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Observational Study

Patients' perception of proton pump inhibitors use and their risks

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Abstract

BACKGROUND

Long-term proton pump inhibitor (PPI) therapy is widely prescribed for acid-related disorders. Emerging evidence associates prolonged use with potential adverse outcomes, including gastric cancer. Despite increasing prescriptions, little is known about patients' awareness of these risks or factors influencing discontinuation. We hypothesized that limited risk awareness and family support significantly affect patients' willingness to deprescribe PPIs.

AIM

To evaluate patients' awareness of PPI risks and factors associated with deprescribing.

METHODS

A cross-sectional observational study was conducted in community clinics and pharmacies across Israel, including 3000 adult PPI users recruited consecutively. Participants completed a multilingual survey (Hebrew, Arabic, Russian) assessing risk awareness, family support, and quality of life. A composite risk scale (0-12) was used to quantify perceived cancer risk. Descriptive statistics and multivariate logistic regression were performed to identify factors associated with high-risk awareness and willingness to discontinue PPIs.

RESULTS

Among 3000 participants, fatigue occurred in 20%, constipation in 31.3%, infections in 9.3%, renal issues in 4.6%, and no side effects in 12.5%. Pantoprazole cancer-risk perception was 26.5%. Overall, 30% desired to discontinue PPIs and 15% reported symptom recurrence. High composite risk score (≥ 2) was associated with family support [odds ratio (OR) = 1.9, 95% confidence interval (CI): 1.3-2.8; $P < 0.01$] and longer PPI use (> 1 year; OR = 1.6, 95%CI: 1.1-2.4; $P = 0.02$). Attempted discontinuation correlated with high-risk score (OR = 2.1, 95%CI: 1.5-3.0; $P < 0.001$).

CONCLUSION
Patients show limited awareness of long-term PPI risks. Family support and longer treatment duration are strongly associated with higher risk awareness and willingness to discontinue PPIs.

Key Words: Proton pump inhibitors; Gastric cancer; Patient awareness; Adverse effects; Clinical practice; Deprescribing

Core Tip: This study is among the largest cross-sectional surveys of proton pump inhibitor users, involving 3000 patients across Israel. We found that most patients are unaware of the risks associated with long-term proton pump inhibitor therapy, including the potential link to gastric cancer. Despite lansoprazole showing a safer profile and greater improvements in quality of life, it remains underutilized compared with omeprazole and esomeprazole. Family support emerged as a protective factor, encouraging deprescribing attempts and improving patient outcomes. These findings highlight the need for better patient education, risk communication, and alignment of prescribing practices with current clinical evidence.

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INTRODUCTION

Proton pump inhibitors (PPIs) have revolutionized the management of acid-related gastrointestinal disorders, such as gastroesophageal reflux disease, peptic ulcers, Barrett's esophagus, and Zollinger-Ellison syndrome[1]. By irreversibly inhibiting the gastric H^+/K^+ adenosine triphosphatase proton pump, PPIs effectively suppress stomach acid secretion, offering long-term symptom relief for millions of patients worldwide[2]. PPIs are one of the most prescribed drug classes in the world, and include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole[3]. PPI are more potent than histamine H2 receptor antagonists due to their irreversible binding and prolonged duration of action[4].

Despite their clinical success, concern has grown around their long-term safety profile[5,6]. Prolonged PPI use has been linked to vitamin B12, iron, and magnesium deficiencies[7], which can lead to increased risks of bone fractures[8], cardiovascular complications[9], and muscle function loss[10]. These effects are primarily due to chronic hypochlorhydria, which alters the stomach environment and nutrient absorption. Furthermore, PPIs can disrupt the gut microbiome, increasing the risk of *Clostridium difficile* infections and small intestinal bacterial overgrowth[11]. Long-term PPI use has also been associated with an increased risk of chronic kidney disease[12], and progression to end-stage renal disease[13].

More recently, our attention has shifted to a possible connection between long-term PPI use and gastric cancer[14]. Mechanistically, this is explained through hypergastrinemia[15], which can promote abnormal cell growth in the gastric mucosa[16]. Additionally, microbiome shifts due to elevated gastric pH can support carcinogenesis[17]. Several large-scale studies have observed an increase in gastric cancer risk[18-23], particularly in patients with a history of *Helicobacter pylori* infection. Nonetheless, this association remains debated, and more randomized controlled trials are needed for clarity[20,24-27]. Despite emerging safety data, PPIs remain prescribed by most physicians, and in particular gastroenterologists[28]. Likewise, many patients continue long-term therapy without periodic review, or deprescribing strategies. This gap in clinical practice is compounded by a potential lack of patient education, and most users could be unaware of potential risks.

