



# Use and prescription appropriateness of drugs for peptic ulcer and gastroesophageal reflux disease in hospitalized older people

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## Abstract

**Purpose** The aims of this study were to assess the prevalence of use and prescription appropriateness of drugs for peptic ulcer and gastroesophageal reflux disease (GERD) at hospital admission and discharge.

**Methods** Patients aged 65 years or more hospitalized from 2010 to 2016 in 101 Italian internal medicine and geriatric wards in the context of the REPOSI register were scrutinized to assess if they were prescribed with drugs for peptic ulcer and GERD at hospital admission and discharge. Appropriateness of prescription was assessed considering the presence of specific conditions (i.e., history of peptic ulcer or gastrointestinal hemorrhages, advanced age, *Helicobacter Pylori*) or gastro-toxic drug combinations, according to the criteria provided by the reimbursement rules of the Agenzia Italiana del Farmaco (NOTA 1 and 48).

**Results** Among 4715 enrolled patients, 3899 were discharged alive. At hospital discharge, 2412 (61.9%, 95%CI: 60.3–63.4%) patients were prescribed with drugs for peptic ulcer and GERD, a 12% of increase from hospital admission. Almost half of the patients ( $N = 1776$ , 45.6%, 95%CI: 44.0–47.1%) were inappropriately prescribed or not prescribed: among the drugs for peptic ulcer and GERD users, about 60% (1444/2412) were overprescribed, and among nonusers, 22% (332/1487) were underprescribed. Among patients newly prescribed at hospital discharge, 60% (392/668) were inappropriately prescribed. The appropriateness of drugs for peptic ulcer and GERD therapy decreased by 3% from hospital admission to discharge.

**Conclusions** Hospitalization missed the opportunity to improve the quality of prescription of this class of drug.

**Keywords** Proton pump inhibitors · Older people · Hospital setting · Appropriateness · Drug prescription

## Introduction

Drugs for peptic ulcer and gastroesophageal reflux disease (GERD), in particular proton pump inhibitors (PPIs), are the leading evidence-based therapy for the management of the upper gastrointestinal acid-related disorders, as well as for the prevention of gastrointestinal toxicity induced by acetylsalicylic acid (ASA) or nonsteroidal anti-

inflammatory drugs (NSAIDs), the eradication of *Helicobacter pylori*, and the Zollinger-Ellison syndrome [1]. PPI use continues to grow worldwide both in community-dwelling and hospitalized patients, thanks to their undisputed efficacy and tolerability and also for their availability as generic drugs which permitted a price reduction in many countries [2]. Despite the fact that PPIs represent a huge therapeutic advance in controlling and healing acid-related disorders, they are clearly overused, with heavy implications on the costs for the National Health Services (NHS). For instance, in Italy, more than €800 million has been spent on them in 2017 [3]. In this year, four PPIs (i.e., pantoprazole, lansoprazole, omeprazole, and esomeprazole) were among the top ten drugs reimbursed by the Italian NHS [3]. At the same time, an extensive literature has emerged over time reporting adverse events (AEs), especially related to the long-term use of PPIs [4, 5], and many studies have detected a growing and worrisome increasing rate of inappropriate PPI prescription [6]. The inappropriate prescriptions of

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medications are a matter of concern especially in older people (65 years or more), who are affected by multiple diseases, often exposed to polypharmacy and thus at increased risk of potential drug-drug interactions and AEs [7–10].

With this background, the aims of the study were to assess the prevalence of use and appropriateness of prescription of drugs for peptic ulcer and GERD at hospital admission and discharge in a large sample of older people.

## Methods

### Setting

This was a cross-sectional study. Data were obtained from the register REgistro POLiterapie – Società Italiana Medicina Interna (REPOSI), an ongoing collaboration between the Italian Society of Internal Medicine (SIMI), IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, and the Istituto di Ricerche Farmacologiche Mario Negri IRCCS. The REPOSI is a multicenter register that started in 2008 to collect clinical and therapeutic information on patients aged 65 or older acutely and consecutively admitted to unselected internal medicine and geriatric wards in Italy during four index weeks during each season (at least 5 patients in each index week). Data collection were carried out in 2008, 2010, 2012, 2014, and then yearly since 2016. More details are available elsewhere [11]. The data collected by the hospital physicians included socio-demographic factors, clinical and laboratory parameters, performance in activities of daily living, the patterns of co-morbidities, and their severity according to the Cumulative Illness Rating Scale (CIRS) [12], as well as the drugs prescribed at hospital admission, during hospital stay and at discharge. Drugs at hospital admission mainly represented those prescribed by general practitioners (GPs). Participation was voluntary, and all patients provided signed informed consent. REPOSI was approved by the Ethics Committee of the participating centers. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki.

