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Research Article

Assessing the Appropriateness of Proton Pump Inhibitor Use in Ambulatory Patients: Findings from a Single-Centre Retrospective Study

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ABSTRACT

In Thailand, there is a lack of comprehensive evaluations regarding the appropriateness of prescribing proton pump inhibitors (PPIs) to outpatients. This study aimed to evaluate guideline-discordant prescribing of PPIs for therapy and prophylaxis, as well as potentially inappropriate co-prescribing of drugs interacting with omeprazole. This cross-sectional, descriptive study was conducted at a tertiary care hospital in Thailand. A prescription audit assessed the appropriateness of prescribing oral PPIs to outpatients between January 1, 2023, and December 31, 2023. The appropriateness of PPI therapy and prophylaxis, as well as drug interactions with omeprazole, was determined according to current recommendations for PPI use. The rates of potentially inappropriate use for each assessment were determined using descriptive statistics and are presented as percentages. A total of 2,099 prescriptions were included for therapy assessment, 1,263 prescriptions for prophylaxis assessment and 3,298 prescriptions for omeprazole-related drug interaction assessment. The rate of potentially inappropriate PPI therapy was 81.71%, with the most common reason being the absence of an approved indication (49.91%), followed by potentially inappropriate treatment duration (45.42%) and daily dosing (8.05%). The rate of potentially inappropriate PPI prophylaxis was 57.24%. The percentage of prescriptions that included drugs interacting with omeprazole was 5.37%. Two medications with a major level of interaction were clopidogrel (0.58%) and methotrexate (0.33%). PPIs may be prescribed inappropriately to outpatients. This study suggests that a comprehensive review of PPI prescriptions should be conducted to ensure their appropriateness and promote more rational use of PPIs.

Keywords:
proton pump inhibitors; potentially inappropriate prescribing; medication appropriateness; drug-drug interactions; deprescribing

1. INTRODUCTION

Proton pump inhibitors (PPIs) are medications that reduce the secretion of stomach acid. They are clinically used to treat acid-related gastrointestinal (GI) disorders and to prevent GI bleeding caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and dual antiplatelet therapy (DAPT)[1]. In Thailand, PPIs are frequently prescribed medications in outpatient settings, with orthopaedics, cardiology and gastroenterology departments accounting for 45.96%, 32.86% and 21.17% of the prescribed volume of PPIs, respectively[2].

The widespread use of PPIs has raised concerns regarding their excessive and potentially inappropriate prescription[3]. A large observational study revealed an increasing trend in the incidence of PPI prescriptions, which rose from 19.7% in 2012 to 23.1% in 2017, as well as in potentially inappropriate PPI prescriptions (i.e., excessive doses), which increased from 2.7% in 2012 to 6.4% in 2017[4].

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Rates of potentially inappropriate use of PPIs among outpatients have been reported to range from 38.6% to 56%[5-8]. A recent systematic review of 23 countries revealed that nearly two-thirds of PPI users were on high doses (≥ defined daily dose), 25% continued PPI use for more than a year and 28% continued for more than three years[9]. Improper use of PPIs can lead to ineffective treatment and adverse events. These events may include enteric infections, pneumonia, renal disease, malabsorption of vitamins and minerals and an increased risk of cardiovascular disease[10, 11]. Additionally, the potentially inappropriate use of PPIs leads to increased medical costs of $1 1 8,6 5 9 per year for inpatients and $214,663 per year for outpatients[8].

To assess the appropriateness of medication use, it is essential to consider all aspects of drug safety and effectiveness. These include indications, dose, frequency of administration, duration of therapy, drug- disease interactions and drug- drug interactions[12]. PPI therapy should only be used for approved indications, each requiring a specific dose, frequency and treatment duration[13,14]. PPI prophylaxis is recommended for individuals who take NSAIDs or DAPT and have a moderate to high risk of developing GI bleeding[15]. Furthermore, PPIs can interact with many co-prescribed medications through various pharmacokinetic pathways[16,17]. Therefore, when assessing the appropriateness of prescribing PPIs, it is important to consider all of the above to encourage their rational use.

In outpatient settings, prescriptions for PPIs may not undergo a thorough review to determine their appropriateness across various aspects, as mentioned earlier. This can lead to potentially inappropriate use of PPIs. Omeprazole is widely recognized as a PPI agent that is highly likely to interact with other drugs[1,3]. In Thailand, physicians have unrestricted access to omeprazole, making it the most commonly prescribed PPI in clinical practice[2]. Although some research has been conducted on the appropriateness of using PPIs among outpatients, these studies have mainly focused on specific aspects of potentially inappropriate PPI therapy. Furthermore, only a few studies have reported the prevalence of potential drug interactions involving omeprazole. The objective of this study was to evaluate guideline-discordant prescribing of PPIs for both therapy and prophylaxis, as well as to identify potentially inappropriate drug interactions with omeprazole.

