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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Use of proton pump inhibitors in adults in France: a nationwide drug utilization study

Marion Lassalle[1] · Thien Le Tri[1] · Marc Bardou[2] · Michel Biour[3] · Julien Kirchgesner[4] · Frank Rouby[5] · Nathalie Dumarcet[6] · Mahmoud Zureik[1] · Rosemary Dray-Spira[1]

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Abstract

Purpose Proton pump inhibitor (PPI) drugs are approved for the management of gastric acid–related diseases, mainly treatment of gastroesophageal reflux disease, treatment of nonsteroidal anti-inflammatory drugs (NSAID)–related gastrointestinal complications and prevention in at-risk patients, *Helicobacter pylori* eradication, and treatment of ulcers. PPIs are one of the most commonly prescribed drug class worldwide, and off-label use is widespread. The aim of this study was to describe outpatient PPI use of the whole adult population in France, based on the French National Health Data System (SNDS).

Methods All individuals aged 18 years or older, with at least one dispensing for PPI between January 1, 2015 and December 31, 2015, were identified as PPI users. PPI users were considered as new users if they received no dispensing for PPI in the prior year. New users were followed until treatment discontinuation or up to 1 year, whichever occurred first. Characteristics of new users and of their PPI treatment were described, overall and separately by treatment indication.

Results In total, 15,388,419 PPI users were identified in 2015 (57.0% women; mean age 57.0 years), accounting for 29.8% of the French adult population. Of them, 7,399,303 were new PPI users; mean treatment duration was 40.9 days, and 4.1% received a continuous PPI therapy lasting more than 6 months (10.2% among new users > 65 years versus 2.4% among those 18–65 years). For 53.5% of new users, indication for PPI therapy was a co-prescription with NSAID; in this indication, the large majority of patients (79.7%) had no measurable risk factor supporting a systematic prophylactic co-prescription of PPI. A proportion of 32.4% of new users did not have any identified comedication or inpatient diagnosis supporting an indication for PPI therapy; among them, only a small proportion (7.3% overall, and 8.4% of patients aged > 65 years) underwent a procedure investigating the digestive tract at the time of PPI initiation.

Conclusion The results of this study suggest PPI overuse in France, not always in line with the French guidelines. In particular, inappropriate co-prescription with NSAID was frequent. Efforts should be made to limit PPI treatment to appropriate indications and durations.

Keywords Proton pump inhibitors · Drug use · Acid-related diseases · Pharmacoepidemiology · Nationwide

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✉ Marion Lassalle
marion.lassalle@ansm.sante.fr

[1] EPI-PHARE, Epidemiology of Health Products (French National Agency for the Safety of Medicines and Health Products [ANSM], and French National Health Insurance [CNAM]), Saint-Denis, France

[2] Department of Hepato-gastroenterology, CHU de Dijon, Dijon, France

[3] Regional Pharmacovigilance Center, Assistance Publique des Hôpitaux de Paris, Paris, France

[4] Department of Gastroenterology and Nutrition, Assistance Publique des Hôpitaux de Paris, Paris, France

[5] Regional Pharmacovigilance Center, Assistance Publique des Hôpitaux de Marseille, Marseille, France

[6] Department of Dermatology, Hepato-gastroenterology and Rare Metabolic Diseases, French National Agency for the Safety of Medicines and Health Products, Saint-Denis, France

Introduction

Proton pump inhibitors (PPIs) are a class of drugs suppressing gastric acid secretion. Their use has dramatically grown since their market introduction in the late 1980s, and they are currently one of the most commonly prescribed drugs worldwide [1]. In the UK, PPI use more than doubled since 2007, ranking second by prescription items in 2017, with nearly 59 million items dispensed annually [2]. In France, PPI sales increased by 20% between years 2010 and 2013, with 80 million packs in 2013 (source: National Agency for Medicines and Health Products Safety [ANSM]), with esomeprazole, omeprazole, and pantoprazole being among the top 30 best-selling drugs in pharmacies [3]. PPIs are approved in the following main indications [4–7]: treatment of gastroesophageal reflux disease (GERD) and reflux esophagitis, treatment of nonsteroidal anti-inflammatory drugs (NSAID)–associated gastrointestinal (GI) lesions and prevention in at-risk patients (aged > 65 years, with a history of GI ulcer, or with concomitant antiplatelet, anticoagulant, or corticosteroid therapy), *Helicobacter pylori* eradication, and treatment of peptic ulcer. Off-label prescribing has been widely reported, including in non-at-risk patients taking antiplatelet, anticoagulant, or corticosteroid drugs without concomitant NSAID, in prevention of chemotherapy or radiotherapy-associated lesions in patients with cancer, or in the management of extra-digestive symptoms potentially from gastroesophageal reflux, including non-cardiac chest pain, laryngeal complaints, asthma, or chronic cough [8, 9]. The estimated rate of inappropriate use reaches 50% [10]. In France, previous studies on PPI use were limited to specific subpopulations or healthcare settings [11–22]. The objective of this study was to describe PPI use, and its appropriateness, at the whole French population level, based on data from national medico-administrative databases.

