# Descriptive Analysis of Transactional Database Date on the Use of Gastroprotective Drugs in Patients With Polypharmacy in a Colombian Population

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## Abstract

**Objective:** The objective of this study was to describe and analyze patterns of use of prescription ulcer drugs, factors associated with prescriptions by physicians, and costs for outpatients With polypharmacy at a Colombian healthcare promotion entity (EPS) over a six-month period. **Methodology:** This is a retrospective and descriptive cross-sectional study based on electronic records of drugs prescribed to 2,458,447 outpatient members. Patients who took five or more prescription drugs per month were included. Patient were excluded if their records in the transactional data were not complete enough for analysis. Associations between anti-ulcer drugs and factors justifying their prescription were evaluated by the odds ratio (OR) which was calculated from a logistic regression model. **Results:** Of the 2,458,447 affiliates of the EPS, on average 60,671 patients had polypharmacy each month: 40% used anti-ulcer drugs and 70% used gastro-damaging drugs. Of the gastroprotected patients, 47% were elderly and 12% had associated diagnoses of upper gastrointestinal risk. Gastroprotection was not justified in 35% of patients with polypharmacy. This represents 75 million Colombian pesos every month. There was no statistical association between prescription of anti-ulcer drugs and factors that justify their prescription (OR: 1.13; 95% CI: 1.00 to 1.27). **Conclusion:** Given the lack of association between prescription of anti-ulcer drugs and factors which justify such prescriptions, it is likely that prescriptions contribute to polypharmacy per se. We recommended optimizing gastroprotection by reserving it for patients with more than one gastrointestinal lesion and with upper gastrointestinal risks whether or not they have polypharmacy.

## Keywords

Polypharmacy, antiulcer, proton-pump inhibitor, NSAIDs, elderly.

## INTRODUCTION

More than 50% of all patients over 65 have two or more chronic diseases. (1) Chronicity and multimorbidity lead to polypharmacy which is defined as the use of 5 or more drugs simultaneously. (2) This increases the likelihood of visits to the doctor for adverse drug events (ADEs) by 88% and increases costs for patients and health systems. (3, 4) Gastrointestinal, psychotropic and cardiovascular medications are often associated with polypharmacy. (5) Drugs that are most frequently prescribed for chronic patients include antihypertensives (82.6%), anti-ulcer (73.8%), antithrombotics (70.3%) and nonsteroidal anti-inflammatory drugs (NSAIDs) (36.5%). (6 ) In Korea in 2002,

81.6% of internists included antiulcer medications in their prescriptions. (7, 8) Prescription of antiulcer medications is a predictor for polypharmacy. (9)

In 2014, it was clarified that only certain patients require gastroprotective medication. They include patients being treated with more than one gastrolesive drug, patients who have risk factors such as previous histories of upper gastrointestinal disease, diabetes mellitus and hypertension, patients who are 65 years of age or older, patients undergoing concomitant therapy with other gastro-damaging drugs, patients with severe comorbidities and/or patients undergoing long-term treatment at maximum doses of gastro-damaging drugs. (10, 11) Not all patients with gastro-damaging drugs or polypharmacy need gastric protection. (12) Therefore, the objective of this study was to describe and analyze patterns of prescriptions of ulcer drugs, factors associated with prescribing and outpatient costs of polypharmacy over a 6 month period throughout Colombia at the facilities of one Healthcare Promotion Entity (EPS).

## MATERIALS AND METHODS

This is a descriptive retrospective cross-sectional study about patterns of prescriptions of anti-ulcer drugs to the patients of an EPS with polypharmacy. The EPS' average monthly membership is 2,458,447, it has 420 health institutions (IPS) in 136 municipalities in Colombia. The study looked at electronic records of outpatient prescriptions at the EPS over the six month period from September 2014 to February 2015. We included patients who received five or more prescription drugs per month and excluded those whose transaction records were not complete enough for analysis. Electronic prescription records were obtained from MC21 Colombia Pharmacy Benefit Management. Relations of this data to age, medical diagnosis, medication prescribed by month, anti-ulcer drugs, gastrolesive drugs and costs were then analyzed.