### Data collection

For this study, data from patients enrolled from 2010 up to 2016 were evaluated. All patients were scrutinized in order to establish whether or not they were prescribed with at least one drug for peptic ulcer or GERD (Anatomical Therapeutic Chemical classification system (ATC) codes: A02B\*), both at hospital admission and discharge. Additional drug categories were considered in order to assess the appropriateness of drugs for peptic ulcer or GERD, such as NSAIDs (ATC: M01A\*), corticosteroids (ATC: H02\*), ASA (ATC:

B01AC06, N02BA01), and other antithrombotic drugs (ATC: B01A\*) chronically used. Furthermore, we considered antibiotics such as amoxicillin (ATC: J01CA04), metronidazole (ATC: J01XD01), and clarithromycin (ATC: J01FA09) with indication for *Helicobacter Pylori* eradication. Additional NSAIDs in combination with corticosteroids (ATC codes M01B\*) were not included because these combinations are not available in the Italian market. Co-morbidities were defined through the International Classification of Diseases (ICD), 9th edition, and in particular those related to *Helicobacter pylori* infection (041.86) and ulcer or hemorrhages of esophagus, stomach, or duodenum (530.1–2, 530.7–8, 531–534, 535.\*1, 578).

### Appropriateness of prescription of proton pump inhibitors

The appropriateness of drugs for peptic ulcer or GERD was evaluated both for users and nonusers. For the purpose of this study, appropriateness of drug prescription for peptic ulcer, GERD, and gastro-protection was assessed according to the main criteria provided by the reimbursement rules of the Agenzia Italiana del Farmaco (AIFA) and summarized in NOTA 1 and 48 [13–15]. Reimbursement rules of AIFA are a regulatory instrument with the dual goal of promoting the appropriate use of drugs in accordance with the therapeutic needs of patients and of limiting costs for the National Health System (NHS). These criteria were developed on the basis of the main results of evidence-based medicine and a critical evaluation of available clinical-epidemiological data [13]. They indicate for which pathologies and/or under which conditions the use of specific drugs is recognized as appropriate so that they can be reimbursed by the NHS. The text of the NOTA 1 and 48 is reported in the Supplementary materials Box 1.

According to NOTA AIFA 1 [13], long-term PPI and misoprostol prescription are appropriate for the prevention of occurrence of gastroduodenal ulcers in patients chronically administered with NSAIDs or low doses of ASA for cardio- or cerebrovascular prevention, provided that at least one of the following condition is satisfied:

1. Advanced age
2. Concomitant therapy with other antithrombotic drugs or corticosteroids
3. Previous history of peptic ulcer or gastrointestinal hemorrhages

The NOTA AIFA does not specify a cut-off for age. Given that advanced age is only suggestive of an increased risk of bleeding, the cut-off of 75 years old was used in this study.

According to NOTA AIFA 48 [13], intermittent (or on-demand) prescription of drugs for peptic ulcer or GERD

(i.e., no more than 4/6 weeks) is appropriate for the first-line treatment of GERD and of gastroduodenal ulcer, associated or not with *Helicobacter pylori* infection (in combination with specific antibiotics) in order to prevent recurrence and to control symptoms. Long-term prescription (to be re-evaluated after 1 year) is appropriate for the Zollinger-Ellison syndrome or in case of recurrence of GERD or gastroduodenal ulcer.

Pertaining to this NOTA, the duration of drug therapy cannot be assessed on the basis of the data collected in the REPOSI register. Furthermore, we cannot discriminate among the first episode and the recurrences of GERD. Thus, all patients diagnosed with GERD or peptic ulcer during hospital stay were assessed as appropriately/inappropriately managed.

### Statistical analysis

Data were summarized as frequencies (%), means and standard deviations or medians, and interquartile ranges. Confidence intervals for proportions were calculated according to the Wilson score formula. Univariate and multivariable logistic regression models were used to determine among users of drugs for peptic ulcer or GERD possible factors associated with appropriate prescription at hospital discharge. Risk factors considered were sex, age, year of the REPOSI, geographical area, and number of drugs excluding drugs for peptic ulcer or GERD.