Methods

Datasources

The French National Health Data System (Système National des Données de Santé, SNDS) covers the entire French population (66 million inhabitants) irrespective of employment status. It contains two main databases: the health insurance claims database (DCIR) and the national hospital discharge database (PMSI). An anonymous, unique identifier for each individual links the DCIR information to the PMSI. The DCIR contains individual data on sociodemographic characteristics and all medical claims since 2008. It provides information on dispensed drugs (recorded according to the Anatomical Therapeutic Chemical [ATC] classification system) with date of delivery, therapeutic procedures coded using a common classification of medical procedures (Classification Commune des Actes Médicaux [CCAM]), and laboratory tests. The database also contains medical information on the presence of any serious and costly long-term disease giving entitlement to a 100% health insurance coverage, with information on diagnosis encoded in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) and date of disease onset. The PMSI includes information on every admission in a public or private hospital in France since 2006, either for an inpatient stay or ambulatory care. Diagnoses (in ICD-10 codes) and medical or surgical procedures provided during hospital stays are available.

Study population

All individuals aged 18 years or older, with at least one dispensing for PPI between January 1, 2015 and December 31, 2015, were identified as PPI users. The first dispensing date for PPI in 2015 was the index date. PPI users were considered as new users if they did not receive any dispensing for PPI in the year prior to the index date. New users were followed from the index date until treatment discontinuation, if any, or up to 1 year.

PPI treatment characteristics

PPIs were identified by the ATC classification A02BC. Treatment duration was estimated by the number of dispensed tablets of PPIs, assuming that one tablet corresponds to 1 day of exposure, except for eradication of *H. pylori*, requiring double dose. If a patient failed to fill a new prescription within the estimated dispensing duration plus a 30-day grace period, we considered that the treatment was discontinued. PPI users with a treatment lasting more than 6 months were considered as long-term users. Prescribers were categorized as hospital or private practice practitioner. Information on prescriber specialty was available for private practitioners only.

Although the reason for prescription is not explicitly recorded in the SNDS, individual information on concomitant medications, inpatient diagnoses, and medical and laboratory procedures was collected to identify the probable indication for PPI treatment among new users, according to an algorithm detailed in Fig. 1. The sequence of indications was established based on data from the international literature, experts' opinion, and prescribing recommendations. The algorithm was designed to identify, as much as possible for each patient, an indication in accordance with the French guidelines, if any. This included eradication of *H. pylori* (defined by both dispensing data suggestive of eradication antibiotic regimens, and inpatient diagnosis of *H. pylori* infection/or specific laboratory testing [23]), or treatment/prevention of NSAIDs-associated ulcers. We then considered indications potentially not in line with the French guidelines but observed in clinical

