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Evaluation of Proton Pump Inhibitor Use of Patients Registered in Family Health Centers Regarding Rational Drug Use

Aile Sağlığı Merkezlerine Kayıtlı Hastaların Proton Pompa İnhibitörü Kullanımlarının Akılcı İlaç Kullanımı Açısından Değerlendirilmesi

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Abstract

Background: Proton Pump Inhibitors (PPIs) have become mainstay medications for acid-related gastrointestinal diseases like Gastro-Esophageal Reflux Disease and peptic ulcer disease. However, emerging data indicates potential adverse effects with long-term PPI use, including infections, fractures, kidney injury, vitamin deficiencies, and dementia. The aim of this study is to evaluate the prevalence, inappropriate use frequency, medication behaviors, and knowledge levels of PPI usage among patients presenting to family health centers in Samsun, Turkey.

Materials and Methods: This cross-sectional and prospective study was conducted over a 3-month period between December 1, 2022 and March 1, 2023. The data were collected with a questionnaire filled by face-to-face interviews.

Results: The study included 826 participants with a mean age of 44.5◙14.9 years. The PPI prescription rate was 60.8%, with 42.4% (n=213) having used PPIs in the past 8 weeks. The most common reason for use was concurrent medication effects (31.6%), heartburn (29.5%), and stomach pain (15.0%). Most (74.5%, n=615) had no Gastro-Intestinal (GI) complaints, and among those with complaints the median duration was 6 months (range 1-240 months).

Conclusions: The findings highlight the need for continued research and awareness efforts to curb the irrational use of these important medications, an emerging global public health crisis. Implementation of clinical practice guidelines can help optimize utilization, improve patient outcomes, and prevent serious side effects and drug interactions due to excessive use.

Keywords: Proton pump inhibitors, drug misuse, primary health care, drug prescriptions, education of patients

ÖZ

Amaç: Proton Pompası İnhibitörleri, Gastro-Özofageal Reflü Hastalığı ve peptik ülser hastalığı gibi asitle ilişkili Gastro-İntestinal hastalıklar için temel ilaçlar haline gelmiştir. Ancak, ortaya çıkan veriler enfeksiyonlar, kırıklar, böbrek hasarı, vitamin eksiklikleri ve bunama dahil olmak üzere uzun süreli Proton pompa inhibitörü kullanımıyla olası olumsuz etkilere işaret etmektedir. Bu çalışmanın amacı, Türkiye'nin Samsun kentindeki aile sağlığı merkezlerine başvuran hastalarda Proton pompa inhibitörü kullanımının yaygınlığını, uygunsuz kullanım sıklığını, ilaç davranışlarını ve bilgi düzeylerini değerlendirmektir.

Gereç ve Yöntem: Bu kesitsel ve prospektif çalışma, 01.12.2022 ile 01.03.2023 tarihleri arasındaki 3 aylık bir süre boyunca yürütülmüştür. Veriler yüz yüze görüşmelerle doldurulan bir anketle toplanmıştır.

Bulgular: Çalışmaya ortalama yaşları 44,5◙14,9 yıl olan 826 katılımcı dahil edilmiştir. PPİ reçete oranı %60,8'di ve bunların %42,4'ü (n=213) son 8 haftada PPİ kullanmıştı. Kullanımın en yaygın nedeni eş zamanlı ilaç etkileri (%31,6), mide ekşimesi (%29,5) ve mide ağrısı (%15,0) idi. Çoğunun (%74,5, n=615), Gİ şikâyeti yoktu ve şikâyeti olanlar arasında medyan süre 6 aydı (1- 240 ay).

Sonuç: Bulgular, ortaya çıkan küresel bir halk sağlığı krizi olan bu önemli ilaçların mantıksız kullanımını engellemek için sürekli araştırma ve farkındalık çabalarına ihtiyaç olduğunu vurgulamaktadır. Klinik uygulama kılavuzlarının uygulanması, kullanımı optimize etmeye, hasta sonuçlarını iyileştirmeye ve aşırı kullanımdan kaynaklanan ciddi yan etkileri ve ilaç etkileşimlerini önlemeye yardımcı olabilir.