2. MATERIALS AND METHODS

2.1. Study design and setting

This cross-sectional descriptive study was conducted at a tertiary care hospital in Phayao Province, Thailand. The hospital, affiliated with the University of Phayao, serves as an academic and referral centre for residents of the province and surrounding provinces. The hospital's outpatient department (OPD) prints and stores patients' medication prescriptions daily. The prescription includes basic patient information, the diagnosis and prescribed medications.

2.2. Source of data and inclusion criteria

We included all PPI prescriptions from the OPD between January 1, 2023, and December 31, 2023. Prescriptions for intravenous *(*IV*)* PPIs only, individuals under 18 years old and those with incomplete data were excluded from the study.

We then classified the eligible PPI prescriptions as either therapy or prophylaxis. Prescriptions for PPI prophylaxis referred to those for NSAIDs or DAPT (a combination of low-dose aspirin and a P2Y12 inhibitor, such as clopidogrel, prasugrel, or ticagrelor) without an approved clinical indication. Prescriptions for PPI therapy included all other prescriptions. We identified prescriptions for omeprazole to assess potential drug interactions with it.

2.3. Data collection

All data were collected primarily from prescriptions and categorised into the following groups: demographics (including sex, age and health insurance), diagnostic groups (classified based on the International Statistical Classification of Diseases 10th revision [ICD-10]) and information on prescribed PPIs (including dosage forms, approved clinical indications, regimens and treatment duration). PPIs available at the hospital included oral forms, such as omeprazole 20 mg capsules, lansoprazole 30 mg tablets and esomeprazole 20 mg capsules, as well as IV forms, such as omeprazole 40 mg and pantoprazole 40 mg injections. All clinically approved indications for PPIs were identified based on the ICD-10 codes documented in each prescription, as summarized in **Table 1**. We determined the daily dose of an oral PPI by multiplying the drug dose (e.g., omeprazole 2 0 mg) by the frequency of administration (e.g., once or twice daily), and then classified it into two PPI regimens: PPI with a standard dose (SD) and PPI with a double dose (DD). We determined the duration of treatment for each prescription by dividing the dispensed quantity of a PPI by the frequency of administration, and then classified it into four intervals: less than 2 weeks, 2 to less than 4 weeks, 4 to 8 weeks and more than 8 weeks. Prescription features included polypharmacy (≥5 oral medications), as well as co-prescriptions with IV PPIs, NSAIDs, oral glucocorticosteroids (GCs), antiplatelets (only prasugrel is unavailable) and oral anticoagulants.

2.4. Evaluation of the appropriateness of PPI use

To determine the recommended regimens and duration of PPI therapy for each approved clinical indication, we followed the treatment guidelines established by the Gastroenterological Association of Thailand and the American College of Gastroenterology (ACG). Additionally, we considered guidelines for deprescribing and optimizing PPI use[13,14]. A summary of PPI therapy recommendations for each approved indication, along with the corresponding guidelines, is provided in **Table 1**. Prescriptions that did not meet the predefined criteria were deemed potentially inappropriate for PPI therapy.

To determine the appropriateness of PPI prophylaxis, we followed international guidelines. Specifically, we used the 2009 ACG guidelines for assessing risk factors associated with NSAID-related ulcer complications[18] and the 2023 European Society of Cardiology guidelines for the management of acute coronary syndromes, which include recommendations for gastroprotection in patients receiving DAPT[19]. These guidelines define key risk factors and provide a structured approach to risk stratification for GI bleeding, ensuring a systematic evaluation of the need for PPI co-administration in patients using NSAIDs or DAPT. Each prescription was examined to identify the relevant risk factors as follows: patient age 65 or older (for both NSAID and DAPT users); co-prescription of high-dose NSAIDs or multiple NSAIDs (for NSAID users); co-prescription of low-dose aspirin, oral GCs or oral anticoagulants (for NSAID users) and co-prescription of NSAIDs, oral anticoagulants or oral GCs (for DAPT users). For NSAID users, the risk levels of GI bleeding were classified as low risk (no risk factors), moderate risk (1–2 risk factors) and high risk (>2 risk factors)[18]. For DAPT users, the risk levels were classified as low risk (age <65 years) and high risk (co-prescription of NSAIDs, oral anticoagulants or oral GCs[19]. Prescriptions for NSAID or DAPT users with a low risk of GI bleeding were deemed potentially inappropriate for PPI prophylaxis.

To identify drugs that interact with omeprazole, we used the following readily available data sources: UpToDate[20], Micromedex[21] and the 2015 Drug Interaction Facts[22]. All medications, regardless of their level of interaction significance (major, moderate or minor), were assessed. Prescriptions for medications known to interact with omeprazole were considered potentially inappropriate PPI prescriptions

2.5. Statistical analysis

The unit of analysis was the prescription. The data were analysed using descriptive statistics. Continuous variables with normal distributions were presented as mean ± standard deviation (SD), while those with non-normal distributions were presented as median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages.

The rate of potentially inappropriate PPI use was calculated separately for therapy, prophylaxis and drug interactions involving omeprazole. This was achieved by dividing the number of prescriptions deemed potentially inappropriate by the total number of prescriptions assessed and expressing the result as a percentage. All statistical analyses were performed using STATA 18.0 (StataCorp LLC, College Station, TX, USA).