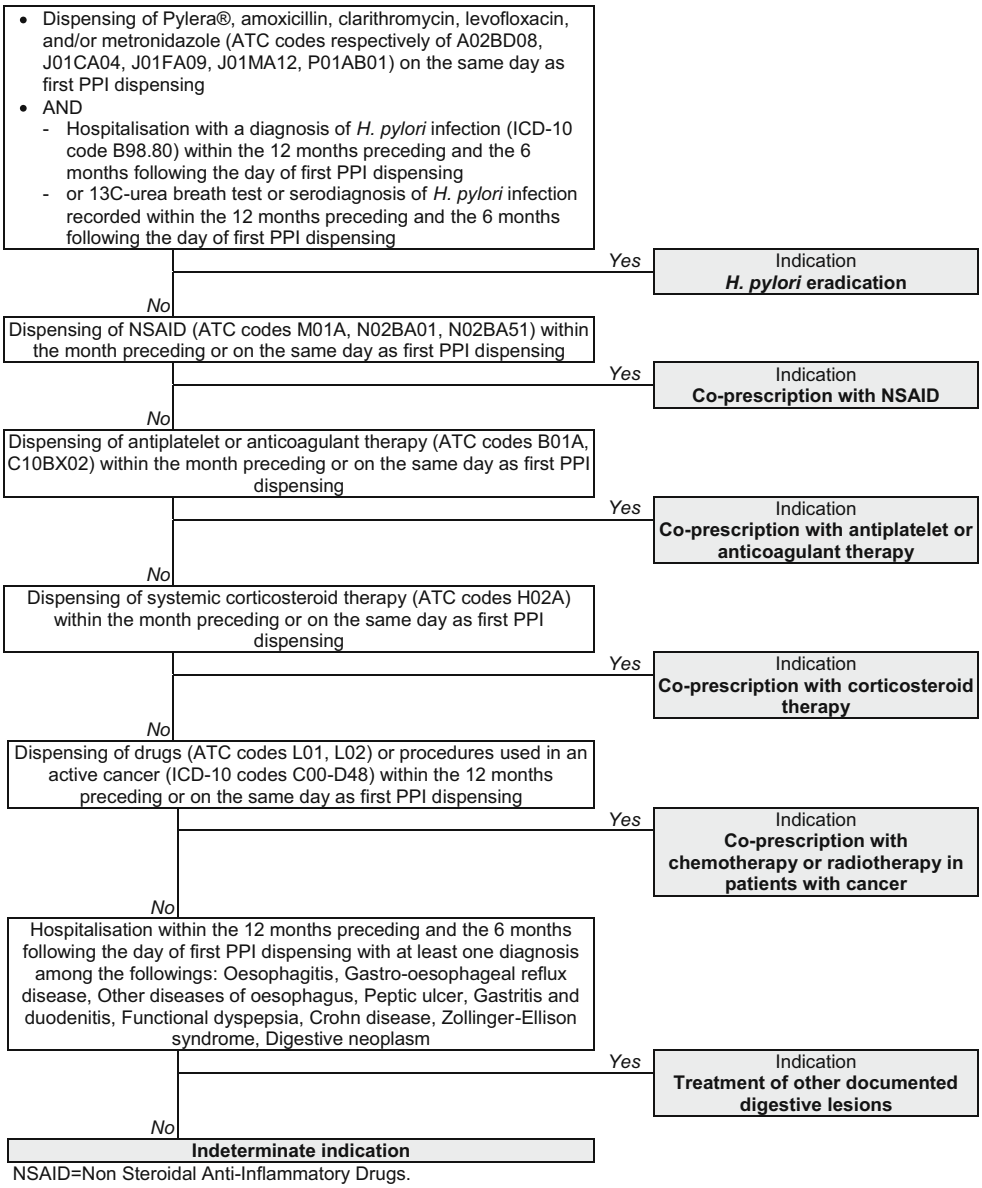

Fig. 1 Algorithm of identification of PPI treatment indication among new users

NSAID=Non Steroidal Anti-Inflammatory Drugs.

practice, including co-prescription with antiplatelet or anticoagulant therapy, corticosteroid therapy, or chemotherapy or radiotherapy in patients with cancer. For patients remaining uncategorized, we searched for inpatient diagnosis of digestive lesion. Finally, in the absence of informative data, the indication was considered indeterminate. For the sake of simplicity, every new PPI user was assigned a unique indication. Nevertheless, for each indication, patients' characteristics regarding concomitant medications, gastro-intestinal procedures, and diagnosis were also described.

Sociodemographic and medical characteristics

For each PPI user, individual information was available on the following: sociodemographic characteristics at the index date, including sex and age; medical characteristics including gastrointestinal procedures (upper gastrointestinal endoscopy, with or without biopsy, upper gastrointestinal series, esophageal manometry, and pH examination) and inpatient diagnoses of gastrointestinal diseases (ICD-10 codes listed in the supplementary materials), recorded within the 12 months preceding the index date and, taking into account possible diagnostic process delays after PPI initiation, in the 6 months following; and comedications defined by drugs dispensed within the 30 days preceding or following the index date.