Anahtar kelimeler: Proton pompası inhibitörleri, Uygunsuz ilaç kullanımı, Temel sağlık hizmeti, İlaç reçeteleri, Hastaların Eğitimi

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Highlights

- Inappropriate long-term use of PPIs was identified in more than half of recent users.
- More than half of the participants reported using PPIs, often without active GI symptoms.
- Notably, knowledge about the side effects and cost of PPIs was low.

Introduction

Proton pump inhibitors (PPIs) effectively suppress gastric acid secretion by blocking H+/K+-ATPase enzymes in parietal cells (1). Consequently, PPIs have become mainstay medications for acid-related gastrointestinal diseases like gastroesophageal reflux disease (GERD) and peptic ulcer disease. However, emerging data indicates potential adverse effects with long-term PPI use, including infections, fractures, kidney injury, vitamin deficiencies, and dementia (2).

Recent meta-analyses suggest PPIs increase risks of Clostridium difficile and other enteric infections by enabling pathogen survival from reduced gastric acidity (3,4). A 2021 meta-analysis reported a 73% higher C. difficile infection risk among PPI users versus non-users. Risks of recurrence or recurrent infections also increased with PPI exposure (5,6).

The relationship between PPIs and pneumonia remains contentious, with some meta-analyses suggesting increased risks while others note uncertainties from residual confounding. Proposed mechanisms center on facilitated gastrointestinal bacterial colonization, micro aspiration, and impaired immunity. Overall evidence linking PPIs with incident pneumonia is inconclusive (7-9).

Collagenous colitis and lymphocytic colitis manifesting as chronic diarrhea have recently been associated with PPI exposure too (10). Proposed explanations include PPI-induced changes in intestinal permeability, immunity, microbiome composition and intraluminal milieu. Up to 25% long-term PPI users can also develop benign gastric fundic gland polyps that often regress on discontinuation (11).

Various meta-analyses indicate inconsistent evidence between PPI exposure and increased fracture risks (12). Impaired calcium absorption from hypochlorhydria likely mediates PPI-associated fracture risks rather than direct skeletal effects. Because hepatic metabolism clears PPIs, impairment can augment bioavailability and toxicity. PPIs also frequently interact with clopidogrel, warfarin, methotrexate, and antivirals via cytochrome enzymes (2).

While biological plausibility and worrisome case reports link PPI-induced hypergastrinemia with gastric neuroendocrine tumors, population data show no consistent evidence between PPI exposure and incident gastric or colorectal cancers. Confidence remains low regarding causal associations between PPI use and incident neoplasms (13,14).

Inappropriate PPI overprescribing is common, with use without clear indications in up to 90% inpatients and 50% outpatients (15). Canadian and American gastroenterology societies emphasize deprescribing PPIs when benefits no longer outweigh potential harms of continued therapy, through reassessment of indications, dosing minimization, switching to alternative drugs like histamine receptor-2 antagonists, or gradual discontinuation. Such judicious use aids minimizing needless expense and consequences (2).

The aim of this study is to evaluate the prevalence, inappropriate use frequency, medication behaviors, and knowledge levels of PPI use among patients presenting to family health centers in Samsun, Turkey. It also aims to provide up-to-date data on rational PPI use to the literature through a real field study conducted at primary care clinics.

Material and Methods

Study design

This cross-sectional and prospective study was conducted over a 3-month period between 01.12.2022 and 01.03.2023. The study population consisted of individuals registered at Family Health Centers (FHC) affiliated with the Samsun Provincial Health Directorate. According to Turkish Statistical Institute (TUIK) data obtained from the Samsun Governor's Office, the population of Samsun was 1,335,716 as of 2018. Using the Raosoft program, sample size calculation with 5% acceptable error, 50% frequency, and 99% confidence interval required reaching at least 664 people. Considering the populations of central (Atakum, Canik, Ilkadim, Tekkekoy) and peripheral (Alacam, Asarcik, Ayvacik, Bafra, Havza, Carsamba, Ladik, Kavak, Ondokuzmayis, Salipazari, Terme, Yakakent, Vezirkopru) districts, two FHCs were visited in central districts (8 working days) and one FHC in peripheral

districts (13 working days). One full day (total 21 working days) visit was planned for each FHC. Reviewing the registered population data from the Samsun Provincial Health Directorate, the busiest FHCs were selected based on district population. Target enrollment from each FHC was determined considering district populations, with 50 participants from central district FHCs and 16, 12, 12, 88, 24, 88, 10, 14, 16, 16, 42, 6, 56 participants, respectively, from the peripheral district FHCs listed above, totaling 800 targeted participants. Simple random sampling was used. Patients participated voluntarily.