Table 1 A summary of treatment with proton pump inhibitors

Approved clinical indications	ICD-10 codes	Daily dose (mg)	Treatment duration (weeks)
Helicobacter pylori eradication[23-25]	B98.0	DD	1-2
Oesophagitis[23]	K20	SD	4-8
Gastro-oesophageal reflux disease without oesophagitis[23, 26, 27]	K21.9	SD	4-8
Erosive esophagitis[23, 26, 27]	K21.1	DD	>8
Oesophageal stricture[23]	K22.2	SD	>8
Barrett's oesophagus[23, 28]	K22.7	SD	>8
Gastric ulcer[23, 29]	K25.3, K25.4, K25.5, K25.7, K25.9	DD	8
Duodenal ulcer[23, 29]	K26.3, K26.4, K26.7, K26.9	SD	2-4
Peptic ulcer[23, 29]	K27, K27.4, K27.5, K27.7, K27.9	SD	4-8
Functional dyspepsia[23, 30, 31]	K30	SD	4-8
Pathological hypersecretory conditions such as Zollinger-Ellison syndrome, multiple endocrine adenomas, and systemic mastocytosis in adults[24, 32]	K31.8	>DD	>8

SD, standard dose; DD, double dose
Oral PPI standard doses (SD) include omeprazole 20 mg daily, lansoprazole 30 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily and esomeprazole 20 mg daily.
Oral PPI double doses (DD) consist of omeprazole 40 mg daily, lansoprazole 60 mg daily, pantoprazole 80 mg daily, rabeprazole 40 mg daily and esomeprazole 40 mg daily, administered either once or twice daily.

3. RESULTS

3.1 Characteristics of PPI prescriptions

The process of including PPI prescriptions is illustrated in **Figure 1**. A total of 3,632 outpatient PPI prescriptions were identified. Out of these, 270 prescriptions were excluded as ineligible. The 3,362 prescriptions included in this study were divided into two groups: 2,099 for treatment evaluation and 1,263 for prophylaxis assessment. In assessing drug interactions, 3,298 omeprazole prescriptions were used.

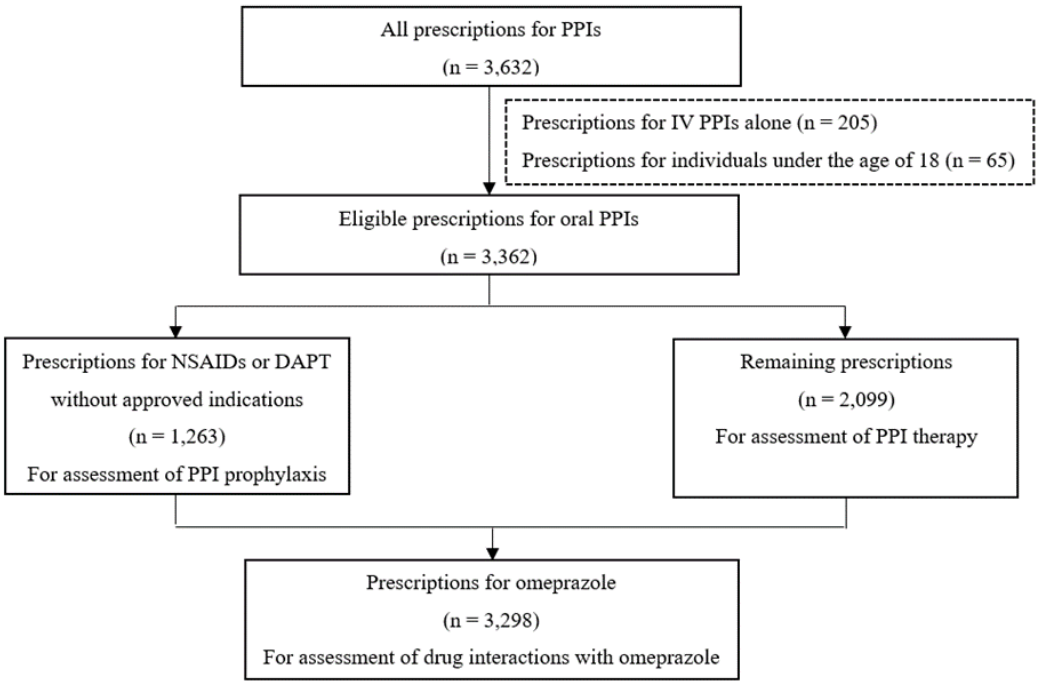

Figure 1 The recruitment process for outpatient PPI prescriptions

The prescription characteristics are presented in **Table 2**. The majority of prescriptions were for female patients (70.55%) with an average age of 47.82 ± 21.04 years. Older adults (aged 65 years and older) accounted for approximately 27.63% of all prescriptions. GI diseases were the most frequent diagnostic group (42.83%), followed by musculoskeletal diseases (40.18%) and cardiovascular diseases (7.11%). Omeprazole SD was the most commonly prescribed regimen, accounting for 91.11% of prescriptions. The most prevalent approved clinical indication was functional dyspepsia (34.65%), followed by gastro-oesophageal reflux disease (GERD) (1.87%) and peptic ulcer disease (PUD) (0.33%). PPIs were often prescribed for a duration of 2 to less than 4 weeks (53.06%).