### Results

Among 4715 patients enrolled in the REPOSI register from 2010 to 2016, 4488 patients were enrolled in Italian internal medicine and geriatric wards, and 3899 patients were discharged alive (Fig. S1).

#### Hospital discharge

At hospital discharge, 2412 (61.9%, 95%CI: 60.3–63.4%) patients were prescribed with drugs for peptic ulcer or GERD. Table 1 reported the main patients' characteristics at hospital discharge, according to users or not. Prescriptions for drugs for peptic ulcer or GERD increased from 57.8% in 2010 to 63.9% in 2014 (being 56.0% in 2008) and subsequently decreased to 57.3% in 2016. The drug class most commonly prescribed at hospital discharge was that of PPIs (96%), with pantoprazole (27.9%) being the most frequently prescribed (Table S1). Sucralfate and alginate were always co-prescribed with PPIs or H<sub>2</sub> receptor antagonists.

All in all, 2123 (54.4%, 95%CI: 52.9–56.0%) patients were appropriately prescribed or not prescribed with drugs for peptic ulcer or GERD. Among the users, 968 (40.1%, 95%CI: 38.2–42.1%) were considered appropriately prescribed. On the other hand, among 1487 patients nonusers, 332 (22.3%,

95%CI: 20.3–24.5%) presented at least one of the indications to be treated, the most of them being prescribed with NSAIDs or ASA. Details are in Table 2. Among 1444 (= 2412–968) patients inappropriately prescribed, 162 (11.2%) aged 65–74 years were prescribed NSAIDs or ASA, but they did not present additional risk factors for gastrointestinal bleeding.

In the adjusted multivariable logistic regression model, being male (OR = 1.18, 95%CI: 0.99–1.40), being older (OR<sub>1year</sub> = 1.06, 95%CI: 1.05–1.08), and using an increasing number of drugs (OR = 1.11, 95%CI: 1.08–1.14) were associated with appropriate use. Nevertheless, when we considered only patients aged 75 years or more, i.e., the cut-off used for assessing appropriateness according to NOTA 1, only the increasing number of drugs remained associated (OR = 1.08, 95%CI = 1.04–1.12).

#### Hospital admission

At hospital admission, 1954 (50.1%, 95% CI: 48.5–51.7%) patients were prescribed drugs for peptic ulcer or GERD, being lansoprazole (27.0%) the most frequently prescribed drug (Table S1). In general, 2238 (57.4%, 95% CI: 55.8–58.9%) patients were appropriately prescribed/not prescribed. Among the users, 797 (40.8%, 95% CI: 38.6–43.0%) patients were appropriately prescribed. Instead, among 1945 nonusers, 504 (25.9%, 24.0–29.9%) were inappropriately not prescribed. Also at hospital admission, the main reason for inappropriateness among nonusers was being prescribed with gastro-toxic drugs.

#### Changes from hospital admission to discharge

Among 2412 users of drugs for peptic ulcer or GERD at hospital discharge, 668 (27.7%) were newly prescribed during hospitalization. On the other hand, among 1954 patients who were prescribed at hospital admission, 210 (10.7%) patients stopped them. These results led to a 11.7% (95% CI: 10.8–12.8%) increment in the prevalence of users at hospital discharge. On the contrary, the appropriateness of prescription decreased from admission to discharge by 3.0% (95% CI: 2.5–3.5%). In particular, 1210 (31.0%, 95% CI: 29.6–32.5%) patients were inappropriately prescribed or not prescribed both at hospital admission and at discharge. Among 668 patients newly prescribed at hospital discharge, 392 (58.7%) were inappropriately and unduly prescribed. Among them, 60 patients were prescribed with ASA but with no additional risk factor.

