

## Evaluate the effectiveness and safety of proton pump inhibitors (PPIs) in the treatment of upper GIT disorders

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### Abstract

**Introduction:** Proton pump inhibitors (PPIs) are most prescribed medication classes and have similar efficacy between generic and brand names. PPIs are used for treatment upper GIT disorders. The aim of the present study was to evaluate the effectiveness and safety of proton pump inhibitors (PPIs).

**Methods:** A cross sectional study conducted randomly on pharmacies, patients and Doctors to collect a data regarding the effectiveness and safely use of PPI through predesigned questionnaire containing information about dosage, types, side effect, effectiveness and safety of PPIs. The collected data was analysis by using Chi-square for determine the significant differences at  $\alpha < 0.05$ .

**Result:** The result of present study revealed numbers of points in which the questionnaire were intended for pharmacies, patients and doctors knowledge, effectiveness and safety of PPIs. The data gathered from pharmacy shown PPI dispensed without prescription ( $P < 0.05$ ) in dose of 20 mg of omeprazole and for treatment of gastritis, stomachache and on medication use ( $P < 0.05$ ). No side effect or any problem, safe, and effective of PPIs was from patients seeking PPIs to the drug dispensers. Furthermore, questionnaire for patients whom seeking treatment shown some similarity to pharmacies answers, however lack the knowledge about side effect of PPIs, and PPIs withdraw among patients. PPIs was found to be used by patients due to the advices of friends ( $P < 0.05$ ). The last part in this study was doctors involved in which some common similarity were also identified between doctors, patients and pharmacies responses. Although, Doctors responses were revealed that PPIs should be used by prescription in single dose of common types of PPIs ( $P < 0.05$ ).

**Conclusion:** Due to the short time use of PPIs have been reported. This study suggested that, even no side effect and highly effective of PPIs reported, the PPIs should be monitoring and use under prescription.

**Keywords:** PPIs; Patients; Pharmacies; Doctors; Effectiveness; Safety.

### 1. Introduction

Proton pump inhibitors (PPIs) have been identified in 1990s [1] and defined as class of drugs effect on lowering stomach acid production via irreversibly inhibiting the  $H^+/K^+$  ATPase proton pump of the stomach [2]. PPIs play significant role

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in the alleviated of *Helicobacter pylori* infection and also in the deterrence of upper gastrointestinal tract disorders, ulcers and bleeding in patients under antiplatelet therapy and/or non-steroidal anti-inflammatory drugs [2]. Furthermore, the medical options for the management of gastrointestinal reflux disease include antacids, histamine-2 receptor antagonists (H2RAs), and PPIs. PPIs treatment are consistently demonstrated to have higher healing response rates and lesser relapse rates in remedy of erosive esophagitis than H2RAs or placebo [3].

Currently, proton pump inhibitors (PPIs) is considered among the most commonly prescribed medications [4]. During the last decades, PPIs enhances the optimizing the healthcare community worldwide regarding its safety and effectiveness profile [5, 6]. Though, the part of effectiveness remains true, disquiets have been arise regarding the outcome of long term use of PPIs and the serious adverse effects it may rises. The long term use of PPIs are associated with increased risk for gastric cancer, dementia, diarrhea pneumonia, increased gastric infection, gastric neuroendocrine tumor, hypomagnesemia, colon cancer, spontaneous bacterial peritonitis and hepatic encephalopathy and bacteria overgrowth of small intestine [7, 8].

In several studies, reported that improving the gastrointestinal function, ulcer, and GERD with PPIs than with H2RAs or placebo [8-10]. Additionally, the cumulative incidence has been found in healing rate irrespective of treatment duration among PPIs users (84%) as compared to H2RAs (52%) and placebo (28%) [11]. Furthermore, A comparison between on-demand PPI therapy to continuous PPIs treatment result in patient satisfaction was no differences to on-demand PPI therapy in patients with non-erosive reflux disease [12]. However, on-demand PPIs therapy is not approved by FDA for this patient population [12]. The single therapy with a PPI is not effective in eradicating *H. pylori* infection. Therefore,, the addition of a PPIs to a combination of antibiotics improves eradication rates compared to those achieved with antibiotics alone [13, 14]. Due to lack of information if PPIs is safe and effectives among patients, and pharmacies and doctor opinion related PPIs used. Sacred data was found in the literature in which evaluated of safety and effectiveness of PPIs through direct interview to gathers enough background of PPIs side effect, safe, and effectiveness. The aims of the study is to evaluate the safety, possible side effect and effectiveness of proton pump inhibitors (PPIs) in terms of symptom resolution and relieve of upper GIT disorders.