Table 2 The characteristics of the included PPI prescriptions (n = 3,362)

Characteristics	n	%
Sex		
Male	990	29.45
Female	2,372	70.55
Age, mean ± SD (years)	47.82 ± 21.04	
Age <65 years	2,433	72.37
Age ≥65 years	929	27.63
Health insurance schemes		
CSMBS	1,692	50.33
UCS	871	25.91
Self-payment	528	15.70
SSS	271	8.06
Diagnostic groups		
Gastrointestinal diseases	1,440	42.83
Musculoskeletal diseases	1,351	40.18
Cardiovascular diseases	239	7.11
Endocrine and metabolic diseases	211	6.28
Infectious diseases	202	6.01
Respiratory diseases	118	3.51
Mental and behavioural disease	113	3.36
Nervous diseases	92	2.74
Genitourinary diseases	66	1.96
Oral PPI regimens		
Omeprazole, SD	3,063	91.11
Omeprazole, DD	235	6.99
Esomeprazole, SD	40	1.19
Lansoprazole, SD	21	0.62
Esomeprazole, DD	2	0.06
Lansoprazole, DD	1	0.03
IV PPI regimens		
Omeprazole 40 mg	423	12.58
Pantoprazole 40 mg	1	0.03
Approved clinical indications		
Functional dyspepsia	1,165	34.65
Gastro-oesophageal reflux disease	63	1.87
Peptic ulcer disease	11	0.33
Oesophagitis	2	0.06
Gastric ulcer disease	2	0.06
Duration of treatment		
<2 weeks	662	19.69
2 to <4 weeks	1,784	53.06
4–8 weeks	786	23.38
>8 weeks	130	3.87
Polypharmacy	1,941	57.73
Medications co-prescribed with a PPI		
NSAIDs or COX-2 inhibitors*	1,346	40.04
Glucocorticosteroids	53	1.58
Low-dose aspirin	49	1.46
Clopidogrel	19	0.57
Warfarin	5	0.15

Age is expressed as mean ± standard deviation.
PPIs, proton pump inhibitors; SD, standard dose; DD, double dose; CSMBS, Civil Servant Medical Benefit Scheme; SSS, Social Security Scheme; UCS, Universal Health Coverage Scheme.
*The total number of prescriptions for naproxen, etoricoxib, ibuprofen, diclofenac, celecoxib, aspirin (>325 mg), mefenamic acid and piroxicam was 1,133, 101, 46, 39, 22, 2, 2 and 1.

3.2 Appropriateness of PPI therapy

The assessment of the appropriateness of PPI therapy is presented in **Table 3**. Of the 2,099 prescriptions, 1,715 were classified as potentially inappropriate, yielding a rate of 81.71%. Among these, the most common reason was the absence of an approved indication (49.91%), followed by potentially inappropriate treatment duration (45.42%) and dosage (8.05%).

Among prescriptions with identified approved indications (n = 1,243), the highest rate of potentially inappropriate therapy was observed in cases of oesophagitis (100.00%), followed by PUD (81.82%) and GERD (74.60%). Potentially inappropriate prescribing of PPI at DD for conditions generally indicated for SD was found in 16.07% of cases, while 82.77% were possibly prescribed for too short a duration and 7.92% for too long.

For prescriptions with unidentified approved indications (n = 856), the most commonly recorded diagnoses were abdominal pain (13.43%), acute gastritis (8.29%) and gastroenteritis and colitis (6.78%). In this group, where no approved indication was identified, PPIs were prescribed as DD in 10.05% and for prolonged durations in 6.19% of prescriptions.

Table 3 Assessment of the appropriateness of PPI therapy (n = 2,099)

Approved indication	Total prescriptions, n (%)	Potentially inappropriate therapy, n (%)	Reasons for potentially inappropriate therapy, n (%)
Identified approved indications (n=1,243, 59.22%)	1,243 (100.00)	859 (69.11)	Dosage too high (138, 16.07%) Duration too short (711, 82.77%) Duration too long (68, 7.92%)
Functional dyspepsia	1,165 (93.72)	801 (68.76)	Dosage too high (111, 13.86%) Duration too short (678, 84.64%) Duration too long (63, 7.87%)
Gastro-oesophageal reflux disease	63 (5.07)	47 (74.60)	Dosage too high (26, 55.32%) Duration too short (23, 48.94%) Duration too long (4, 8.51%)
Peptic ulcer disease	11 (0.88)	9 (81.82)	Dosage too high (1, 11.11%) Duration too short (8, 88.89%) Duration too long (1, 11.11%)
Oesophagitis	2 (0.16)	2 (100.0)	Duration too short (2, 100.0%)
Gastric ulcer	2 (0.16)	0 (0.00)	–
Unidentified approved indications (n=856, 40.78%)	856 (100.00)	856 (100.0)	Common indications Abdominal pain (115, 13.43%) Acute gastritis (71, 8.29%) Gastroenteritis and colitis (58, 6.78%) Viral intestinal infection (38, 4.44%) Dosage too high (86, 10.05%) Duration too short (586, 68.46%) Duration too long (53, 6.19%)
Overall prescriptions for PPI therapy	2,099 (100.00)	1,715 (81.71)	Unidentified approved indications (856, 49.91%) Identified approved indications with potentially inappropriate dosage (138, 8.05%) Identified approved indications with potentially inappropriate duration (779, 45.42%)