Statistical analyses

The frequency of PPI use was computed by dividing the total number of PPI users in 2015 by the estimated total French adult population on January 1, 2015 [24]. The proportion of new PPI users was calculated by dividing the number of new

PPI users by the total number of PPI users in 2015. Characteristics of new PPI users and of their PPI treatment were described, overall and separately by PPI treatment indication. All analyses were performed with SAS EG® (SAS Institute, Cary, NC, USA), 7.13.

Results

In total, 15,388,419 adults aged 18 years or older had at least one dispensing for PPI in 2015 (57.0% women; mean age 57.0 years). PPI users accounted for 29.8% of the estimated French adult population (15,388,419/51,645,958): 25.1% among the 18–65 years (10,096,055/40,229,778) and 46.4% among those aged > 65 years (5,292,364/11,416,180).

Among all PPI users in 2015, 7,399,303 (48.1%) were new users. Omeprazole was the most commonly dispensed PPI at treatment initiation (44.7% of new users) (Table 1). PPI therapy was initiated by a private practitioner in 73.9% of cases, 87.1% of them being general practitioners and 1.7% hepato-gastroenterologists. A majority of new users (78.0%) had only one dispensing. Mean treatment duration was 40.9 days overall, and was higher among patients aged > 65 years than among those aged 18–65 years (65.0 days versus 34.3 days). Patients among whom PPI therapy was prolonged > 6 months accounted for 4.1% of new users overall. This proportion was higher among patients aged > 65 years than among those aged 18–65 years (10.2% versus 2.4%).

Each new PPI user was assigned a unique indication: *H. pylori* eradication was identified for 0.5% of patients; co-prescription with NSAID for 53.5%; co-prescription with antiplatelet/anticoagulant therapy for 5.2%; co-prescription with corticosteroid therapy for 5.3%; co-prescription with chemotherapy or radiotherapy in patients with cancer for 0.5%; and treatment of other documented digestive lesions for 2.5%. Indication could not be established for 32.4% of new users. Marked differences were observed between age categories, especially regarding co-prescription with NSAID (43.5% among new users aged > 65 years versus 56.2% among those aged 18–65 years) or with antiplatelet/anticoagulant therapy (15.3% among new users aged > 65 years versus 2.4% among those aged 18–65 years) (Table 1).

Characteristics of new PPI users and of their treatment are described separately by indication in Table 2.

In new PPI users treated for *H. pylori* eradication (59.1% women; mean age 50.7 years), PPI therapies were most often initiated by private practitioners (in 71.7% of cases; 64.2% of them being general practitioners and 30.3% hepato-gastroenterologists). Mean treatment duration was 24.7 days.

In new PPI users with a co-prescription of NSAID (54.7% women; mean age 49.8 years), PPI treatments were largely initiated by private general practitioners. Mean PPI treatment duration was 24.6 days. Only a small proportion of patients in this indication had received a procedure investigating the digestive tract (2.3%) or a prescription of another anti-acid drug (2.4%), or had been hospitalized with a diagnosis of gastrointestinal disease (1.1%). Although in most cases (90.7%), PPI and NSAID therapies were initiated on the same day, the large majority of patients (79.7%) had no measurable risk factor supporting a systematic prophylactic prescription of PPI with NSAID (i.e., age > 65 years and concomitant antiplatelet, anticoagulant, or corticosteroid therapy).

In new PPI users with a co-prescription of antiplatelet/anticoagulant therapy (53.8% men; mean age 69.4 years), mean PPI treatment duration was 133.3 days, with 28.3% of patients with continuation of PPI therapy > 6 months. A procedure investigating the digestive tract had been performed in 13.7% of patients, and 7.2% had been hospitalized with a diagnosis of gastrointestinal disease.

In new PPI users with a co-prescription of corticosteroid therapy (56.8% women; mean age 52.2 years), mean PPI treatment duration was 36.5 days. Only 4.8% of patients had received a procedure investigating the digestive tract, and 2.7% had been hospitalized with a diagnosis of gastrointestinal disease.

In new PPI users with a co-prescription of chemotherapy or radiotherapy in patients with cancer (58.8% women; mean age 63.9 years), mean PPI treatment duration was 72.1 days. A procedure investigating the digestive tract had been performed in 18.3% of patients (mainly upper GI endoscopy), and 10.3% had been hospitalized with a diagnosis of gastrointestinal disease (mainly gastritis or duodenitis).

