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Original article

Prevalence and appropriateness of drug prescriptions for peptic ulcer and gastro-esophageal reflux disease in a cohort of hospitalized elderly

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ABSTRACT

Background: Proton pump inhibitors (PPI) are among the most commonly prescribed medicines and their overuse is widespread in both primary and secondary care. Inappropriate prescription is of particular concern among elderly patients, who have often multiple comorbidities and need many drugs.
Methods: We evaluate the appropriateness of drugs for peptic ulcer or gastro-esophageal reflux disease (GERD) in a sample of elderly patients (65 years old or older) at admission and discharge in 38 internal medicine wards between January 2008 and December 2008, according to the presence of specific conditions or gastro-toxic drug combinations.
Results: Among 1155 patients eligible for the analysis, 466 (40.3%) were treated with drugs for GERD or peptic ulcer were at hospital admission and 647 (56.0%) at discharge; 62.4% of patients receiving a drug for peptic ulcer or GERD at admission and 63.2% at discharge were inappropriately treated. Among these, the number of other drugs prescribed was associated with greater use of drugs for peptic ulcer or GERD, even after adjustment for age, sex and number of diagnoses at admission (OR 95% CI = 1.26 (1.18–1.34), $p = .0001$) or discharge (OR 95% CI = 1.11 (1.05–1.18), $p = 0.0003$).
Conclusions: Prevalence of inappropriate prescription of drugs for peptic ulcer or GERD remained almost the same at admission and discharge. Inappropriate use of these drugs is related to the concomitant use of other drugs. Careful assessment of clinical conditions and stricter adherence to evidence-based guidelines are essential for a rational and cost-effective use of drugs for peptic ulcer or GERD.

1. Background

Drugs for peptic ulcer or gastro-esophageal reflux disease (GERD), especially proton pump inhibitors (PPI), are among the most commonly prescribed medicines. PPI overuse is widespread in both primary and secondary care with great implications on drug costs in the industrialized world [1]; in Italy it accounts for about 7% of gross pharmaceutical expenditure [2]. PPI certainly offer an improvement in the treatment of common and important gastrointestinal diseases. They are effective in the cure or prevention of peptic acid disorders and in the management of GERD, esophagitis, gastric ulcer, bleeding peptic ulcer, eradication of *Helicobacter pylori*, dyspepsia, Zollinger–Ellison syndrome and prevention of gastrointestinal (GI) toxicity induced by non-steroidal anti-inflammatory drugs (NSAID).

However, some studies have suggested that between 25% and 81% of patients taking PPI had no appropriate indication and in many cases physicians fail to provide specific instructions about how long to continue treatment [3–11]. PPI are frequently used in patients who do not meet the criteria for appropriate use or for non-evidence-based indications where less powerful, cheaper agents would be effective for the treatment of symptoms. Although there is evidence about superiority of the PPI over H_2 receptor antagonists and others drugs for the treatment of GERD or peptic ulcer, thanks to their stronger and longer action, other drugs could often be an effective and safe alternative for many patients [12–14].

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[1] REPOSI denotes Registry of Polytherapies SIMI (Società Italiana di Medicina Interna).

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Inappropriate prescriptions are of particular concern among elderly patients, who normally have multiple comorbidities, take many drugs and are at higher risk of adverse drug reactions [15–17]. Although generally well tolerated, PPI can cause serious adverse reactions. Their short-term use has been associated with infections such as community-acquired pneumonia [18–21] or *Clostridium difficile* diarrhea [22,24] due to low gastric acidity, and with a loss of efficacy of clopidogrel as a result of drug interaction [25–30]. Long-term use has been related to increases in hip fractures [31–33], delayed diagnosis of gastric cancer and increased risk of all-cause mortality [34,35].

The aims of the present analysis, in the cohort of elderly patients enrolled in the REPOSI study, were to evaluate the rate of prescriptions of drugs for peptic ulcer or GERD at admission and discharge in a sample of Italian internal medicine wards and to analyze the appropriateness of use in relation to evidence-based indications.