Note:
Percentages were calculated based on the number of prescriptions in each respective row. For example, functional dyspepsia accounted for 93.72% (1,165/1,243) of prescriptions with approved indications. Among these, 68.76% (801/1,165) were potentially inappropriate, with high-dose regimens identified as the reason in 13.86% (111/801) of cases. Multiple reasons may apply to a single prescription. For the Unidentified approved indications group, dosage and duration were not assessed for appropriateness but are presented descriptively to illustrate prescribing patterns.

3.3 Appropriateness of PPI prophylaxis

The assessment of the appropriateness of PPI prophylaxis is presented in **Table 4**. The majority of prescriptions (99.37%) were for NSAIDs, while only a small percentage (0.63%) were for DAPT (aspirin plus clopidogrel). Prescribing PPIs to NSAID or DAPT users with low risk levels of GI bleeding resulted in a potentially inappropriate PPI prophylaxis rate of 57.17%. Specifically, the rate was 56.97% for NSAID users and 87.50% for DAPT users. Among NSAID users, appropriate PPI prescriptions were given to individuals with moderate risk levels. This includes people aged 65 years or older (42.39%); those who were co-prescribed low-dose aspirin, warfarin or oral GCs (0.16%) and those who had both of these risk factors (0.48%). Among DAPT users, only 12.50% received an appropriate PPI prescription when co-prescribed with NSAIDs, warfarin or oral GCs. Among the appropriate prescriptions, the commonly prescribed regimens were omeprazole (98.89%) and esomeprazole (0.18%) at SD, while omeprazole at DD was used to a lesser extent (0.92%).

Table 4 Assessment of the appropriateness of PPI prophylaxis (n = 1,263)

Risk assessment	n	%
Prescriptions for NSAIDs (n = 1,255)		
Risk factors		
Age ≥65 years	538	42.87
High-dose NSAIDs or multiple NSAIDs	0	0.00
Co-prescription with low-dose aspirin, warfarin or glucocorticosteroids	8	0.64
Risk levels		
Low (no risk factor)	715	56.97
Moderate (1–2 risk factors)	540	43.03
Age ≥65 years	532	42.39
Co-prescription with low-dose aspirin, warfarin or glucocorticosteroids	2	0.16
Age ≥65 years + Co-prescription with low-dose aspirin, warfarin or glucocorticosteroids	6	0.48
High (>2 risk factors)	0	0.00
Appropriate PPI prophylaxis		
Appropriate	540	43.03
Potentially inappropriate	715	56.97
Prescriptions for DAPT (n = 8)		
Risk factors		
Age ≥65 years	4	50.00
Co-prescription with NSAIDs, warfarin or glucocorticosteroids	1	12.50
Risk levels		
Low	7	87.50
No risk factors	3	37.50
Age ≥65 years	4	50.00
High	1	12.50
Co-prescription with NSAIDs, warfarin or glucocorticosteroids	1	12.50
Appropriate PPI prophylaxis		
Appropriate	1	12.50
Potentially inappropriate	7	87.50
Prescriptions for NSAIDs or DAPT (n = 1,263)		
Appropriate PPI prophylaxis		
Appropriate	541	42.83
Potentially inappropriate	722	57.17

DAPT, dual antiplatelet therapy; NSAIDs, nonsteroidal anti-inflammatory drugs

3.4 Appropriateness of drug interactions with omeprazole

A list of prescribed medications that interact with omeprazole is presented in **Table 5**. Out of all omeprazole prescriptions, 5.37% were considered potentially inappropriate due to the inclusion of interacting medications. The number of medications that interact with omeprazole, as well as the significance level of their interactions, varied among the three data sources. The 2015 Drug Interaction Facts listed the highest number of interactions. Clonazepam (1.55%) was the medication most commonly prescribed with omeprazole, followed by sertraline (0.91%) and ferrous fumarate (0.76%). Prescriptions for clopidogrel and methotrexate, both of which have a major level of interaction according to the three references, were found to be 0.58% and 0.33%, respectively.