### Discussion

In a large cohort of older patients acutely hospitalized in internal medicine and geriatric wards from 2010 to 2016,

**Table 1** Patient characteristics at hospital discharge according to being user or nonuser of drugs for peptic ulcer and gastroesophageal reflux disease (GERD)

Patient characteristics	Users, <i>N</i> (%)	Nonusers, <i>N</i> (%)
Overall	2412	1487
Age (mean, SD)	78.7 (7.5)	78.6 (7.6)
Males	1170 (48.5)	719 (48.3)
Year		
2010	739 (30.6)	439 (29.5)
2012	724 (30.0)	446 (30.0)
2014	580 (24.1)	327 (22.0)
2016	369 (15.3)	275 (18.5)
Italian geographical area*		
North	1321 (54.8)	838 (56.4)
Center	492 (20.4)	325 (21.8)
South	599 (24.8)	324 (21.8)
Diagnoses		
Disease of the esophagus	160 (6.6)	25 (1.7)
Gastric ulcer	49 (2.0)	12 (0.8)
Duodenal ulcer	26 (1.1)	3 (0.2)
Peptic ulcer (site unspecified)	11 (0.5)	1 (0.1)
Gastrojejunal ulcer	3 (0.1)	0 (0.0)
Gastritis and duodenitis with hemorrhages	25 (1.0)	5 (0.3)
Gastrointestinal hemorrhage	10 (0.4)	4 (0.3)
<i>Helicobacter Pylori</i>	3 (0.1)	2 (0.1)

SD standard deviation

\*North includes Aosta Valley, Piedmont, Lombardy, Autonomous Province of Trento and Bolzano, Veneto, Friuli-Venezia-Giulia, Liguria, Emilia-Romagna; Center includes Tuscany, Umbria, Lazio, Marche; South includes Abruzzo, Molise, Campania, Basilicata, Calabria, Apulia, Sicily, Sardinia

62% of them were discharged with prescription of drugs for peptic ulcer or GERD. The use of these drugs increased over time to slightly decrease in 2016. However, this was not associated with a more appropriate management of the therapy during the study period. At hospital discharge, almost half of patients (46%) were inappropriately prescribed or not prescribed with drugs for peptic ulcer or GERD: among the users, 60% were overprescribed, and among nonusers, 22% were underprescribed. Furthermore, from hospital admission to discharge, there was a 12% increase in their use; although among the newly prescribed patients at hospital discharge, 60% were unduly prescribed. This is also highlighted by a 3% reduction in the appropriateness of prescription from hospital admission to discharge.

Drugs for peptic ulcer or GERD, especially PPIs, are widely used worldwide and generally perceived as a safe class of therapeutics. However, both this study and the literature show that PPIs are often overprescribed, less frequently under prescribed, and started inappropriately during an hospital stay and that their use is often extended for long-term duration with no appropriate indication [6, 16, 17]. Even if the short-term use of PPIs is associated with few side effects (i.e., headache, dizziness,

gastrointestinal symptoms), the potential adverse effects associated to the longer use (such as increased risk of community-acquired pneumonia, *Clostridium difficile*-associated diarrhea, hip fracture, chronic kidney disease, acute myocardial infarction, dementia, mortality) are established [5, 18–21]. Moreover, it is interesting to note that pantoprazole was the most commonly prescribed PPI at hospital discharge, even if it is listed (along with lansoprazole, omeprazole, and esomeprazole) as a drug with a conditional risk for QT prolongation that carries a possible risk of torsades de pointes occurrence, as a result of drug-drug interaction [22]. Notwithstanding, in this study, we found an overall increased use of PPIs with a slight decrease only in 2016, perhaps due to the stringent requests to contain public spending by regulatory agencies. Unfortunately, this decreased prescription was not matched by an increase in appropriateness. Hospitalization, which should offer the possibility to review pharmacological therapies taken by the patients, failed in this mission: from hospital admission to discharge, we have seen an increased use of PPIs, a reduction of their appropriateness and even a huge amount of patients newly prescribed with no indication.

As another study conducted in Italy using the same AIFA criteria of reimbursement for the assessment of appropriateness

**Table 2** Appropriateness of drug prescribing for peptic ulcer and gastroesophageal reflux disease (GERD), at hospital admission and discharge, according to users and nonusers