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## 2. Material and methods

### 2.1. Study designed and sample size

A Cross sectional survey conducted from beginning of November 2020 to the end of March 2021 on randomly selected patients suffering from upper GIT disorder visiting doctors, a doctors and pharmacies for receiving PPI in Benghazi city, Libya.

The sample in this study were selected randomly and divided into three categories in which questions intending for interview doctors, patients or drug dispensers (pharmacist)

The sample of this study comprised 83 Patients, 63 Doctors and 117 Pharmacies.

- Patients in this study whom seeking medical remedy for any chronic disease recruited from clinics and hospitals.
- Pharmacies: questionnaires were intended for the people who dispense the drugs in the pharmacies for PPI effectiveness and safety.
- Doctors: whom in charge for patient's treatment in clinics and hospitals.

### 2.2. Questionnaires

Pre-designed questionnaires was validity in which contain number of questions related to personal information, safety and effectiveness of PPI , types of PPI , side effect, dosages of PPI , frequent uses , purpose of PPI used, and knowledge of PPI withdraw suddenly.

### 2.3. Ethical consideration

This study was approval by the local Ethics Committee of the Libyan international medical university (LIMU). Informed written consent was obtained through a consent form that was given to the participants along with the questionnaire.

### 2.4. Data analysis

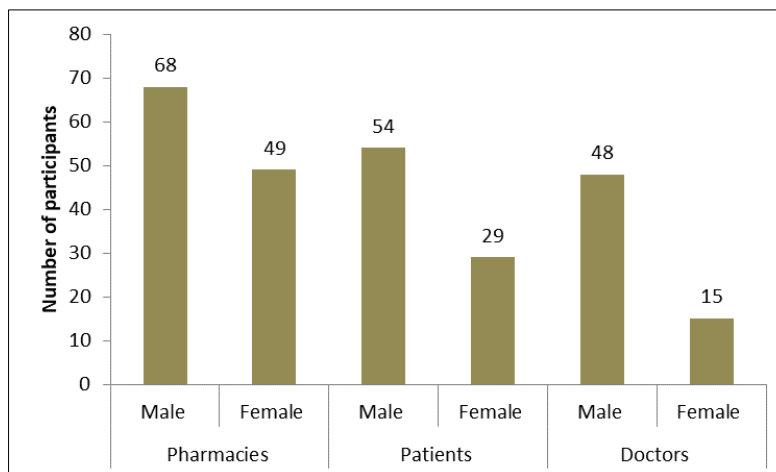
The data from the questionnaires was entered using Excel. Data set was exported to SPSS v.22 and Epi-info for complete analysis. Statistical analysis was carried out for the complete sample which were created according to measurements in which frequencies and percentages were used. To determine the differences regarding each categorical variable in the groups, Chi-square test was performed.  $p \leq 0.05$  was considered to be statistically significant.

### 3. Results

In the table 1, no age specified has been reported by drug dispensers, and the interviewed with patients attended clinics and hospitals found that 41% of patients fall under age groups 24-40 years old were use PPIs, followed by age groups between 18-25 years old 30.1%. Furthermore, the doctors reported that, the age of patients most common attended to the clinic and seeking medical remedy were found those age groups between 26-40 years old 79.4%. The male patients in three categories of studied samples were found mostly seeking PPIs than female.(Figure 1).

**Table 1** Ages distribution of the subjects from drugs dispenser, patients, and doctors.

Age categories of patients		N	N %	P values
Ages of patients recurrent buy PPI from pharmacies (Reporting of drugs dispensers)	Not defined	117	100.0%	
	Total	117	100.0%	
Age of patients participate in the study	18-25 years	25	30.1%	
	26-40 years old	34	41.0%	
	41-60 years old	22	26.5%	
	Older than 60 years	2	2.4%	
	Total	83	100.0%	
Age of patients attended the clinic for visiting doctor (ages reported by doctors)	18-25 years	7	11.1%	
	26-40 years old	50	79.4%	0.000
	41-60 years old	6	9.5%	
	Total	63	100.0%	