Table 5 The assessment of drug interactions with omeprazole (n = 3,298)

Drugs*	UpToDate	Micromedex	Drug interaction fact	Effects of drug-drug interactions	n	%
Clonazepam			○	Reduced clearance, prolonged $t_{1/2}$ and increased serum levels of certain benzodiazepines may occur. Certain actions, especially sedation or ataxia, may be enhanced.	51	1.55
Sertraline			◐	Serum concentrations and the pharmacologic effects of certain SRIs may be increased.	30	0.91
Ferrous fumarate		◐	●	Concurrent use of iron and omeprazole may result in reduced iron salts absorption.	25	0.76
Propranolol		◐		Concurrent use of propranolol and CYP2C19 inhibitors may result in increased propranolol exposure.	22	0.67
Clopidogrel	●	●	●	Concurrent use of clopidogrel and omeprazole may result in reduced clopidogrel's active metabolite exposure and reduced antiplatelet activity.	19	0.58
Methotrexate	●	●	●	Concurrent use of methotrexate and omeprazole may result in increased methotrexate exposure and an increased risk of methotrexate toxicity.	11	0.33
Glipizide			◐	Serum sulfonylureas concentrations may be elevated, increasing the hypoglycaemic effects.	11	0.33
Multivitamin	◐			Inhibitors of the proton pump may decrease the serum concentration of multivitamins/minerals (with ADEK, folate, iron).	10	0.30
Escitalopram	◐	●	◐	Concurrent use of escitalopram and CYP2C19 inhibitors may result in increased escitalopram exposure.	8	0.24
Clorazepate		●	○	Concurrent use of clorazepate and omeprazole may result in an increased risk of clorazepate toxicity.	6	0.18
Clarithromycin			○	Serum concentrations of clarithromycin and omeprazole may be increased. In addition, the gastric mucus concentration of clarithromycin may be increased.	5	0.15
Clozapine	◐			Omeprazole may decrease the serum concentration of clozapine.	5	0.15
Levothyroxine		◐		Concurrent use of levothyroxine and proton pump inhibitors may result in decreased levothyroxine effectiveness.	5	0.15
Warfarin	◐	●	◐	Concurrent use of omeprazole and warfarin may result in elevations of International Normalized Ratio (INR) serum values, prothrombin time and potentiation of anticoagulant effects.	4	0.12
Theophylline			◐	The rate of theophylline absorption from slow-release forms of theophylline may be increased.	3	0.09
Diazepam		●	○	Concurrent use of diazepam and omeprazole may result in increased diazepam exposure.	2	0.06
Mycophenolate	◐	●	◐	Concurrent use of mycophenolate mofetil and proton pump inhibitors may result in reduced mycophenolic acid exposure.	2	0.06

Alprazolam		◐	○	Concurrent use of alprazolam and omeprazole may result in benzodiazepine toxicity (CNS depression, ataxia, lethargy).	1	0.03
Ketoconazole	●	●	◐	Concurrent use of ketoconazole and proton pump inhibitors may result in decreased ketoconazole exposure.	1	0.03
Midazolam		◐	○	Concurrent use of midazolam and omeprazole may result in benzodiazepine toxicity (CNS depression, ataxia, lethargy).	1	0.03
Appropriate PPI prescriptions						
Appropriate					3,121	94.63
Potentially inappropriate					177	5.37

Significance levels are categorised as major (●), moderate (◐) and minor (○).

*Listed in descending order of frequency.

4. DISCUSSION

The current study aimed to assess the appropriateness of prescribing PPIs for outpatients in terms of therapy, prophylaxis and drug interactions involving omeprazole. The potentially inappropriate use of PPIs was identified in all three cases. This study emphasizes the need for healthcare providers to adhere to guidelines on PPI use to ensure rational application.

4.1 Appropriateness of PPI therapy

Regardless of the specific aspects assessed, the reported rates of potentially inappropriate PPI use generally range from 38.6% to 59.9%, reflecting a widespread issue across various settings[5-8, 33]. When compared with a study conducted in a similar tertiary care hospital using the same unit of analysis (i.e., prescriptions), our study found a higher rate of potentially inappropriate PPI therapy (81.71%) than the 50.0% reported by Liu et al.[6] in an outpatient prescription review conducted in China. This discrepancy may be partly explained by differences in the clinical aspects assessed. While our study evaluated appropriateness based on indication, dose and duration, Liu et al. assessed appropriateness based on indication, duration of therapy and the concurrent use of NSAIDs, GCs, antiplatelets and anticoagulants. Additionally, differences in prescribing practices and prescriber characteristics between the two hospitals may help explain the variation in potentially inappropriate PPI use rates.

The primary reason for potentially inappropriate PPI therapy in our study was the absence of approved indications. We found that 40.78% of all prescriptions involving PPI therapy lacked a clearly documented indication. Similarly, Liu et al.[6] identified the absence of a valid indication as the leading cause of inappropriate PPI use, accounting for 47% of cases. This finding is also consistent with a previous study conducted in a tertiary care hospital in Thailand, where 47.3% of patients attending follow-up visits at the OPD were receiving a PPI without a clear indication[8]. Our study found that abdominal pain, acute gastritis and gastroenteritis and colitis were frequently diagnosed in prescriptions without approved indications, which is consistent with previous research[6, 33]. PPIs are commonly used as empirical treatment to relieve symptoms in patients with GI conditions unrelated to acid. However, these conditions do not warrant the use of PPIs for treatment[13]. The highest priority recommendation in the guidelines for optimising PPI use is to review ongoing indications regularly in patients receiving a PPI. If indications for its use no longer exist, deprescription of the PPI should be considered[13,14].