The current study examined patient conceptions of risks associated with PPI. We assessed the awareness, usage patterns, and attitudes toward discontinuation, through a cross-sectional survey of 3000 PPI users from diverse demographic backgrounds. Our findings offer a post-marketing self-reported surveillance trial, and emphasize the need for better communication, prescribing habits, and guideline alignment.

MATERIALS AND METHODS

Study structure

This cross-sectional study involved adult PPI users who responded to a questionnaire. The questionnaire was made available across a variety of healthcare settings, such as medical clinics, physicians' office, and local pharmacies. First, the questionnaire collected background information, such as demographic details and medical history. Then the questionnaire queried PPI usage patterns, such as PPI name, dose, and regimen. Finally, the questionnaire probed the perceived PPI risks, as well as any side effects experienced. To capture a broad demographic spectrum, the questionnaire was prepared in Hebrew, Arabic, and Russian. This study received approval from the institutional review board of Bar-Ilan University (Safed, Israel; Approval No. 300625649).

Inclusion criteria
The study included adults, above 18 years, who had been using PPIs continuously for at least 1 month.

Exclusion criteria
The study excluded participants who submitted incomplete responses, or who had been using PPIs for less than 1 month.

Composite risk scale
A composite risk scale with a range between 0 and 4 was developed. The scale was based on four questionnaire responses: (1) Perceived risk of gastric cancer; (2) Perceived risk of other adverse effects; (3) Personal desire to stop treatment; and (4) Perceived family support, defined as emotional or informational support from family or friends, which may influence willingness to discontinue therapy and improve treatment adherence.

Statistical analyses
To process data, we employed descriptive statistics to summarize demographic information and clinical backgrounds. χ^2 tests, logistic regression, and multivariate analysis were used to examine the relationships between demographic variables and awareness levels.

RESULTS

Demographics
Our questionnaire was completed by 3000 respondents, and comprised responses across three languages: 2250 in Hebrew (75%), 450 in Arabic (15%), and 300 in Russian (10%). The demographics data are listed in Table 1. Sex distribution was balanced, with 48% male, 50% female, and 2% that did not respond, or identified as other. The patient age groups started at 18 years, with an average age of 52 years. Educational backgrounds varied greatly, with 5% having no education, 15% primary school education, 35% secondary school education, 30% a bachelor's degree, and 20% postgraduate qualifications.

Perceived risk of gastric cancer
Table 2 summarizes the patients' perceived risk of gastric cancer associated with PPIs, and is grouped by PPI use. Notably, less than 27% of all users were aware of any potential cancer risk across all drugs. Pantoprazole users had the highest perception (26.5%), and dexlansoprazole users had the lowest perception (18.9%), but variations remained modest across different PPIs. Notably, the perceived risk was not correlated with sex (P = 0.716) or education level (P = 0.714). Perceptions did not differ significantly among different language speakers.

Composite risk scale
A composite risk scale ranging from 0 to 4 was developed based on the responses to 4 questionnaire questions. Figure 1 displays the composite risk scores, grouped by age and drug type. The data exhibited a slightly elevated risk perception for esomeprazole users, aged 60-74, but were statistically insignificant (P = 0.953). The difference was subtle, and the figure reinforces the idea that the composite risks varied little among different PPIs and ages. The risk scores taking into account awareness of cancer risk, awareness of side effects, willingness to stop therapy, and perceived family support, remained low regardless of PPI type and age.

Adverse effects
The most common side effects reported by 60% respondents are listed in Table 3. The most common side effect was abdominal pain, and the least common one was constipation.

Outcome
Lansoprazole users were more likely to report improvements in quality of life and had fewer anxiety-related complaints. These findings are further detailed in Table 4 and Figure 2. Table 4 summarizes patient-reported outcomes regarding quality of life improvement and anxiety complaints across PPI types. As shown, 61% of lansoprazole users reported improved quality of life, compared with 40%-47% in the other PPI groups. By contrast, anxiety-related complaints were less frequent among lansoprazole users (9%) than in the other groups (16%-18%). Figure 2A illustrates the distribution of quality of life responses by PPI type. Lansoprazole demonstrates a higher proportion of patients reporting improvement, while other PPIs are more evenly distributed across 'no change' or 'worsened'. Figure 2B presents the percentage of patients reporting anxiety-related symptoms by PPI type. Again, lansoprazole showed the lowest rate (9%), supporting the notion of a more favorable psychological tolerability profile compared with other PPIs.

