who met the following inclusion criteria: (1) willingness to participate in the study, (2) current use of proton pump inhibitors (PPIs), and (3) age between 18 and 75 years. Participants who did not meet these criteria or who submitted incomplete responses were excluded from the study. A total of 462 patients volunteered to participate in the study. However, 11 participants were excluded due to incomplete data, resulting in a final sample of 451 individuals included in the analysis.

Statistical Analysis

The collected data were entered into the IBM SPSS Statistics 21 statistical program and analyzed. Descriptive statistics were expressed as mean ± standard deviation for continuous variables and as number of cases (none) and (%) for nominal variables. Chi-square, Kruskal-Wallis, and Fisher's Exact tests were used to determine the relationship between categorical variables. The statistical significance level of the obtained data was interpreted with the “p” value. $p<0.05$ values were considered statistically significant.

Results

A total of 451 patients, 228 females (50.6%) and 223 males (49.4%), aged between 16 and 96 years and using PPIs, were included in the study. The mean age of the patients was calculated as 54.29±18 years. While 14.2% (n=64) of the patients were illiterate, 45.2% (n=204) were primary school graduates, 25.7% (n=116) were high school graduates, and 14.9% (n=67) were undergraduate/graduate graduates. Sociodemographic data and lifestyle habits of the patients are shown in Table 1.

Table 1. Sociodemographic data and lifestyle habits of patients

		None	%
Sex	Woman	228	50.6
	Man	223	49.4
Education Status	İlliterate	64	14.2
	Primary school graduate	204	45.2
	High school graduate	116	25.7
	Undergraduate/graduate	67	14.9
Do you smoke or use tobacco?	Yes, 1 pack or less per day	108	23.9
	Yes, more than 1 pack per day	25	5.5
	Yes, I drink occasionally.	8	1.8
	No, I don't use it.	310	68.7
What is your frequency of alcohol use?	Every day	10	2.2
	3-6 times a week	5	1.1
	1-2 times a week	20	4.4
	2-3 times a month	44	9.8
	Rare	44	9.8
	None	328	72.7
Are your meals regular?	Yes	370	82.0
	No	81	18.0

Among the participants, 51.2% (n=231) were mostly using the active ingredient Pantoprazole. This was followed by Lansoprazole (24.6%, n=111) and Esomeprazole (16.2%, n=73). The least used drug was Omeprazole (0.4%, n=2). The most frequently prescribed specialties were General Internal Medicine (47%, n=212) and Family Medicine (30.8%, n=139), respectively. 23.9% (n=108) of the patients stated that the physician did not inform them about how long they should take the medication. 38.8% of the patients stated that they were using PPI because of polypharmacy, 59.6% because of stomach complaints, and 1.6% because of other reasons. The frequency of PPI use and the duration of PPI use are shown in Table 2.

Table 2. Frequency and duration of PPI use in patients

		None	%
Frequency of use	1 time a day	325	72.1
	2 times a day	32	7.1
	Occasionally, when he has a stomachache	87	19.3
	Rarely	7	1.6
Duration of use	Less than 4 Weeks	105	23.3
	Less than 8 Weeks	54	12.0
	Longer than 8 Weeks	36	8.0
	3 Months	22	4.9
	6 Month	17	3.8
	1 Year	29	6.4
	2 Year	15	3.3
	Over 2 Years	173	38.4

After the initiation of the medication, 47% of the patients never went for a follow-up visit, 81.2% never took a break from the medication, 35.5% used the medication from the pharmacy voluntarily without consulting the physician, and 39.9% used it inappropriately.

Among those who stopped the medication (n=85); 71.77% (n=61) stated that they restarted the medication on their own decision because their complaints recurred, and 28.23% (n=24) stated that they restarted the medication with the doctor's advice.

Of the patients (n=451); 75.4% stated that they were not informed about the side effects of the drug, and 43.2% stated that they did not receive information about side effects from their physicians.

Table 3 shows the questionnaire questions evaluating the patient-physician communication status and the answers given to them. In addition, it was determined that there was a significant correlation between the physician's mention of the side effects of the drug and inappropriate PPI use in patient-physician communication (p=0.009), (Table 4).