After identification of the patient's PPI indications, it is important to determine the appropriate duration of therapy. For most clinically approved indications, PPIs need to be used for a period of 4 to 8 weeks to achieve their full therapeutic effects[1]. Short-term use of PPIs, which is less than 4 weeks, may result in therapeutic failure due to insufficient ulcer healing or symptom alleviation. On the other hand, long-term usage, which is more than 8 weeks, may be associated with an increased risk of adverse events[1, 10, 13, 14]. In our study, 82.77% of PPI prescriptions with approved indications were for a duration of less than one month. This pattern is comparable to the findings of Liu et al.[6], who reported that 83% of new PPI prescriptions for outpatients were also for less than one month. Long-term use of PPIs is only recommended for specific conditions such as severe erosive oesophagitis, Barrett's oesophagus, peptic strictures, Zollinger-Ellison syndrome (ZES), eosinophilic oesophagitis and gastroprotection in NSAID or DAPT users who are at high risk of GI bleeding. This is because continued medication use promotes ulcer healing, prevents complications such as GI bleeding or stricture formation and reduces the risk of recurrence after discontinuation[13, 14, 34]. However, our investigation did not find any such conditions. Our study also observed a proportion of PPI prescriptions with prolonged durations, with 7.92% of those with approved indications exceeding two months. Similarly, Liu et al.[6] reported that 14% of prescriptions were for 1–3 months, 2% for 3–6 months and 0.4% for more than 6 months. Although functional dyspepsia or GERD with recurrence after PPI withdrawal are conditionally indicated for long-term use, PPIs are recommended to

be used on-demand rather than continuously[13, 14, 34]. However, this study discovered that physicians were prescribing PPIs for durations longer than 8 weeks to patients with functional dyspepsia (7.87%) and GERD (8.51%). This finding aligns with a previous study by Giannini et al.[5], which found that among outpatients with a history of PPI use longer than 8 weeks, dyspepsia and GERD were frequently reported as the underlying conditions—accounting for 83.3% and 35.0% of cases, respectively.

This study revealed minimal use of PPIs at high doses, accounting for 8.05% of prescriptions deemed potentially inappropriate—consistent with a previous study by Giannini et al.[5], which reported a 4.4% use of PPIs at high doses. However, Liu et al.[6] observed a markedly higher proportion of high-dose PPI use, reported at 73%. Oral PPIs at SD have been proven sufficiently effective in treating most acid-related illnesses, whether used as initial therapy, maintenance therapy or for gastroprotection[1,13,14]. Only a few conditions—such as *H. pylori* eradication, severe erosive oesophagitis, peptic stricture and ZES—require initial treatment with high doses[13, 14]. The use of high-dose PPIs is also believed to increase the risk of adverse events[1, 10]. In this study, considerable use of PPIs at DD was found among patients with GERD (55.32%), even though SD is generally sufficient for symptom relief and healing erosive oesophagitis[14]. Notably, no prescriptions for low-dose PPI therapy were identified in our study, which may be attributable to the limited availability of formulations that can be easily adjusted to lower doses.

4.2 Appropriateness of PPI prophylaxis

In this study, 57.17% of prescriptions containing NSAIDs or DAPT and classified as low GI bleeding risk included a PPI, indicating potentially inappropriate PPI prophylaxis. This finding is consistent with several previous studies reporting similar patterns of unnecessary prophylactic use[5,6,8,33]. A study conducted in Thailand likewise reported that 76.1% of patients received a PPI for ulcer prophylaxis despite being classified as low risk[8]. Similarly, Liu et al.[6] found potentially inappropriate PPI use in prescriptions containing antiplatelets (32%), NSAIDs (57%), GCs (76%), and anticoagulants (9%). This reflects a common practice of prescribing PPIs prophylactically based solely on the use of medications known to increase GI risk, without a comprehensive risk assessment. Although multiple factors—such as advanced age and the use of GI-risk medications—are recognized risk factors for GI ulcers, they should be evaluated collectively to determine the necessity of PPI prophylaxis[18, 19]. According to deprescribing guidelines, not all patients using NSAIDs or DAPT should routinely receive a PPI; rather, prophylaxis is recommended only for those at moderate to high risk of GI bleeding, using PPIs at SD[13,14].