2. Methods

2.1. Data collection

The Registro Politerapie SIMI (REPOSI) study is a collaborative, independent, voluntary effort by the Italian Society of Internal Medicine (SIMI) and the Mario Negri Institute for Pharmacological Research, run between January 2008 and December 2008 in a sample of 38 internal medicine wards in various Italian regions. This multicenter collaborative longitudinal study was designed to create a network of internal medicine and geriatric wards in order to collect information on a sample of elderly in-patients with multiple diseases, needing polytherapy, to describe the prevalence of these diseases and the treatments, to analyze the predictors, and to record the main clinical outcomes at hospital discharge.

To ensure an unselected population of elderly patients admitted to internal medicine wards, during four-week period three months apart (one in February, one in June, one in September, and one in December 2008) the first ten patients admitted to the wards participating in the study were consecutively recruited if they were 65 years old or older. For this observational study, conducted on anonymous patient records, approval by the Ethics Committee was not required. Participation in the study was voluntary and all the patients gave signed informed consent. For each patient, a standardized web-based case report form was completed by the attending physician, including socio-demographic factors, clinical parameters, diagnoses and treatments at hospital admission and discharge, clinical events while in hospital, and outcome. All the data were collected and checked by a central monitor at the Mario Negri Institute for Pharmacological Research, Milan.

2.2. Diseases and drug appropriateness

Diagnoses examined were recorded at hospital admission and discharge and confirmed by caregivers on the basis of clinical examination, anamnesis, laboratory and instrumental data. Diagnoses were made using standardized criteria. The International Classification of Diseases-Ninth Revision (ICD-9) (World Health Organization, 1987) [36] was used for classifying all diseases. Drugs were recorded according to the Anatomical Therapeutic Chemical classification system (ATC) (WHO 1990) [37].

The appropriateness of drug prescriptions for peptic ulcer and GERD (ATC classification code: A02B) was assessed retrospectively taking into account the presence of a pathological condition requiring their use or the presence of gastro-toxic drug combinations [6,38,39], which we defined as concomitant therapy with NSAIDs or low doses of acetylsalicylic acid (ASA) together with oral corticosteroids or antithrombotic therapy. Criteria used to identify gastro-toxic drug combinations are in accordance with the stronger evidence-based indications [6], which reflect the rules [7] of the Agenzia Italiana del Farmaco (AIFA, the Italian Drug Agency) for gastroprotection with PPIs and misoprostol in order to prevent gastrointestinal toxicity in patients using gastro-toxic drug combinations (Box 1).

The pathological conditions in which we assessed the appropriateness of A02B drug use were classified on the basis of the diagnosis at hospital admission and/or at discharge, with the specific ICD-9 codes. We considered all patients with diseases of the esophagus, stomach, and duodenum (ICD-9 codes from 530 to 538 and 578), or with *H. pylori* infection (ICD-9 code 041.86).

Drugs for peptic ulcer or GERD were identified from the list of drugs administered at admission and discharge according to the ATC classification (the third level code A02B). Similarly, gastro-toxic drug combinations were identified according to the second, third, fourth or fifth level of the ATC code as follows: H02 for corticosteroids, M01A and N02BA for non-steroidal anti-inflammatory drugs, B01A, B01AB, and B01AC for oral antithrombotic drugs other than ASA, and B01AC06 and for ASA. M01B were not included in analysis because no drug is available in Italy with this code. All N02BA drugs recorded at hospital admission corresponded to acetylsalicylic acid 100 mg prescribed for cardioprotection on the basis of clinical indication recorded. So these medication were coded as B01AC06. In accordance with this criteria, patients appropriately treated with drug for peptic ulcer and GERD were those with gastrointestinal diseases, such as ulcer, esophageal diseases, gastritis, duodenitis or Helicobacter infection or those receiving a gastro-toxic drug combinations, such as concomitant therapy with NSAIDs or low doses of acetylsalicylic acid (ASA), together with oral corticosteroids or antithrombotic therapy.