To obtain participants' sociodemographic and clinical data, a 35-item questionnaire was administered face-to-face to collect information on age, sex, marital status, education, occupation, household size, income level, knowledge of acid suppressants, their prices, side effects, interactions, need for prescription, appropriate timing and dosage, how treatment was initiated and continued, prescribing clinician and indication, insurance coverage, where prescriptions were filled, lifestyle modification recommendations, follow-up after initiation, and treatment cessation. The 8-week period was used to define long-term PPI use (16). The questionnaire was developed using relevant literature. Participant income levels were compared to November 2022 data from the Turkish Confederation of Labor Unions (hunger line 7786 ₺ (◎418 $), poverty line 25364 ₺ (◎1362 $)) since 2022 TUIK data was unavailable at the time of the study considering recent high inflation. Each form took approximately 8-10 minutes to complete through face-to-face interviews. Participants received no financial compensation.

Inclusion criteria were presented to the designated FHCs during the specified dates and being age 18 or older. Exclusion criteria were failure to complete the interview and communication disorders that could impede participation.

Statistical analysis

Data was analysed using SPSS version 25.0. Frequency distributions and mean ± standard deviation were calculated for parametric data and median (minimum-maximum) for non-parametric data. Chi-square and Fisher's exact tests were used to compare categorical variables. The level of statistical significance was accepted as $p<0.05$. The sample size study was calculated using the Raosoft program with a 5% acceptable error, 50% frequency, and 99% confidence interval, and it was determined that at least 664 individuals needed to be included. The relationships between PPI use and education level, income status and presence of a health professional in the family were assessed using the chi-squared test.

Ethical approval

The study protocol was approved by the Samsun Provincial Health Directorate on November 10, 2022, and the Samsun University Clinical Research Ethics Committee. (Number: SUKAEK-2022-12/7 date :23.11. 2022. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice principles. Participants provided informed verbal consent after receiving detailed information about the study.

Results

The study included 826 participants with a mean age of 44.5±14.9 years. Over half (54.1%) were male, 74.7% were married, and 33.5% had a secondary education. Most participants were below the poverty line. 25% of participants had a relative who was a healthcare worker. Urban and rural participant selection was approximately equal. The characteristic features of the participants are shown in **Table 1**.

Table 1. Characteristic features of the participants

Participant Characteristics	**n (%)**
Mean age (years)	44.5 ± 14.9
Gender	
- Male	447 (54.1)
- Female	379 (45.9)
Marital status	
- Married	617 (74.7)
- Single	209 (25.3)

Education level	
- Primary school	270 (32.7)
- Secondary school	277 (33.5)
- University	252 (30.5)
- Graduate degree	27 (3.3)
Monthly income per capita	
- Below poverty line (<7786 TRY / (~418 $))	501 (60.7)
- Above poverty line (≥7786 TRY / (~418 $))	325 (39.3)
Healthcare worker family member	209 (25.3)
Region	
- Urban	407 (49.2)
- Rural	419 (50.8)

The PPI usage rate was 60.8% (n=502), with 42.4% (n=213) having used PPIs in the past 8 weeks. Just over half (53.5%, n=269) reported inappropriate long-term PPI use (>8 weeks). Most (74.5%, n=615) had no Gastro-Intestinal (GI) complaints, and among those with complaints the median duration was 6 months (range 1-240 months). The most reported complaint was gastroesophageal reflux (46.0%). Among current or prior users, 82.7% required no dose reductions, and 94.8% began using via prescription. The specialty that most frequently prescribed PPIs was Family Medicine, and the healthcare institution that most frequently prescribed PPIs was Family Health Centers. While 71.6% obtained PPIs from family health centers, 93.6% obtained them using a prescription and 64.8% would not use without a doctor's recommendation. Those with lower education levels and no healthcare worker family members were more likely to use PPIs without a recommendation (both $p<0.001$). **Table 2** shows PPI use patterns and prescribing details.