4.3 Appropriateness of drug interactions with omeprazole

PPIs can interact with various drugs through pharmacokinetic mechanisms such as increased gastric pH, inhibition of cytochrome P450 (CYP) enzymes and modulation of drug transport systems[16]. Among PPIs, omeprazole carries the highest risk for drug–drug interactions due to its strong inhibition of CYP2C19 and its role as a major substrate[1, 16, 17]. In our study, drug interactions involving omeprazole were identified in 5.37% of omeprazole prescriptions. In comparison, a recent study among PPI users in community pharmacies in Brazil reported a prevalence of severe PPI–drug interactions of 16.4%, with omeprazole and pantoprazole being most frequently involved. The most common interacting drug pairs included levothyroxine, clopidogrel and cilostazol, with potential clinical consequences[35]. Among the identified omeprazole–drug interaction pairs in our study, clopidogrel was classified as a major interaction in all three drug interaction references. However, it was found in only 0.58% of outpatient prescriptions (19 out of 3,298), indicating relatively infrequent co-prescribing. In contrast, a retrospective study at a tertiary care university hospital in Northeastern Thailand involving 10,877 older adults identified omeprazole–clopidogrel as the most common major interaction, accounting for 6.3% of all identified pairs[36]. This low prevalence in our setting may reflect the relatively low occurrence of cardiovascular diseases, such as coronary artery disease, among outpatients in our hospital. Most studies assessing the clinical impact of PPI–drug interactions have been retrospective and have shown minimal clinical consequences[17]. Nonetheless, it is essential to monitor such interactions, especially in patients receiving high-dose or long-term PPI therapy. Managing non-fatal interactions may involve adjusting the dosage of co-administered drugs—for example, reducing the dose of CYP2C19-metabolized agents like escitalopram when used with omeprazole[14]. When dose adjustment is not feasible, alternative therapies or substitution with PPIs with lower CYP2C19 inhibitory activity—such as pantoprazole, rabeprazole or dexlansoprazole—should be considered[1,17].

To support the optimisation and deprescribing of PPIs in outpatient settings, patients should undergo a comprehensive evaluation to determine the ongoing appropriateness of PPI use. This includes confirming whether a valid indication remains, reviewing treatment duration to identify unnecessary short- or long-term use, assessing the need for high-dose regimens, evaluating

GI ulcer risk to guide prophylactic use and checking for potential drug interactions—particularly with omeprazole—and managing them appropriately. Practical implementation strategies may involve integrating deprescribing prompts (e.g., alerts for missing indications or prolonged therapy durations) into electronic clinical decision support systems, providing real-time alerts or recommendations to prescribers at the point of care. In addition, targeted educational programmes should be developed to enhance prescriber awareness of appropriate PPI use and guideline-based optimisation and deprescribing. Pharmacist-led medication reviews can also play a key role in identifying inappropriate PPI prescriptions by assessing their use for treatment, prophylaxis and potential drug interactions, thereby supporting evidence-based decision-making.

4.4 Advantages

This study has several advantages. First, the appropriateness of prescribing PPIs was evaluated in terms of therapy, prophylaxis and drug interactions involving omeprazole. Second, the recommendations for PPI use from the current guidelines for treating each approved clinical indication, preventing ulcers induced by NSAIDs or DAPT and optimising PPI use were applied. Lastly, three data sources on drug interactions were used to create a comprehensive list of drugs that interact with omeprazole and to highlight the differences in their interaction effects.

4.5 Limitations

This study also had limitations. First, the study did not evaluate the appropriateness of PPI therapy for approved indications that were not observed among the included prescriptions, such as *Helicobacter pylori* eradication, erosive oesophagitis, oesophageal stricture and Barrett's oesophagus. Second, the assessment may be inaccurate in certain cases, for example, when high-dose PPIs are administered to individuals who did not respond to a PPI at the SD or when PPIs are prescribed intermittently before resuming therapy at the next appointment. Third, some prescriptions classified as having unidentified approved indications may have involved uninvestigated dyspepsia (UD), especially those with symptoms such as abdominal pain or gastritis. As recommended in the Thailand dyspepsia guideline, PPI therapy may be empirically used in such cases. However, due to the absence of a specific ICD-10 code for UD, these cases could not be clearly identified or assessed. Fourth, the patient's risk of GI bleeding may have been underestimated due to the prescription omitting their history of GI bleeding. Fifth, potentially inappropriate PPI-drug interactions were broadly defined as concurrent prescribing without considering dosage adjustments; therefore, some interactions classified as potentially inappropriate might have been clinically appropriate in actual practice, particularly if managed through dose modification. Finally, our findings may not be applicable to other hospitals due to variations in prescribing patterns and service systems.

5. CONCLUSIONS

PPIs may be inappropriately prescribed to outpatients for treatment, prophylaxis or in the context of drug interactions with omeprazole. To promote rational PPI use and reduce the risk of adverse drug events, both proactive and reactive strategies are essential. Proactive strategies such as guideline-based educational programmes should be implemented to enhance prescriber awareness and optimise prescribing. Reactive strategies should involve pharmacist-led reviews of PPI prescriptions, assessing their use for treatment, prophylaxis and potential drug interactions to support evidence-based decision-making.

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Author contribution

Conceptualization, K.J.; methodology, K.J., K.K., K.T., and W.K.; software, K.J.; validation, K.J.; formal analysis, K.J., K.K., K.T., and W.K.; investigation, K.J., K.K., K.T., and W.K.; resources, K.J.; data curation, K.J., K.K., K.T., and W.K.; writing-original draft preparation, K.J.; writing-review and editing, K.J.; visualization, K.J., K.K., K.T., and W.K.; supervision, K.J.; project administration, K.J.; All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declared that they have no competing interests.

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Ethics approval

Prior to data collection, the study protocol was certified by the Human Ethics Committee of the University of Phayao (study code: HREC-UP-HSST 1.1/011/67, approval date: December 7, 2023).

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