3. Statistical analysis

Confidence intervals on percentages of drug use were computed using score confidence intervals.

Statistical significance of differences in possible predictors for inappropriate prescription of drugs for the treatment of GERD or peptic ulcer was evaluated using logistic regression, at the univariate and multivariate levels. Analyses were done with JMP, v. 8.0.2 (SAS Institute Inc.). Multivariate analyses were corrected for age, sex, number of drugs and number of diagnoses.

4. Results

In all 38 departments of internal medicine and geriatric wards participated in the REPOSI study and recruited 1332 patients; 111 were excluded because of lack of discharge information (they were transferred to another hospital ward not participating in the study) and 66 because they died inhospital. Therefore 1155 patients were eligible for this analysis.

Drugs for GERD or peptic ulcer were given to 466 patients (40.3%) at admission and 647 (56.0%) at discharge. The mean number of drugs used and diagnoses made were higher in patients given drugs for peptic ulcer or GERD than in untreated patients (Table 1). PPI were the

Box 1
Rules of AIFA for gastroprotection with PPIs and misoprostol

Rules of the AIFA allow the prescription of PPIs or misoprostol for gastroprotection in the case that a patient chronically treated with NSAIDs or ASA has concomitantly the presence of history or active peptic ulcer; or concomitant therapy with an anticoagulant agents or corticosteroids; or advanced age (not specified if older than 65 or 75). Rules underline that advanced age or anticoagulant therapy is not a criteria to treat all elderly with gastropotector, but must be considered a factor suggestive of populations at increased risk and not a recommendation.

Table 1
Main characteristics of patients recruited for the analyses.

	At admission ($n=1155$)		At discharge ($n=1155$)	
	Treated with A02B[a]	Not treated with A02B	Treated with A02B	Not treated with A02B
Total	466	689	647	508
Patients with disease or gastro-toxic combinations (%)	175 (37.6)	59 (8.6)	238 (36.8)	41 (8.1)
Age, years (mean ± SD)	79.2 ± 7.7	79.2 ± 7.5	79.1 ± 7.7	79.3 ± 7.4
Women (%)	55.2	52.7	53.0	54.5
Drugs, no (mean ± SD)[b]	5.4 ± 2.7	3.9 ± 2.4	5.8 ± 2.9	4.9 ± 2.4
Diagnoses, No (mean ± SD)	4.9 ± 2.4	3.8 ± 2.2	6.3 ± 2.5	5.5 ± 2.4

[a] Drugs for peptic ulcer or gastro-esophageal reflux disease.
[b] Excluding the drugs for peptic ulcer or GERD.

most frequently prescribed drugs for these indications, accounting for about 95.3% of prescriptions at admission and 95.5% at discharge. Lansoprazole and omeprazole were the main active principles prescribed (Table 2).

At admission 291 patients (62.4% of those receiving a drug for peptic ulcer or GERD) and 409 at discharge (63.2%) were treated even though they had no specific pathology or gastro-toxic drug combinations that could justify the use of these drugs. Furthermore, 227 patients (78.0%; 95% CI, 72.9%–82.4%) received a drug for peptic ulcer or GERD inappropriately at both admission and discharge. Only in 36 cases (12.4%; 95% CI, 9.1%–16.7%) were these drugs appropriately withdrawn at hospital discharge. At admission 59 patients (5.1%; 95% CI, 4.0%–6.5%) with gastrointestinal diseases or receiving a gastro-toxic drug combinations and 41 (3.6%;95% CI, 2.6%–4.8%) at discharge were inappropriately not treated with a drug for peptic ulcer or GERD. Among patients inappropriately not treated ad admission 27 (48.5%; 95% CI, 33.7%–58.3%) received the treatment at discharge. Sex and mean age were not different for patients who received these drugs appropriately or inappropriately at either admission or discharge. The mean numbers of drugs prescribed were higher among patients with inappropriate prescription at admission (5.4 ± 2.7 and 5.1 ± 2.8) and discharge (5.7 ± 2.8 and 5.4 ± 2.8). However the mean number of diagnoses was higher in patients treated appropriately than inappropriately at admission (4.9 ± 2.2 and 4.3 ± 2.3) and discharge (6.2 ± 2.4 and 5.9 ± 2.4). In addition, among patients appropriately not treated at admission with a drug for peptic ulcer or GERD, the drug was prescribed at discharge to 149 (23.3%, 95% CI, 20.2%–26.7%), although it did not need to be continued.