	At discharge		At admission	
	Users (N = 2412)		Users (N = 1954)	
<i>Appropriate</i>	968 (40.1)		797 (40.8)	
1. ASA or NSAIDs user	766 (79.1)		641 (80.4)	
Old ( $\geq 75$ years)		655 (58.5)		549 (85.6)
Other antiplatelet or corticosteroid		317 (41.4)		220 (34.3)
GERD		85 (11.1)		65 (10.1)
2. GERD or HP infection	199 (20.6)		156 (19.6)	
3. <i>Helicobacter pylori</i> eradication in combination with amoxicillina and claritromicina	3 (0.3)			
<i>Not appropriate</i> <sup>*§</sup>	1444 (59.9)		1157 (59.2)	
	Nonusers (N = 1487)		Nonusers (N = 1945)	
<i>Not appropriate</i>	332 (22.3)		504 (25.9)	
1. ASA or NSAIDs user	290(87.3)		458(90.9)	
Old ( $\geq 75$ years)		264 (91.0)		428
Other antiplatelet or corticosteroid		65 (22.4)		60
GERD		10 ( )		25
2. GERD or HP infection	42 (12.7)		46 (9.1)	
<i>Appropriate</i>	1155 (77.7)		1441 (74.1)	

\*Among these patients, 162 were prescribed NSAIDs or ASA, but they did not present additional risk factor for gastrointestinal toxicities

§ Among these, 298 patients was reported an appropriate GERD indication for PPI use

ASA acetylsalicylic acid, NSAIDs nonsteroidal anti-inflammatory drug, GERD gastroesophageal reflux disease, HP *Helicobacter pylori*

[13–15], we found that being older and having an increasing number of drugs were associated to a higher likelihood to be appropriately prescribed with PPIs. There are several possible explanations: first, older age is a criterion of appropriateness, and second, the increasing number of drug taken is probably associated with the prescription of combination of gastro-toxic drugs.

Studying the appropriateness of prescription of a specific class of drug draws attention on the evaluation of the appropriateness of co-prescribed drugs. In this study, the use of drugs for peptic ulcer and GERD was most frequently prescribed to prevent gastrointestinal toxicities of antiplatelets or NSAIDs. In a previous study based on data derived from the REPOSI register, we highlighted a largely inappropriate use of ASA, in the frame of primary prevention [10]. In this study, it must be pointed out that among patients not appropriately prescribed with drugs for peptic ulcer and GERD, 160 were prescribed also with ASA, and among them, 100 (62.5%) had no evidence of previous cardiovascular event (data not shown). Furthermore, among 753 patients appropriately prescribed with drugs for peptic ulcer and GERD to prevent gastrointestinal lesions induced by ASA, only 346 (45.9%) were appropriately prescribed with ASA. This appears to create a

prescribing cascade where one inappropriate prescription has resulted in another inappropriate prescription.

### Strengths and limitations

The study has some strengths and limitations. The main strength is that the large number of internal medicine and geriatric wards throughout Italy participating to the REPOSI register provides a representative and unselected sample of older in-patients reflecting the overall prescribing habits for these drugs in these wards in the country. Moreover, at variance with studies conducted on administrative databases, in the REPOSI register, PPI prescriptions are fully collected by clinicians, while community-dwelling patients could buy PPIs also without a medical prescription, thus resulting in underestimation of the prevalence of use of these drugs. On the other hand, in the frame of the REPOSI, we do not know the duration of the therapy of these drugs over time that is important to address the NOTA AIFA 48. Another limitation is that NOTA AIFA 1 does not clearly specify a cut-off for advanced age ( $\geq 65$  or  $\geq 75$  years old) but is suggestive of an increased risk of bleeding. Anyway, in this study, only 162 patients of 2412 (6.7%) aged 65–74 years were identified as inappropriately

prescribed when the cut-off of 75 years old has been chosen. Furthermore, using register data in order to evaluate appropriateness of drug prescriptions, we are not cognizant of the complex clinical decision-making process performed by physicians during prescribing, as well as of the patient preferences on taking these drugs.

## Conclusions

In conclusion, this study shows a large and inappropriate use of drugs for peptic ulcer and GERD in acutely hospitalized older people in internal medicine and geriatric wards from 2010 to 2016. Paradoxically, as in our previous studies [9, 10, 22–25], hospitalization failed once more to improve the quality of drug prescription in this at high risk and frail population, by exhibiting a decrease in the appropriateness of use or non-use of drugs for peptic ulcer and GERD. The large PPI overuse in this population suggests the development and implementation of a stewardship program, specifically aimed to deprescribe PPIs, both among GPs and hospital physicians [26–28].

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**Authors' contributions** C.F. wrote the manuscript; C.F. and I.A. designed the study research; C.F. and I.A. performed the research; I.A. analyzed the data; P.M.M. and A.N. critically revised the manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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