DISCUSSION

Our comprehensive study including 3000 respondents, revealed little patient awareness about the risks of long-term PPI use. Despite the widespread prescription of these medications, most patients remained uninformed about potential side

Table 1 Demographic data of study participants

Variable	Values
Total participants	3000 (100%)
Language distribution	Hebrew 73.8%, Arabic 16%, Russian 10.2%
Sex	Male 46.1%, female 51.9%, other/NR 1.9%
Age groups	18-30: 17%, 31-45: 21.7%, 46-60: 20.1%, 61-75: 21.3%, > 76: 19.9%
Education	None 49%, primary 15.1%, secondary 34.6%, BA 31.3%, postgrad 14.1%
Medical conditions	GERD 16.3%, ulcer 17.1%, gastritis 16.7%, liver/kidney 15.7%, other 17.3%
PPI duration	< 1 month: 11.1%, 1-6 months: 29.4%, 6-12 months: 28.8%, > 1 year: 30.7%
PPI type	Dex 2.3%, eso 23.4%, lan 24.2%, ome 272%, pan 22.9%

BA: Bachelor of Arts; Dex: Dexlansoprazole; eso: Esomeprazole; GERD: Gastroesophageal reflux disease; lan: Lansoprazole; NR: Not reported; ome: Omeprazole; pan: Pantoprazole; PPI: Proton pump inhibitor.

Table 2 Patients' perception of gastric cancer risk with proton pump inhibitor

PPI type	Risk perceived (%)	*n*
Dexlansoprazole	18.9	14/74
Esomeprazole	22.8	164/719
Lansoprazole	24.1	172/715
Omeprazole	24.0	198/823
Pantoprazole	26.5	177/669

PPI: Proton pump inhibitor.

Table 3 Self-reported adverse effects of proton pump inhibitors

Side effect	Respondents (%)
Abdominal pain	36.5
B12 deficiency	24.8
Fatigue	20.0
Iron deficiency	15.3
Infections	9.3
Renal issues	4.6
Constipation	31.3
None	12.5

effects and the possible link to gastric cancer. This aligns with prior research suggesting that PPIs are often overprescribed and insufficiently monitored[29]. The high rate of side effects reported, ranging from abdominal pain to nutrient deficiencies, highlights the need for healthcare providers to monitor patients regularly, and consider alternative treatments when appropriate. The data also indicate that risk awareness is not associated with demographic background, suggesting that educational initiatives should target all patients alike.

Our comprehensive survey of 3000 PPI users, across diverse demographic backgrounds, was a self-reported post-marketing surveillance trial. It analyzed the interplay among outcome, adverse effects, and real-world prescribing patterns, and aspired to contribute to the development of improved clinical guidelines. The study encourages the wise use of PPIs, and advocates for better prescribing deprescribing strategies, patient education initiatives, and increased consideration of alternative treatments such as antacids, H2 receptor antagonists, lifestyle modifications, and step-down therapy approaches where appropriate. Future investigations should focus on identifying high-risk subgroups, refining risk stratification models, and further elucidating the mechanistic links between chronic PPI use and adverse outcomes.

Table 4 Quality of life and anxiety by proton pump inhibitor type

PPI type	Improved QoL (%)	Anxiety (%)
Omeprazole	42%	18%
Esomeprazole	40%	17%
Lansoprazole	61%	9%
Pantoprazole	44%	16%
Dexlansoprazole	47%	14%

PPI: Proton pump inhibitor; QoL: Quality of life.

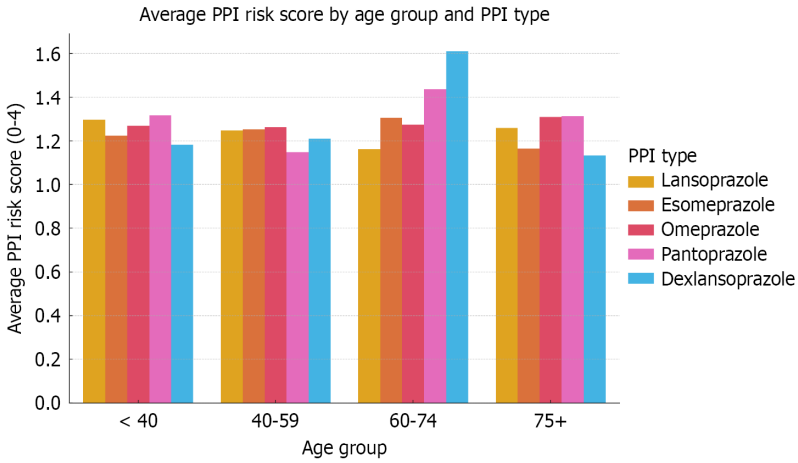

Figure 1 Risk scores across age groups and proton pump inhibitor types. Shown are the composite risk score of respondents grouped by age (rising from left to right) and proton pump inhibitor (PPI) (lansoprazole colored in amber, esomeprazole in orange, omeprazole in red, pantoprazole in magenta, and dexlansoprazole in blue).