**Figure 1** Gender distribution reported by pharmacists (drug dispensers), patients, Doctors

### 3.1. Analysis the data collected from drug dispenser (Pharmacies) regarding PPI safety and affectivity

The survey in this study includes 117 pharmacies in which 117 questionnaires were collected. The data present in table 2 revealed that drug dispensers was not only dispense by the qualified person (pharmacists) 38.5% but this job also participate by medical doctor, dentist and public health professional,. Significant high number of patients ( $P=0.000$ ) were used PPIs by drug dispensers by their own experiences (76.1%). Furthermore, it was found that no differences in PPIs types dispensed by drugs dispensers. The reason beyond the drug dispensers prescribe the PPIs were due to their effective and safety 41% and 41.9% respectively. The question regarding most common types of PPIs prescribed by doctor shown that Omeprazole was the significant prescribed ( $P=0.000$ ). The most common dose of PPIs were consumed by patients seeking PPI was 20 mg ( $P=0.00$ ). The data in table 2 also revealed that the drug dispensers prescribe the PPIs for treatment of both Gastritis, stomachache and on medication uses ( $P=0.001$ ).

The table 3, shown that approximately 72.6% of patients recurring improve after use the PPI ( $P=0.000$ ). Regarding the side effect reported by drug dispensers on PPIs users revealed that no any side effect in which represent 100% and PPIs were shown effectiveness and safely in about 29.1% and 43.6% respectively and the rest 27.4% of the customers use PPIs were found no improvement .

**Table 2** information gathering from the drug dispenser at pharmacies on PPI uses.

		N	N %	P values
Qualification of drugs dispensers	Pharmacist	45	38.5%	
	Medical doctor	10	8.5%	
	dentist	37	31.6%	
	Public health	25	21.4%	
	<b>Total</b>	117	100.0%	
Dispense of PPIs	With prescription	28	23.9%	
	Without Prescription	89	76.1%	0.000
	<b>Total</b>	117	100.0%	
Most common PPIs prescribed by doctor	Omeprazole	74	63.2%	0.000
	Esomeprazole (Nexium)	43	36.8%	
	<b>Total</b>	117	100.0%	
If PPIs is not prescribed which PPIs is dispensed	Omeprazole	63	53.8%	
	Esomeprazole (Nexium)	54	46.2%	
	<b>Total</b>	117	100.0%	
The reason for choose and dispense the particular PPIs are due to	Cheap	20	17.1%	
	Effective	48	41.0%	
	safe	49	41.9%	
	<b>Total</b>	117	100.0%	
Dose of PPIs dispensed	10 mg	19	16.2%	
	20 mg	73	62.4%	0.00
	40 mg	25	21.4%	
	<b>Total</b>	117	100.0%	
Dispensed PPIs to the patient for treatment of	Ulcer	1	0.9%	
	<i>H pylori</i>	5	4.3%	
	Ulcer and gastritis	10	8.5%	
	Gastritis, stomachache and on medication use	76	65.0%	0.001
	Gastritis and <i>H pylori</i>	25	21.4%	
	<b>Total</b>	117	100.0%	

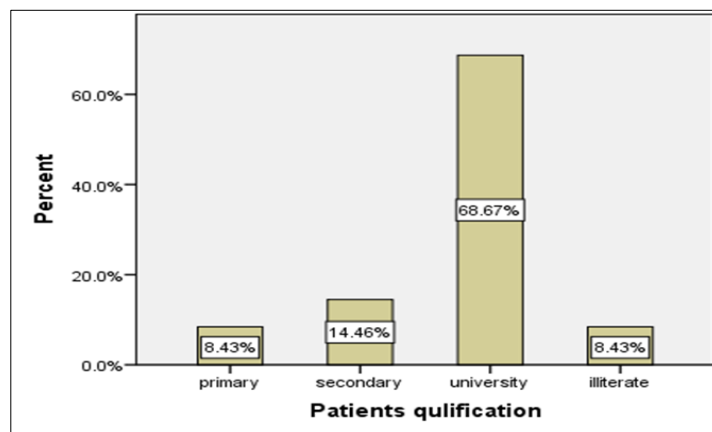
Chi-square test was performed within groups and considered significant at  $\alpha < 0.05$ .