New PPI users treated for other documented digestive lesions (52.9% women; mean age 53.8 years) had a diagnosis of gastritis or duodenitis in 60.3% of cases, GERD (20.3%), esophagitis (13.2%), or other (6.2%). Prescriptions were mostly initiated by private general practitioners or hepato-gastroenterologists. Mean treatment duration was 89.4 days. At the time of PPI initiation, a large majority (91.4%) received a procedure investigating the digestive tract (mainly upper GI endoscopy) and 20.2% had a prescription of another anti-acid drug.

In new PPI users in an indeterminate indication (61.2% women; mean age 48.9 years), PPI therapy was most often initiated by a private general practitioner. Mean treatment duration was 49.8 days. A procedure investigating the digestive tract had been performed in 7.3% of patients overall (mainly upper GI endoscopy), and 8.4% among patients aged > 65 years.

Discussion

We found that more than 15 million health insurees, i.e., almost 30% of the French adult population, were PPI users in France in 2015. Nearly half of them were new users. Among

Table 1 Characteristics of New PPI Users, overall and by age category

	Overall (N=7,399,303) *n (%)*	18-65 years (N=5,792,716) *n (%)*	> 65 years (N=1,606,587) *n (%)*
Sociodemographic characteristics			
Sex			
Men	3,220,199 (43.5%)	2,553,167 (44.1%)	667,032 (41.5%)
Women	4,179,104 (56.5%)	3,239,549 (55.9%)	939,555 (58.5%)
Age (years), mean (SD)	50.8 (17.6)	44.0 (12.8)	75.5 (7.5)
Characteristics of PPI treatment			
PPI at treatment initiation			
Omeprazole	3,306,758 (44.7%)	2,657,983 (45.9%)	648,775 (40.4%)
Pantoprazole	1,043,274 (14.1%)	764,058 (13.2%)	279,216 (17.4%)
Lansoprazole	620,727 (8.4%)	470,077 (8.1%)	150,650 (9.4%)
Rabeprazole	297,391 (4.0%)	222,632 (3.8%)	74,759 (4.7%)
Esomeprazole	2,131,153 (28.8%)	1,677,966 (29.0%)	453,187 (28.2%)
Primary prescriber			
Private practitioner*	5,466,855 (73.9%)	4,335,449 (74.8%)	1,131,406 (70.4%)
General medicine	4,759,479 (87.1%)	3,777,308 (87.1%)	982,171 (86.8%)
Hepato-gastroenterology	94,885 (1.7%)	72,712 (1.7%)	22,173 (2.0%)
Other	570,523 (10.4%)	448,083 (10.3%)	122,440 (10.8%)
Missing	41,968 (0.8%)	37,346 (0.9%)	4,622 (0.4%)
Hospital practitioner	1,033,158 (14.0%)	815,996 (14.1%)	217,162 (13.5%)
Missing	899,290 (12.2%)	641,271 (11.1%)	258,019 (16.1%)
Number of PPI dispensings			
Mean (SD)	1.7 (2.2)	1.5 (1.7)	2.5 (3.3)
1	5,769,936 (78.0%)	4,683,009 (80.8%)	1,086,927 (67.7%)
2	844,477 (11.4%)	645,506 (11.1%)	198,971 (12.4%)
3 or more	784,890 (10.6%)	464,201 (8.0%)	320,689 (20.0%)
Treatment duration			
Mean (SD), days	40.9 (65.9)	34.3 (51.5)	65.0 (98.4)
6 months or less	7,097,584 (95.9%)	5,655,055 (97.6%)	1,442,529 (89.8%)
More than 6 months	301,719 (4.1%)	137,661 (2.4%)	164,058 (10.2%)
Indication for PPI treatment			
H. pylori eradication	38,760 (0.5%)	31,239 (0.5%)	7,521 (0.5%)
Co-prescription with NSAID	3,956,386 (53.5%)	3,257,793 (56.2%)	698,593 (43.5%)
Co-prescription with antiplatelet or anticoagulant therapy	386,035 (5.2%)	139,611 (2.4%)	246,424 (15.3%)
Co-prescription with corticosteroid therapy	393,643 (5.3%)	300,513 (5.2%)	93,130 (5.8%)
Co-prescription with chemotherapy or radiotherapy in patients with cancer	37,799 (0.5%)	19,544 (0.3%)	18,255 (1.1%)
Treatment of other documented digestive lesions	187,879 (2.5%)	137,710 (2.4%)	50,169 (3.1%)
Indeterminate indication	2,398,801 (32.4%)	1,906,306 (32.9%)	492,495 (30.7%)

*Information on specialty is available only for private practitioners

new users, PPI were mainly used in co-prescription with NSAID (54%), but mostly in patients without measurable risk factors for NSAID-related complications which would support the use of a gastroprotective therapy. Based on available information, indication was undocumented for almost one-third of new PPI users.