Patients were grouped into the four age categories established by the National Health Statistics Group in the United States: pediatric patients (0-12 years), young adult patients (13-44 years), mature adult patient (45-64 years) and elderly patients (over 65 years). (13) They were also grouped into five categories based on medical diagnoses and study objectives: *gastrointestinal pathologies* (gastritis; duodenitis; esophagitis; gastric, duodenal, peptic and gastric-jejunal ulcers; gastroesophageal reflux disease (GERD); esophageal, gastric and duodenal varices, and cancers of the upper gastrointestinal tract); *serious pathologies* (sepsis, other cancers, hepatitis and other liver diseases, chronic renal failure and other renal dysfunctions; severe trauma and severe burns); *hypertension*; *diabetes mellitus* and *others*. The tenth edition of the International Classification of Diseases of the World Health Organization (WHO) used to definie the five categories.

Anti-ulcer and gastrolesive drugs were grouped by pharmacological groups according to the Anatomical, Therapeutic and Chemical Classification System (ATC) of the WHO. The anti-ulcer drugs were classified as antacids (A02A), H2 antagonists (A02BA), prostaglandins (A02BB), proton-pump inhibitors (PPI) (A02BC) and direct protectors of the gastric mucosa (A02BX). Gastrolesive drugs were grouped into nonsteroidal anti-inflammatory drugs (NSAIDs) (M01A), antiplatelet agents (B01AC), anticoagulants (B01AA, B01AB, B01AE, B01AF, B01AX), selective reuptake inhibitors (SSRIs) (N06AB ) and systemic corticosteroids (H02AB).

Univariate and multivariate descriptive analyses were performed. Pearson and Phi Correlation coefficients were calculated to measure the correlation between prescription anti-ulcer medications and factors that justify prescriptions. Odds ratios (OR) were calculated with a logistic regression model. The specificity and sensitivity of the model was verified by the ROC curve (AUC: 0.62, the model predicted actual behavior at 62%). The analysis was performed using R statistical software. (14) Manipulation of variables that were dates was carried out with the Lubridate package. (15) Transformation, extraction and aggregation processes were done with the sqldf package (16) and goodness of fit was found with the pROC  package. (17)

## RESULTS

Of the 2,458,447 members per month, 13% (321,184) received medications. Of these, 18% (60,671) were cases of polypharmacy: 11% (6,644) had 10 or more prescriptions drugs and 49 patients had had 20 to 30 drugs prescribed in the same month. 31% of the polypharmacy patients (18,808) were elderly, 35% (21,235) were mature adults, 24% (14, 561) were young adults and 10% (6,067) were pediatric patients. Most patients were between 50 and 70 years (Figure 1). Nationally, the polypharmacy index (PI - polypharmacy patients/patients receiving drugs x 100) increased from 16% in November 2014 to 22% in February 2015. In that month, 22 of 100 patients who received drugs had had five or more drugs prescribed to them, and three out of 100 patients had had 10 or more active ingredients prescribed to them in the same month.

Forty percent of the polypharmacy patients (23,738) received anti-ulcer medications. PPIs were the most frequently used (19,157), followed by antacids (Figure 2a). Of the total patients receiving gastroprotection medications, 17% (4,060) had had two or more types of antiulcer drugs prescribed simultaneously. The most frequent association, PPIs with antacids, occurred in 1644 patients (65%). PPIs,
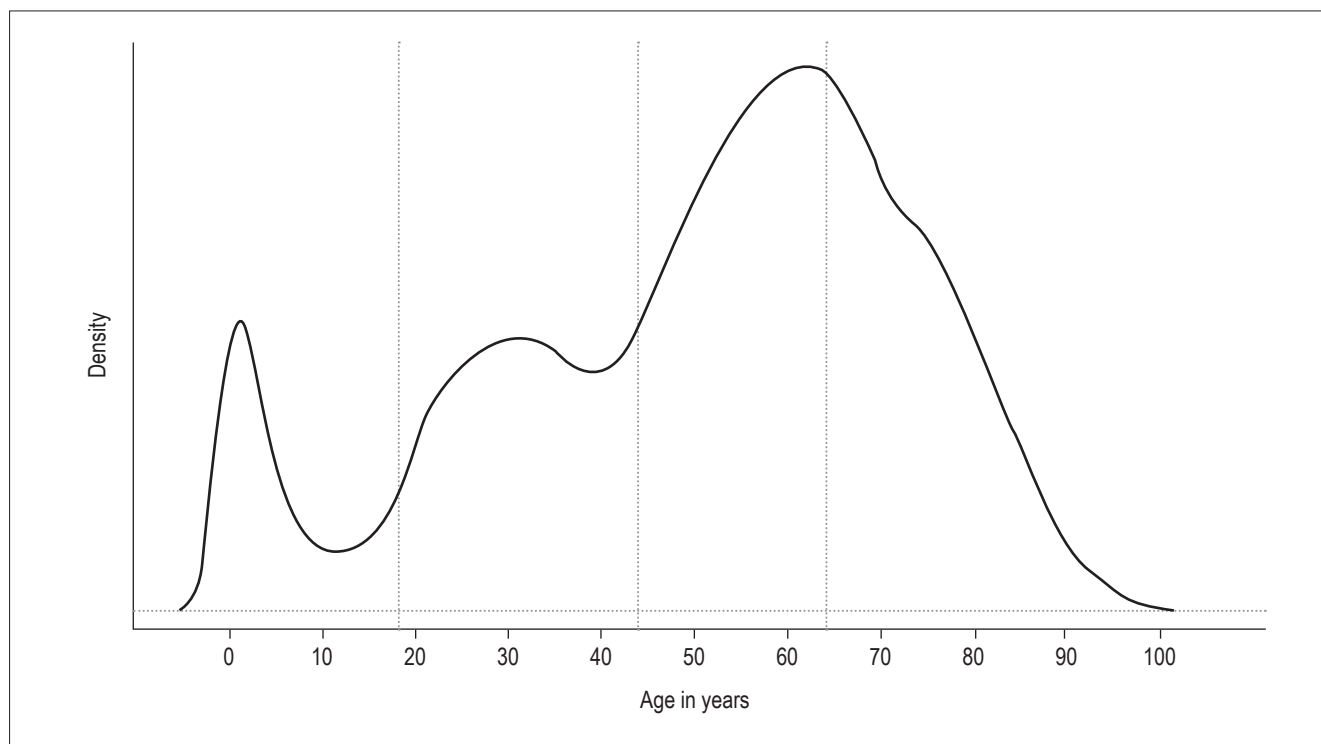
**Figure 1.** Population density of polypharmacy patients.