**Table 3** information gathering from the drug dispenser at pharmacies on PPI uses.

		N	N %	P values
Know the side effect of PPIs	<b>Yes</b>	117	100.0%	
	Total	117	100.0%	
Time of taken PPIs	Before breakfast	61	52.1%	
	Before breakfast and dinner	56	47.9%	
	<b>Total</b>	117	100.0%	
The patients improved after use PPIs	Yes	85	72.6%	0.000
	No	32	27.4%	
	<b>Total</b>	117	100.0%	
Drug dispenser asked the patients once improved for PPIs	Non improved	32	27.4%	
	Effectiveness	34	29.1%	
	Safely	51	43.6%	
	<b>Total</b>	117	100.0%	
If Patients complain on any side effect	No	117	100.0%	
	<b>Total</b>	117	100.0%	
Option for trial after the failure of first PPIs	No failure	117	100.0%	
	<b>Total</b>	117	100.0%	
The patients used same PPIs	Yes	117	100.0%	
	<b>Total</b>	117	100.0%	

Chi-square test was performed within groups and considered significant at  $\alpha < 0.05$ .

**3.2. Analysis the data collected from patients regarding PPIs safety and affectivity:**



**Figure 2** Qualifications of the patients involve in the study and use PPIs

The patients in this study recruited from hospital and/or clinics seeking treatment for chronic diseases. In the figure 2, about tow third of patients have high levels of educations (university levels) followed by secondary education levels (14.46%) while the other education levels being the least include primary and illiterate (8.43%) for each. There was no significant differences between patient’s answers for PPIs can purchasing with or without prescription (Table 4). Omeprazole was significantly highly consumed by patients than other types of PPIs ( $P < 0.05$ ). The patients reported that used PPI due to their friend advices. Furthermore, the reason for selected particular type of PPI by patients was due to number of factors include prescribed by doctors, effective and as well as cheap. The significant dose of PPIs

consumed by patients was 20 mg twice a day mainly used before main meals. ( $P < 0.05$ ) (Table 5). The question regarding the purpose of using PPI, the most respondent was for treatment of GERD followed by ulcer and stomachache 32.5%, 21.7% and 18.1% respectively. Effectiveness of PPI has been reported by patients through pain disappear after using of PPI ( $P < 0.05$ ), no side effect ( $P < 0.05$ ) and significant numbers of patients were not have knowledge in case of withdraw PPI should be done gradually ( $P < 0.05$ )

**Table 4** information gathering from the patients on PPIs uses.

		N	N %	P values
Patient Taken PPIs	With prescription	44	53.0%	
	Without prescription	39	47.0%	
	<b>Total</b>	83	100.0%	
Most common PPIs used	Omeprazole	53	63.9%	0.001
	Pantoprazole	3	3.6%	
	Esomeprazole	16	19.3%	
	Omeprazole+ Pantoprazole+ Esomeprazole	11	13.3%	
	<b>Total</b>	83	100.0%	
Used PPIs under advice from	Friends	50	60.2%	0.043
	Pharmacists (drug dispensers)	33	39.8%	
	<b>Total</b>	83	100.0%	
The reason for use the particular type of PPIs	cheap	5	6.0%	
	Got prescription from doctor	29	34.9%	
	Effective	35	42.2%	
	Altogether	14	16.9%	
	<b>Total</b>	83	100.0%	
Dose of PPIs	10 mg	11	13.3%	
	20 mg	47	56.6%	0.003
	30 mg	9	10.8%	
	40 mg	12	14.5%	
	10 + 20 mg	4	4.8%	
	<b>Total</b>	83	100.0%	
Frequency of use of PPIs	Once	29	34.9%	
	Twice	51	61.4%	0.04
	Triple	3	3.6%	
	<b>Total</b>	83	100.0%	
Time for using PPI	Before breakfast	26	31.3%	
	When pain arises	3	3.6%	0.001
	Before main meals	54	65.1%	
	<b>Total</b>	83	100.0%	

Chi-square test was performed within groups and considered significant at  $\alpha < 0.05$ .