Among appropriately treated patients the main gastrointestinal diseases associated with prescriptions at hospital admission or discharge are reported in Table 3. Gastro-toxic drug combinations were the second cause of prescription. Low doses of ASA with another antithrombotic drug was the combination most frequently prescribed (45.5% and 54.0%), followed by low doses of ASA and corticosteroids. Drugs for peptic ulcer or GERD in patients with inappropriate prescriptions were taken for a median of 436 days, before the admission. Comparing the characteristics of patients inappropriately receiving a drug for peptic ulcer or GERD with those appropriately not treated, the mean number of drugs was related to greater use of drugs for peptic ulcer or GERD in univariate analysis and also after adjustment for age, sex and number of diagnoses at either admission (OR 95%CI = 1.26 (1.18–1.34), $p = .0001$) and discharge (OR 95%CI = 1.11 (1.05–1.18), $p = 0.0003$). The mean number of diagnoses was only weakly associated with use of these drugs, and in multivariate analyses the results did not reach statistical significance (Table 4).

Table 2
Number of patients treated with active principles for peptic ulcer or GERD at admission and discharge.

Antisecretory drug	At admission ($n=466$)		At discharge ($n=647$)	
	Number of patients	% (95% CI)	Number of patients	% (95% CI)
Lansoprazole	177	38.0 (33.7–42.5)	238	36.8 (33.2–40.6)
Omeprazole	138	29.6 (25.6–33.9)	197	30.4 (27.0–34.1)
Esomeprazole	58	12.4 (9.8–15.8)	68	10.5 (8.4–13.1)
Rabeprazole	43	9.2 (6.9–12.2)	88	13.6 (11.2–16.5)
Pantoprazole	38	8.2 (6.0–11.0)	44	6.8 (5.1–9.0)
Ranitidine	10	2.1 (1.2–3.9)	9	1.4 (0.7–2.6)
Alginic acid	7	1.5 (0.7–3.1)	9	1.4 (0.7–2.6)
Sucralfate	5	1.1 (0.5–2.5)	10	1.5 (0.8–2.8)
Misoprostol	0	0	1	0.2 (0–0.9)

5. Discussion

This analyses shows mainly the high prevalence of inappropriate prescription of drugs for peptic ulcer or GERD, at hospital admission and discharge. Hospitalization is associated with rise in the rate of use of these drugs: at admission 40% of patients were taking one of these drugs, but 56% at discharge. Although these medications should be prescribed in accordance with evidence-based guidelines in order to keep down unnecessary costs and prevent adverse drug reactions, which are a particular concern in the elderly, among patients prescribed drugs for peptic ulcer or GERD, 66% at admission and 64% at discharge did not have any appropriate indication. Though the prevalence of inappropriate use of drugs for peptic ulcer or GERD was not different at admission and discharge, it is important to underline that at discharge more patients were receiving these drugs inappropriately (304 at admission and 415 at discharge). Moreover, 23% of patients who were appropriately not receiving these drugs at admission, were nevertheless prescribed these at discharge even without a specific indication. Furthermore prevalence of patients inappropriately not treated at admission or discharge were similar and we don't know if they were not receiving the treatment due to drug intolerance or if they were inappropriately not treated. These findings are comparable to studies conducted in other countries to evaluate the licensed or unlicensed prescription of PPI. In Greece, PPI were inappropriately prescribed to 81% of patients in a department of internal medicine [9], in UK PPI were prescribed for unlicensed indications in 67% of patients [40], and in Ireland this rate was nearly 63% [41]. In another Italian study, assessing the appropriateness of acid-suppressive therapy in a cohort of hospitalized patients and its fallout on prescriptions in general practice, anti-secretory drugs, especially PPI, were not indicated in 41.5% of patients admitted to a department of internal medicine, acceptable in 6.5% and indicated in 50.1%; the main reason for inappropriate use was prophylaxis in low-risk patients (64.8%) [42]. In Australia, according to two studies, PPIs were appropriately prescribed only in 37.1% or 31% of cases [5,43]. Similarly in Spain, the prescription of PPIs was reported to be appropriate in 36.4% or 28% of patients [44,45].