Table 3. Questions and responses assessing patient-physician communication about PPI use

		None	%
Has your physician ever warned you about medication?	Yes	125	27.7
	I don't remember	158	35.0
	No	168	37.3
Does your doctor tell you about the side effects of the medicine?	Yes	95	21.1
	I don't remember	161	35.7
	No	195	43.2
Does your doctor ask you how long you have been taking the medicine?	Not prescribed again	7	1.6
	Always asking	83	18.4
	Mostly asking	84	18.6
	Occasionally he asks	81	18.0
	Rarely asked	72	16.0
	Never asks	124	27.5

Table 4. Association between patient-physician communication and inappropriate PPI use

		Inappropriate Use		p-value*
		Yes n(%)	No n(%)	
Did your doctor tell you about the side effects of the medicine?	Yes	25(13.9)	70(25.8)	**0.009**
	I don't remember	71(39.4)	90(33.2)	
	No	84(46.7)	111(41.0)	
Does your doctor ask you how long you have been taking the medicine?	Not prescribed again	1(0.6)	6(2.2)	**0.036**
	Always asking	22(12.2)	61(22.5)	
	Mostly asking	34(18.9)	50(18.5)	
	Occasionally he asks	36(20.0)	45(16.6)	
	Rarely asked	28(15.6)	44(16.2)	
	Never asks	59(32.8)	65(24.0)	
Did your doctor give any warning about the medicine?	Yes	40(22.2)	85(31.4)	**0.034**
	No	140(77.8)	186(68.6)	

p: Chi-square, n: None*

8.2% (n=37) of the patients stated that they experienced side effects while using PPI. In the long term, the most common side effects were nausea (1.8%, n=8) and headache (1.6%, n=7), and in the short term, the most common side effects were nausea (3.1%, n=14) and constipation (2.7%, n=12). In addition, there was a significant relationship between use for more than 2 years and the occurrence of side effects (p=0.001), (Table 5).

Table 5. The relationship between the duration of PPI use and side effects

Side Effect	PPI Time to Use								
	Less than 4 weeks n(%)	**Less than 8 weeks n(%)**	**longer than 8 weeks n(%)**	**3 months n(%)**	**6 months n(%)**	**1 year n(%)**	**2 year n(%)**	**More than 2 years n(%)**	**p***
Yes	14(%13.3)$_a$	8(%14.8)$_a$	3(%8.3)$_a$	4(%18.2)$_a$	2(%11.8)$_a$	3(%10.3)$_a$	1(%6.7)$_{a,b}$	2(%1.2)$_b$	**0.001**
No	91(%86.7)$_a$	46(%85.2)$_a$	33(%91.7)$_a$	18(%81.8)$_a$	15(%88.2)$_a$	26(%89.7)$_a$	14(%93.3)$_{a,b}$	171(%98.8)$_b$	

p: Chi-square (likelihood ratio) , n: None*

In our study, when the relationship between the age of the participants and the physician's information about PPI use was evaluated, it was found that physicians mostly warned older patients about PPI use (p=0.006), (Table 6).

Table 6. Age of the participants and the physician's information on PPI use

	Age(mean±sd)	**p-value***
Physician warning	55.43±17.11	**0.006**
The physician does not remember warning	57.17±17.70	
No physician warning	50.74±18.42	
Physician has a side effect bet	55.28(17.80)	**0.021**
Doesn't remember the side effect bet	56.81(18.50)	
No side effects mentioned	51.73(%17.41)	

p: Kruskal-Wallis, sd: Standard deviation*

Discussion

This study will guide in identifying inappropriate PPI use and showing the magnitude of the problem, and the identification of associated conditions will guide the planning of interventions in terms of rational drug use. In

addition, the lack of any other study determining the frequency of inappropriate PPI use and associated factors in Hatay province reveals the importance of this study.