**Table 5** information gathering from the patients on PPI uses.

		N	N %	P values
Purpose for using PPIs is for treatment of	GERD	27	32.5%	0.04
	Ulcer	18	21.7%	
	Gastritis	6	7.2%	
	Stomachache	15	18.1%	
	H pylori	9	10.8%	
	Assist for digestions	8	9.6%	
	<b>Total</b>	83	100.0%	
Feeling and outcome after use of PPIs	Pain disappeared	50	60.2%	0.00
	Reduced HCL	11	13.3%	
	Eradicated H pylori	2	2.4%	
	GERD disappear	10	12.0%	
	Ulcer remedy	10	12.0%	
	<b>Total</b>	83	100.0%	
Patients Knowledge about The side effect of using PPIs	Yes	27	32.5%	
	No	56	67.5%	0.001
	<b>Total</b>	83	100.0%	
Health problems associated with use PPIs	Non	48	57.8%	0.000
	Headache	9	10.8%	
	Nausea	5	6.0%	
	Diarrhea	10	12.0%	
	Fatigue	6	7.2%	
	Dizziness	1	1.2%	
	Constipation	1	1.2%	
	Flatulence	3	3.6%	
<b>Total</b>	83	100.0%		
Duration of using PPIs	< one week	7	8.4%	
	1-2 weeks	24	28.9%	
	3-4 weeks	25	30.1%	
	One month	9	10.8%	
	1-6 months	7	8.4%	
	1 year	1	1.2%	
	Forever	10	12.0%	
	<b>Total</b>	83	100.0%	
Withdraw or stop using PPI should be gradually	Yes	16	19.3%	
	No	67	80.7%	0.000
	<b>Total</b>	83	100.0%	

Chi-square test was performed within groups and considered significant at  $\alpha < 0.05$ .

### 3.3. Analysis the data collected from Doctors regarding PPIs safety and affectivity:

In the next step, questionnaire was designs and intended for Doctors answers include many points were significant responded, such as PPIs should be given to the patients by prescription, Doctors prescribe different types of PPIs, the particular PPIs given to the patients based on effectiveness 49.2% followed by both cheap and effectiveness 38.1%. Furthermore, the doctors noticed the effectiveness and safety of PPI through high treatment outcome reported by patients 74.6% ( $P < 0.05$ ) and effectiveness of PPIs were the first priorities to the patients (Table 6 and 7).

**Table 6** Doctors opinion regarding use of PPIs.

		N	N %	P values
PPIs should be dispensed by prescription not as OTC	Yes	63	100.0%	
	<b>Total</b>	63	100.0%	
Doctors knowledge regarding PPIs side effect	Yes	63	100.0%	
	<b>Total</b>	63	100.0%	
PPIs most common prescribed	Omeprazole	3	4.8%	
	Esomeprazole	22	34.9%	
	Omeprazole, Pantoprazole and Esomeprazole	15	23.8%	
	Omeprazole and Esomeprazole	17	27.0%	
	Pantoprazole and Esomeprazole	6	9.5%	
	<b>Total</b>	63	100.0%	
Reason for choice the particular type of PPIs	cheap	5	7.9%	
	Safe	3	4.8%	
	Effective	31	49.2%	
	Cheap and effective	24	38.1%	
	<b>Total</b>	63	100.0%	
Dose of PPIs prescribed	10 mg	11	17.5%	0.001
	20 mg	47	74.6%	
	40 mg	5	7.9%	
	<b>Total</b>	63	100.0%	
Frequency of use PPIs	Once	36	57.1%	
	Twice	27	42.9%	
	<b>Total</b>	63	100.0%	

Chi-square test was performed within groups and considered significant at  $\alpha < 0.05$ .

**Table 7** Doctors opinion regarding use of PPIs.

		N	N %	P values
The time for patients to take PPIs	Before breakfast	36	57.1%	
	Before main meals	27	42.9%	
	<b>Total</b>	63	100.0%	
Prescribed PPIs for Treatment of	GERD	5	7.9%	
	GERD, gastritis, <i>H pylori</i> and for assist digestion	16	25.4%	
	GERD and Gastritis	11	17.5%	
	GERD, gastritis, <i>H pylori</i>	21	33.3%	
	For use of medications	10	15.9%	
	<b>Total</b>	63	100.0%	
	Pain gone	47	74.6%	0.000



Outcome of PPIs treatment through	GERD disappear	16	25.4%	
	<b>Total</b>	63	100.0%	
Any side effect reported by patients	No	63	100.0%	
	<b>Total</b>	63	100.0%	
Frequent prescribed PPIs due to	Effectiveness	49	77.8%	0.000
	Cost	1	1.6%	
	Experiences	13	20.6%	
	<b>Total</b>	63	100.0%	

Chi-square test was performed within groups and considered significant at  $\alpha < 0.05$ .

## 4. Discussion

Proton pump inhibitors initially intending for the treatment of esophagitis, and then subsequently been extended for treatment of other conditions of the upper GI tract [15].

The present study revealed a number of points in which this study include data from pharmacies, patients seeking treatment for chronic disease and also doctors.