The frequency of PPI use seems to be higher in France than in other countries, where it generally ranges between 7 and 18% [25–30]. Moreover, PPI prescriptions do not always seem to comply with the guidelines. In France, PPI misuse measured in specific subpopulations, regarding age or healthcare setting, has been reported to reach 40% to more than 80% depending on the definition used [11–22]. In our study, more than half of adult new users initiated a NSAID therapy together with a PPI, 80% of them being young patients without any measurable risk factor of GI complications.

Table 2 Characteristics of new PPI users, by treatment indication

	H. pylori eradication (*N* = 38,760)	Co-prescription with NSAID (*N* = 3,956,386)	Co-prescription with antiplatelet or anticoagulant therapy (*N* = 386,035)	Co-prescription with corticosteroid therapy (*N* = 393,643)	Co-prescription with chemotherapy or radiotherapy (*N* = 37,799)	Other documented digestive lesions (*N* = 187,879)	Indeterminate indication (*N* = 2,398,801)
Sociodemographic characteristics							
Sex							
Men	40.9%	45.3%	53.8%	43.2%	41.2%	47.1%	38.8%
Women	59.1%	54.7%	46.2%	56.8%	58.8%	52.9%	61.2%
Age (years), mean (SD)	50.7 (15.8)	49.8 (16.2)	69.4 (15.6)	52.2 (17.6)	63.9 (13.9)	53.8 (17.2)	48.9 (18.4)
Characteristics of PPI treatment							
PPI at treatment initiation							
Omeprazole	51.0%	50.8%	22.1%	46.8%	29.1%	24.3%	39.6%
Pantoprazole	10.7%	13.2%	26.6%	12.9%	15.4%	18.7%	13.4%
Lansoprazole	4.3%	8.0%	8.4%	8.2%	7.4%	8.1%	9.2%
Rabeprazole	6.1%	2.9%	4.2%	3.5%	3.6%	7.4%	5.7%
Esomeprazole	28.0%	25.1%	38.7%	28.6%	44.5%	41.4%	32.2%
Primary prescriber							
Private practitioner*	71.7%	74.8%	49.5%	73.7%	48.9%	66.2%	77.4%
General medicine	64.2%	87.2%	82.6%	83.1%	76.3%	66.2%	89.8%
Hepato-gastroenterology	30.3%	0.4%	1.0%	0.5%	4.0%	27.3%	2.0%
Other	5.2%	11.7%	16.3%	15.0%	19.4%	6.2%	7.4%
Missing	0.3%	0.7%	0.2%	1.5%	0.3%	0.3%	0.8%
Hospital practitioner	17.7%	13.1%	33.6%	13.2%	38.2%	21.4%	11.3%
Missing	10.6%	12.1%	17.0%	13.2%	12.9%	12.4%	11.3%
Number of PPI dispensings							
Mean (SD)	1.4 (1.3)	1.3 (1.1)	4.7 (4.8)	1.6 (1.9)	2.6 (3.1)	3.1 (3.5)	1.8 (2.3)
Treatment duration							
Mean (SD), days	24.7 (35.7)	24.6 (33.4)	133.3 (139.7)	36.5 (57.6)	72.1 (87.4)	89.4 (103.3)	49.8 (69.3)
More than 6 months	1.1%	0.9%	28.3%	3.1%	9.5%	13.7%	4.9%
GI investigations, treatments, and diagnoses							
GI procedures	69.9%	2.3%	13.7%	4.8%	18.3%	91.4%	7.3%
Other drugs for acid-related disorders	7.2%	2.4%	6.4%	5.3%	18.8%	20.2%	18.3%
Inpatient diagnosis of GI disease	51.4%	1.1%	7.2%	2.7%	10.3%	100.0%	0.0%

*Information on specialty is available only for private practitioners

GI, gastrointestinal

However, history of GI lesions managed in primary care setting is not always identifiable in the French National Health Data System. Thus, inappropriate use with NSAID therapy may have been overestimated. Nevertheless, misuse of gastroprotection for NSAID therapy was also observed in other countries, both regarding underuse in at-risk patients and overuse in non-at-risk patients, with figures respectively as high as 30% and 58% among NSAID users [8, 31].