Compared to other study, the main strength of our findings is that inappropriate use of these drugs is significantly related to the mean number of concomitant drug used, independently by the prescription of gastro toxic drug combinations. However a large number of co-administered drugs should not necessarily indicated the need for gastroprotective agents; closer evaluation of the underlying clinical conditions and prescribing patterns more closely linked to evidence-based guidelines and national recommendations are therefore essential for a rational, cost-effective approach. For patients in the hospital physicians should consider the possibility of withdrawing drugs for peptic ulcer or GERD if there is no pathological condition warranting their use, and in patients not taking gastro-toxic drug combinations. Patients should be given specific recommendations about how long to continue taking the drugs in order to avoid unnecessary, undefined prolongation of treatment. In our study, with a median time of 18 months of drug usage by patients with an

Table 3
Prevalence of gastrointestinal diseases and gastro-toxic drug combinations at admission and discharge among patient who received an appropriate drug for GERD or peptic ulcer.

Diagnoses	At admission ($n=175$)		At discharge ($n=238$)	
	Number of patients	% (95% CI)	Number of patients	% (95% CI)
Gastrojejunal ulcer	107	61.1 (53.8–68.1)	137	57.6 (51.2–63.7)
Gastro-toxic drug combinations	33	18.6 (13.8–25.3)	63	26.5 (21.3–32.4)
Esophageal disease	25	14.3 (9.9–20.2)	36	15.1 (11.1–20.2)
Gastrointestinal haemorrhage	18	10.3 (6.6–15.7)	7	2.9 (1.4–5.9)
Gastritis and duodenitis	5	2.9 (1.2–6.5)	4	1.7 (0.7–4.2)
Gastric ulcer	5	2.9 (1.2–6.5)	7	2.9 (1.4–5.9)
Duodenal ulcer	3	1.7 (0.6–4.9)	7	2.9 (1.4–5.9)
Peptic ulcer, site unspecified	2	1.1 (0.3–4.1)	1	0.4 (0.1–2.3)
Disorders of stomach function	1	0.6 (0.1–3.2)	4	1.7 (0.7–4.2)
Helicobacter pylori infection	1	0.6 (0.1–3.2)	0	0
Prevalence of gastro-toxic drug combinations				
	Admission ($n=33$)		Discharge ($n=63$)	
	Number of patients	% (95% CI)	Number of patients	% (95% CI)
ASA with other antithrombotic drugs	15	45.5 (29.8–62.0)	34	54.0 (41.8–65.7)
ASA with corticosteroids	13	39.4 (24.7–56.3)	24	38.1 (27.1–50.4)
NSAIDs with corticosteroids	4	12.1 (4.8–27.3)	6	9.5(4.4–19.3)
NSAIDs with antithrombotic other than ASA	1	3.0 (0.5–15.3)	3	4.8 (1.6–13.1)
NSAIDs with ASA	1	3.0 (0.5–15.3)	1	1.6 (0.2–8.5)