### 4.1. Data collected form pharmacies

The data collected from pharmacies were unpredicted particular in many pointes include the people in pharmacies were not qualified persons in which the majorities were not pharmacists and professional persons this is could be why the question for PPIs can be sold without prescription given high responses (76.1%). FDA distributed a final law on September 12, 1980, launching a three-year trial period during which PPIs must be described with each new prescription for 10 specific drugs or drug classes. Involved are the drugs cimetidine, clofibrate, propoxyphene, phenytoin, warfarin, digoxin, and methoxsalen, and the drug class's ampicillins, benzodiazepines, and thiazides [16]. The result of this study also indicated that omeprazole and 20 mg as most common were dispense to the patients via drug dispensers this may be due to the reasons mentioned elsewhere in which the increase in PPIs use may be due to policy, prescriber, or patient factors, including increased availability of both branded and generic PPIs [17].

Based on several reported, there has been recent extensive media attention given to the safety of PPIs [15]. In the previous studies were shown PPIs was intended for use for many upper GIT disorder include Barrett esophagus, gastroesophageal reflux disease, dyspepsia, eosinophilic esophagitis, and treatment of *Helicobacter pylori* infection and in the deterrence of upper gastrointestinal tract ulcers and bleeding among patients undertaking antiplatelet therapy and/or non-steroidal anti-inflammatory drugs [15,18] and for some medication use [16]. Similarly has been found in this study in which Gastritis, stomachache and on medication use were reported by drug dispensers. The information gathering from pharmacies also indicated PPIs were safe and effective and no side effect reported among users and this due to PPI used for short time in this study. This finding was disagrees with a number of studies regarding safety and the side effect in which many studies found that PPIs has tremendous effects on the health when in use in long term [19-21]. However, therapeutic effectiveness has been found from the pharmacies once dispense the PPIs through patients responses for what feeling after used PPIs.

### 4.2. Data collected form patients

Some data collected from patients were similar to the data from pharmacies include most common PPIs used, dosages, PPIs used for treatment of GERD, time of use of PPIs, safety, effectiveness. But it seemed that among patients, the used of PPI due to advices of friends and this was not surprising own to similar where also obtained from the study carried out by Ali et al [15]. Furthermore, the patients have low knowledge about gradually withdraw of PPIs and their side effects. PPIs should be abrupt gradually due to withdrawal from PPIs (proton pump inhibitors) can lead to severe rebound acid secretion, a complication that can force users to become dependent on them. In additions, the patients mentioned that use PPIs can be twice a day and this could be dependent on the severity of upper GIT disorders and this intake also be safe for use [22].

### 4.3. Data collected from Doctors

Similarly were also obtained answers from doctors by which the result of PPIs safety, effectiveness, side effect, and doses were similar to those responses from patients and pharmacies. However, the doctors were agree with FDA rules

[16] in which PPIs should not be given as OTC (prescription only). The answers regarding number of PPI dose per day was present with slightly higher response as single dose but was not statistically significant. Overall, the data collected in this study revealed that PPI was generally safe, effective, being with no side effect, in single dose of any types of PPI used mainly before main meals. As with all other drugs, PPIs should be prescribed in the lowest effective doses and only continued for as long as necessary.

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## 5. Conclusion

The present study revealed that, age significant use of PPIs in which the male higher than female. The drug dispensers were found have different and prescribe the PPIs without prescriptions, in dose 20 mg of omeprazole for treatment of Gastritis, stomachache and on medication use. PPIs were found Effective and safe to the patients and no side effect have been reported. The significant numbers of patients were seeking medical remedy for treatment of GERD and were where used PPIs through advices of friends. The last part in this survey was doctors responses in which reported that PPIs should not be given to the patients without prescription, no particular of PPIs over the other to be choice, the most dose reported was 20 mg, PPIs prescribed to the patients based on effectiveness and both cheap and effectiveness, and the effectiveness of PPIs known through no pain raised after use. Altogether the data in this study suggested that, even no side effect and highly effective of PPIs reported in this study should be monitoring and PPIs should be use under prescription.

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## Compliance with ethical standards

### *Acknowledgments*

We grateful to all patients participate in the study.

### *Disclosure of conflict of interest*

No conflict of interest.

### *Statement of informed consent*

This study was approval by the local Ethics Committee of the Libyan international medical university (LIMU). The study was done through an interview of the participants and informed written consent was obtained through a consent form that was given to the participants along with the questionnaire.

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