For almost 2.4 million of adult new PPI users, no concomitant medication or hospital discharge diagnosis supporting the use of PPI could be identified. We can assume that at least a part of them was probably treated for uncomplicated GERD. This figure is consistent with the results of a survey estimating that nearly 3.5 million French adult subjects suffered from frequent GERD in 2003, of which less than half were prescribed a PPI [32]. Of note, although performing upper GI endoscopy is recommended before initiating GERD therapy in elderly subjects [4], only 8% of patients aged over 65 years with an indeterminate indication underwent such a procedure in our study.

Prolonged PPI therapy lasting more than 6 months was observed in 4% of new users overall, and 10% of those aged over 65 years old. However, these results probably underestimate the extent of prolonged exposure to PPIs, and higher figures were reported previously in other countries [26, 27, 30]. Divergences may be explained by the characteristics of the population studied, follow-up durations, and variations in the definitions of long-term use. In this study, the analyses were restricted to new PPI users, and did not take into account prevalent users, the latter potentially having a higher probability of being long-term users. Moreover, the definition of long-term use was constraining, as the grace period (added to the estimated end of a prescription to allow gaps between subsequent prescriptions) was relatively short (30 days).

Recent studies suggested that prolonged PPI exposure was potentially associated with serious adverse effects, including chronic kidney diseases, cardiovascular diseases, or gastrointestinal malignancies, and with a small excess of cause-specific mortality [33, 34]. PPI therapy should be avoided if not necessary, and deprescribing should be considered whenever possible through regular reevaluation. Inappropriate PPI use is a matter of great concern, especially in the elderly. This population is particularly concerned by the increase in PPI treatment duration, with a mean of 65 days per year versus 41 days overall. The combination with polypharmacy due to existing comorbidities may increase the risk of long-term PPI-related adverse outcomes [9].

This study has several strengths. First and foremost, it includes a nationwide, unselected population. Moreover, it is based on comprehensive and high-quality medical utilization claim databases. Thanks to the multiple information provided by the SNDS, a detailed description of PPI users and treatments could be obtained.

Nevertheless, results should be interpreted in light of the following limitations. First, outpatient diagnoses are not available in the SNDS. However, the large amount of individual data, regarding medications, inpatient diagnoses, medical, and laboratory procedures, allows inferring several comorbidities. This method is commonly applied in pharmacoepidemiological studies [35, 36]. Similarly, the indication for treatment is not recorded in the databases, and available information has been compiled to define the clinical context of PPI prescription, used as a proxy of the indication. Consequently, rates of potentially inappropriate prescribing were estimated rather than accurately measured. Second, posology and treatment duration were not directly available but were estimated based on dosage and number of tablets dispensed. Third, there is no guarantee on patient's adherence to the prescription, or even that the patient actually took the drug. Finally, the SNDS does not provide information neither on inpatient nor on over-the-counter PPI use. However, in 2015, in France, 92% of PPI packs have been dispensed in private, non-hospital pharmacies (source: ANSM) and almost 97% have been prescribed by a physician (source: Open Health – Xpr-S0®). This allows us to state that estimates of PPI use based on SNDS databases are quite accurate.

In conclusion, the results of this study suggest widespread PPI use in France, not always in line with the guidelines. In particular, inappropriate co-prescription with NSAID and treatment of GERD in the absence of documentation by an upper GI endoscopy in elderly patients were frequent. PPI overuse is a major concern due to potential serious adverse events, especially in older patients and in case of prolonged exposure. Efforts should be made to limit PPI treatments to appropriate indications and durations.

Authors' contribution Conceptualization and Methodology: ML and RDS; data extraction: ML and TLT; data analyses: ML; interpretation of the results: all authors; writing—original draft preparation: ML; writing—review and editing: all authors; supervision: RDS.

Compliance with ethical standards

Given that data are anonymous, no informed consent is required. This study was approved by the French Data Protection Supervisory Authority (Commission Nationale de l'Informatique et des Libertés). Restrictions apply to the availability of the individual-level data supporting the findings of this study. These data so are not publicly available.

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

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