inappropriate prescription, it is probable that for many patients who had had diseases requiring drugs for peptic ulcer or GERD prescriptions were simply repeated although the disease was no longer present. For hospital in-patients the caregiver plays an essential role for rational and appropriate use of these drugs, discouraging prescription in patients with no symptoms or evidence-based indications. Physicians should recall the authorized indications and recommendations for licensed use of these drugs. They should constantly reassess drug therapy, considering suspending drugs in patients with no specific diseases, symptoms or gastro-toxic drug combinations. We also noted an unjustified increase in the use of gastroprotectors in hospital, which could raise the risk of drug adverse reactions and the cost for the NHS. Although lansoprazole and omeprazole, the main PPI prescribed, are available as generic drugs in Italy and are the cheapest PPI on the market, using these drugs for unlicensed or inappropriate indications is an unjustified cost. We also found that elderly patients taking multiple drugs seemed to be more likely to be inappropriately treated with a drug for peptic ulcer or GERD. The need for a large number of drugs without specific gastro-toxic combinations is not an evidence-based indication, and does not justify the use of a gastroprotective agent. The length of hospital stay was also not associated to a higher probability of receiving these drugs, in both, the univariate and multivariate model.

Patients included in the study are a representative, unselected sample of elderly in-patients in medicine wards in Italy and our analysis reflects the prescribing habits for the drugs considered. The major limit of the study is that information about drug prescriptions at admission were obtained directly from patients or relatives, so real drug use and duration of the therapy may be under-estimated compared to information at discharge, which was collected directly by the persons monitoring this study. This difference in the accuracy of data collection may have contributed to the difference in drug consumption between admission and discharge. Another limit is that we have no follow-up after discharge, whereas it would be useful to evaluate whether or not

Table 4
Main characteristics of patients inappropriately receiving a drug for peptic ulcer or GERD at admission and discharge compared to patients appropriately not treated, and odds ratio (OR) for inappropriate prescription.

Prescription of A02B[a]	At admission ($n=994$)		At discharge ($n=923$)	
	Inappropriately treated with A02B	Appropriately not treated with A02B	Inappropriately treated with A02B	Appropriately not treated with A02B
Total	291	630	415	469
Age, yrs (mean ± SD)	78.9 ± 7.9	79.2 ± 7.4	79.4 ± 7.8	79.4 ± 7.4
Women (%)	54.3	52.9	55.5	55.7
Number of different drugs (mean ± SD[b])	5.4 ± 2.7	3.9 ± 2.4	5.7 ± 2.8	4.9 ± 2.4
Number of different diagnoses (mean ± SD)	4.3 ± 2.3	3.8 ± 2.2	5.9 ± 2.4	5.4 ± 2.4
	OR (95% CI)	*p*	OR (95% CI)	*p*
Univariate analyses				
Number of drugs	1.26 (1.19–1.33)	<.0001	1.13 (1.07–1.19)	<.0001
Number of diagnoses	1.11 (1.04–1.18)	0.001	1.09 (1.03–1.15)	0.003
Multivariate analyses[c]				
Number of drugs	1.26 (1.18–1.34)	<.0001	1.11 (1.05–1.18)	0.0003
Number of diagnoses	0.99 (0.93–1.07)	0.84	1.04 (0.97–1.10)	0.28

[a] Drugs for peptic ulcer or gastro-esophageal reflux disease.
[b] Excluding the drugs for peptic ulcer or GERD.
[c] Results were corrected for age, sex, number of drugs and number of diagnoses.

overuse of drugs for peptic ulcer or GERD in the elderly in hospital is then related to over-prescription in general practice.

Learning points

- In many cases patients taking PPI had no appropriate indication and physicians fail to provide specific instructions about how long to continue treatment.
- Inappropriate use of PPI is significantly related to the mean number of concomitant drug used, independently by the prescription of gastro toxic drug combinations.
- Closer evaluation of the underlying clinical conditions and prescribing patterns more closely linked to evidence-based guidelines and national recommendations are essential for a rational, cost-effective approach.

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