Table 2. PPI use patterns and prescription characteristics among participants

PPI Use Patterns and Prescribing Details	n (%)
Used PPIs in the past 8 weeks	213 (42.4)
Inappropriate long-term use (>8 weeks)	269 (53.5)
Previous or current PPI use	291 (47.3)
Most common reasons for use	
- Concurrent medications	178 (31.6)
- Heartburn	166 (29.5)
- Stomach pain	84 (15.0)
Having GI complaints	211 (25.5)
- Gastroesophageal reflux	97 (46.0)
- Gastritis	53 (25.1)
- Ulcer	47 (22.3)
Most common prescribing specialties	
- Family medicine	181 (37.8)
- Internal medicine	149 (31.1)
- Gastroenterology	26 (5.4)
- General surgery	25 (5.2)
Most common prescribing locations	
- Family health centers	343 (71.6)
- Public hospitals	124 (25.9)
- Private facilities	10 (2.1)
- University hospitals	2 (0.4)

Most participants (66.0%) were unaware of PPI costs. Of those who were aware, 72.6% felt prices were expensive. Responses differed significantly by income level ($p<0.001$), with higher income associated with lower perceived expensiveness. Most (86.7%) felt PPIs should only be used with a doctor's recommendation, though 33.1% admitted

advising others to use PPIs. Those with a healthcare worker family member were significantly less likely to make recommendations compared to others (57.4% vs 70.2%, p<0.001). Recommendation frequency also differed significantly by education level (p=0.002), with a linear trend of decreasing recommendations with higher education. Only 38.0% believed PPIs have side effects, most commonly nausea. Those perceived side effects were more likely to advise others (p<0.001) but not more likely to believe doctor consultation is necessary (p=0.060). Most (86.3%) felt PPIs should be taken before meals and 71.1% felt dosages should remain constant during treatment. Approximately half (52.7%) reported no prior PPI use. The most common reasons for use were concurrent medication effects (31.6%), heartburn (29.5%), and stomach pain (15.0%). There were no significant differences in PPI patterns between central and peripheral regions (p=0.852). Knowledge and attitudes about PPI use are shown in **Table 3**.

Around two-thirds (68.5%) were also counseled on lifestyle changes, most often by family medicine. Only 35.7% were asked to return for follow-up, with 70.2% returning within 1 month, most often by internal medicine. Just over half reported previously self-discontinuing PPI treatment, while 35.7% had treatment stopped by a doctor, most commonly within 1 month. Information on PPI usage follow-ups, discontinuation of treatment and duration of use are given in **Table 4**.

Tablo 3. PPI Perspectives, Knowledge, and Behaviors

PPI Perspectives, Knowledge, and Behaviors	**n (%)**	***p***
Unaware of PPI costs	545 (66.0)	
Perceive PPI costs as expensive	204 (72.6)	
Income Level Association with Perceived Expensiveness		x^2=34.536, *p<0.001*
Use PPIs without doctor's recommendation	176 (35.2)	
Began PPI use via prescription	476 (94.8)	
Obtain PPIs with prescription	468 (93.6)	
Obtain PPIs without doctor's recommendation	176 (35.2)	
Obtain PPIs from family health centers	343 (71.6)	
Recommend PPIs to others	273 (33.1)	
Association Between Perceiving Side Effects and Recommending		x^2=26.086, *p<0.001*
Association Between Having Healthcare Worker Family Member and Recommending		x^2=11.491, *p<0.001*
Association Between Education Level and Recommending		x^2=15.294, *p=0.002*
Unaware if PPIs are similar	315 (38.1)	
Believe PPIs interact with other medications	219 (26.5)	
Believe PPIs have side effects	314 (38.0)	
Most Reported Side Effects		
- Nausea	21 (16.0)	
- Diarrhea	18 (13.7)	
- Headache	13 (9.9)	