Considering the criteria for inappropriate use according to the existing literature, 39.9% of the patients in this study used PPI inappropriately, and 83.6% of the patients never discontinued the medication for more than 1 year. T.Boghossian, R.Nardino, A.Ladd, P.Haastrup, L.Pasina et al. found that the rate of inappropriate PPI use ranged between 25% and 75%.[3, 9-13]

In a study conducted in our country, the rate of drug use without consulting a physician was found to be 5.3%.[14] In our study, it was found that 35.5% of the patients took the medication from the pharmacy voluntarily without consulting a physician. In a study conducted by Nazan K. and Murat K. in our country, it was found that 86.3% of the patients were not informed about the side effects of the drug.[15] In our study, this rate was found to be 75.4%. These high rates indicate inappropriate use of PPIs, further emphasizing the importance of our study in terms of the region, and reveal the need for effective interventions in our region regarding inappropriate PPI use.

In our study, 70% of the patients who discontinued PPI started to use PPI again because their complaints started again. In a study conducted in our country, this rate was 56%.[16] These high rates can be explained by the increase in rebound ascites caused by the use of PPIs for more than 2 weeks. In cases where PPIs should be used for a long time, it is recommended to continue treatment at the lowest effective dose to prevent rebound hyperacid secretion and to terminate the treatment by adjusting the dose every other day in a step-down manner.[17] This information should be internalized by primary care physicians and should be included in their daily practice and shared with their patients.

In the studies conducted by Fatma C. et al. and Pasina L. et al. the 3 most frequently used active substances were found to be Lansoprazole, Pantoprazole, and Esomeprazole. [12, 18] In our study, the most frequently used active substance was Pantoprazole, and the least frequently used active substance was Omeprazole. The fact that Pantoprazole was the most frequently used active ingredient may be because the mean age of the patients who participated in our study was high, and due to the multidrug use, physicians prescribed Pantoprazole more frequently with the idea that the drug interaction rate was lower in Pantoprazole compared to other active ingredients.

In addition, considering that patient-physician communication was significantly associated with inappropriate PPI use (Table 4), the importance of primary care physicians, who have the most contact with patients, is understood, and primary care physicians have great duties in this regard.

In recent years, regulatory measures have been introduced in primary care settings in our country to address the growing concern of inappropriate proton pump inhibitor (PPI) use. These measures include limitations on prescribing rates, particularly for indications not supported by current clinical guidelines. Such interventions aim to promote rational drug use and reduce the potential risks associated with unnecessary long-term PPI therapy.

Future research should focus on evaluating the effectiveness of these prescribing restrictions. Specifically, longitudinal studies could investigate whether these policy changes have led to measurable improvements in prescribing behavior, reduced rates of inappropriate PPI use, and better adherence to evidence-based guidelines. This would provide valuable insight into the long-term impact of such regulatory strategies on clinical practice and public health.

In conclusion, in our study, we observed an increase in side effects due to inappropriate PPI use for more than 2 years. Patients reported that they used PPIs without being under the control of a physician, and they also reported that physicians did not inform them about the duration of PPI use and side effects.

To prevent inappropriate use of PPIs, there is a need for physician-patient training as well as interventions by health authorities to prescribe the drug depending on the duration of use and not to give it to the patient without a prescription. Perhaps these interventions could start by stating that the use of the term 'stomach protector' instead of PPI is not appropriate for these drugs. This term creates the perception that patients should use a PPI with any medication when it is started. As seen in this study, there are serious deficiencies in the follow-up of patients who are prescribed PPI for any reason and in the termination of PPI use. In addition, the perception that polypharmacy requires the use of PPI should be abandoned, and PPI should be prescribed if there is a drug that requires the use of PPI among the drugs used by the patient.

As a result, it would be a correct approach to start PPI at the appropriate dose for patients with a necessary indication, to inform the patient at the first prescription, to inform the patient about when PPI will be terminated, to formulate the physician's plan, and to inform the patient.

Ethical Considerations: This study was approved by the Ethics Committee for Non-Interventional Clinical Research of Hatay Mustafa Kemal University on November 29, 2021, under decision number 01.

Conflict of Interest: The authors declare no conflict of interest.

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