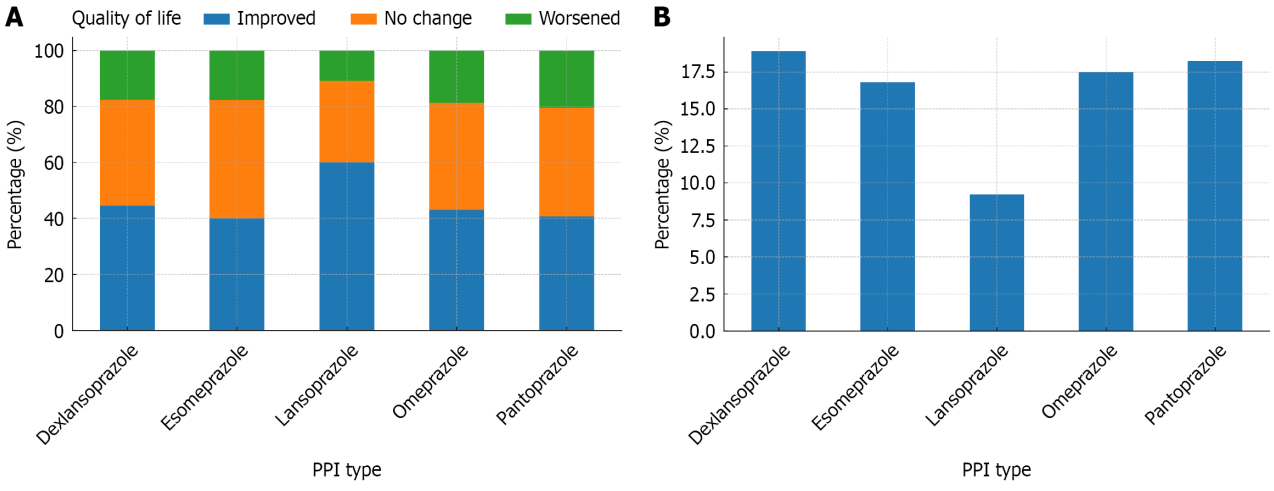

Figure 2 Quality of life and anxiety symptoms (yes) by proton pump inhibitor type. A: Quality of life by proton pump inhibitor (PPI) type; B: Anxiety symptoms (yes) by PPI type.

By promoting a balanced approach to PPI therapy, healthcare professionals can optimize patient safety while ensuring the continued efficacy of these essential medications.

Pharmacokinetics of PPIs

The incidence of adverse effects was low, and could be due to patient genetics. PPIs are prodrugs that require activation in the acidic environment of the stomach. Once ingested, they are absorbed in the small intestine and transported *via* the

bloodstream to the gastric parietal cells, where they accumulate in the secretory canaliculi. In this highly acidic environment, PPIs are converted into their active sulfenamide form, which irreversibly binds to and inhibits the H^+/K^+ adenosine triphosphatase enzyme, leading to prolonged acid suppression. The pharmacokinetics of PPIs vary slightly among different drugs. Omeprazole and lansoprazole exhibit relatively shorter half-lives but prolonged effects due to their irreversible enzyme inhibition. Esomeprazole and rabeprazole demonstrate more predictable pharmacokinetics with fewer interindividual variations in metabolism. The metabolism of PPIs occurs primarily in the liver *via* the cytochrome P450 system, particularly through cytochrome P4502C19 and cytochrome P4503A4 isoenzymes, leading to potential drug interactions with anticoagulants, antiplatelet agents, and some chemotherapeutic drugs. As such, some patients with cytochrome P450 mutations may be predisposed to adverse effects, unlike others[2,3].

Limitations

As a potential limitation to this study, our sample size was limited to 3000 respondents, and a larger cohort could have provided different results. Moreover, a larger sample size may have found correlation between various numerical parameters. The absence of statistically significant correlations does not preclude their existence in other demographics. As another potential limitation, we did not explore other factors influencing awareness of side effects, such as healthcare provider communication styles, cultural perceptions, and media influence.

CONCLUSION

This study highlights an incomplete risk perception by patients of long-term PPI use, particularly the potential association with gastric cancer. Our data suggest that lansoprazole as a more effective, and safe PPI. Finally, our findings reiterate the need for educational interventions to support informed decision-making.

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FOOTNOTES

Author contributions: Sawaid IO, Samson AO, and Golan E designed the research study; Sawaid IO and Golan E performed the research; Sawaid IO analyzed the data and drafted the manuscript; Samson AO critically revised the manuscript and supervised the project; All authors have read and approve the final manuscript.

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