Tablo 4. PPI Follow-up, Discontinuation, and Duration

PPI Follow-up, Discontinuation, and Duration	**n (%)**
Counseled on lifestyle changes with PPI prescription	328 (68.5)
Asked to return for PPI follow-up	171 (35.7)
Returned within 1 month if asked	120 (70.2)
Frequency of specialties calling for follow-up	
- Internal medicine	63 (36.8)
- Family medicine	37 (21.6)
Self-discontinued PPI treatment	277 (55.2)
Doctor stopped PPI treatment	171 (35.7)
Doctor stopped within 1 month	120 (70.2)
PPI treatment duration (weeks) (median)	12 (1-1560)

Discussion

PPIs are among the most prescribed drug classes globally (16). They revolutionized the treatment of acid-related gastrointestinal diseases. PPIs are widely used for GERD, dyspepsia, H. pylori infection, Barrett's esophagus, eosinophilic esophagitis and prevention of NSAID-induced gastric bleeding (17). As per recent data, PPIs constitute 9.2% of all prescription drug expenditure in the US (18). In Turkey, PPI prescription rates exceed 31 million annually, constituting significantly high expenditure (19). This situation leads to excessive healthcare expenditures and necessitates rational PPI prescribing. In our study, we aimed to evaluate the prevalence of PPI prescriptions, compliance with standard indications and durations, and patient perspectives from family medicine centers in Samsun province.

Our results show that personal use of PPIs is high (60.8%) for mostly inappropriate indications or duration. According to studies in the literature, this situation can be defined as irrational (20,21). These real-world insights provide valuable data for health policymakers to implement stewardship programs promoting rational use. Literature shows inappropriate PPI use in 27-80% hospitalized patients and 36-63% primary care patients (7). Hence, improving appropriate PPI prescribing at primary care facilities, the common first point-of-care is essential. The strength of this field-based study is the diversity of participants across Samsun districts, enabling capture of rural-urban differences. The limitations include single-city design, exclusion of children, and comparison of income status with 2022 inflation-affected data. Further studies must explore generalizability in other provinces and pediatric subgroups. Natural experiments measuring the impact of de-prescribing efforts would also inform future policy measures.

Awareness and practice change interventions have successfully improved guideline-concordant PPI use (22). Strategies include education for providers and patients (23), use of electronic decision tools integrating guidance (24), structured patient reviews for de-prescribing, and policy measures limiting over-the-counter availability. Increased physician access through strengthening primary healthcare workforce and infrastructure would also enable adequate patient education and medication reviews during visits.

In our study, 92% of patients obtained PPIs only with prescriptions, and most would stop treatment on physician advice, showing community openness to professional recommendations. Family physicians constituted common prescribers; hence workforce training should engage this vital group (25). Implementation of evidence-based, multipronged strategies adapted for the local health systems context could promote appropriate PPI prescribing.

Study limitations

The limitations of this study include single city setting, exclusion of pediatric population, COVID-19 pandemic affecting routine outpatient flow, and income levels compared to Turkish Statistical Institute 2021 data as 2022 data was unavailable. The strengths are province-wide representative sampling based on population density across districts, real-world field study, and one of few studies from primary care settings.

Conclusion

In conclusion, our study provides valuable insights into PPI prescription prevalence, inappropriate use, patient knowledge and behaviors regarding these important medications. The findings highlight the need for continued research and awareness efforts to curb the irrational use of PPIs, an emerging global public health crisis. Implementation of clinical practice guidelines can help optimize utilization, improve patient outcomes and prevent serious side effects and drug interactions due to excessive PPI use.

At this stage, given the potential side effects and problems associated with overuse of PPIs, their prescription should be regulated using a stepwise approach. The most effective way to address high rates of inappropriate PPI use is through primary care physicians, who are the first point of contact for patients and can provide quick and easy care. For patients with long-term PPI use and chronic conditions, prescriptions should be issued by internal medicine departments; for patients with a history of or need for surgery, PPI prescriptions should be issued by surgical specialties.

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