antacids and sucralfate were prescribed simultaneously to 156 patients (6%) and 17 patients had prescriptions for anti-ulcer drugs from four drug groups simultaneously (PPIs, antacids, mucosal protectants and H2 antagonists) (Table 1). 70% of polypharmacy patients (42,461) had at least one gastrolesive prescription drug, and 17% (10,140) had simultaneous prescriptions for two or more gastrolesive drugs within the same month. Antiplatelet drugs were taken by 52% (27, 078) and were the most frequently prescribed gastrolesive drugs. They were followed by glucocorticoids and NSAIDs (Figure 2b).

On average, every month 280 patients took four gastrolesive prescription drugs simultaneously, twenty-eight patients took five gastrolesive prescription drugs simultaneously, and one 77 year old patient had been simultaneously prescribed with seven gastrolesive drugs (3 glucocorticoids, 2 NSAIDs, and two SSRIs). Of the total number of polypharmacy patients receiving gastroprotective drugs, 47% (11,157) were elderly, 35% (8,308) were mature adults, 13% (3,086) were young adults and 5% (1,187) were pediatric patients. Only 12% (2,901) had had diagnoses of upper gastrointestinal risk and 24% (5,788) had no diagnosis that justified the use of anti-ulcer drugs (Figure 3). 48% of patients (11,182) taking gastroprotective medications did not take gastrolesive medications. Use of two or more gastrolesive agents was justified in only 13% (3,370)

of the case. Patients taking gastroprotective agents included 88% of the patients using anticoagulants (1,116), 35% of those taking antiplatelet medication (8,420), 17% of those taking glucocorticoids (1,645), 11% of those taking SSRIs (452) and 10% of those using NSAIDs (924).

According to the transactional patient information, and pre-established criteria for prescription of gastroprotection, (10, 11), gastric protection was not justified in 35% of these patients (8,364). This represents approximately 75 million Colombian pesos (COP) every month in unjustified anti-ulcer drugs. Proper and justified prescriptions for these patients with polypharmacy would lead to an estimated savings of 450 million Colombian pesos over six months. Calculations of the Pearson and Phi correlation coefficients showed no correlation between the prescription of anti-ulcer drugs and some of the factors that justify their prescription. Correlation coefficients were between zero and 30% for age ≥65 years, consumption of 2 or more gastrolesive drugs and/or diagnosis of gastrointestinal risk. The OR estimates confirmed this result (Table 2). No single factor alone increased the likelihood of prescription of ulcer drugs in patients with polypharmacy although the use of two or more gastro-damaging drugs in patients 65 years and older increased the likelihood of an anti-ulcer drug prescription by 1.2 times (OR: 1.19, 95% CI: 1.13 to 1.24) and the use of two or more gastro-damaging drugs
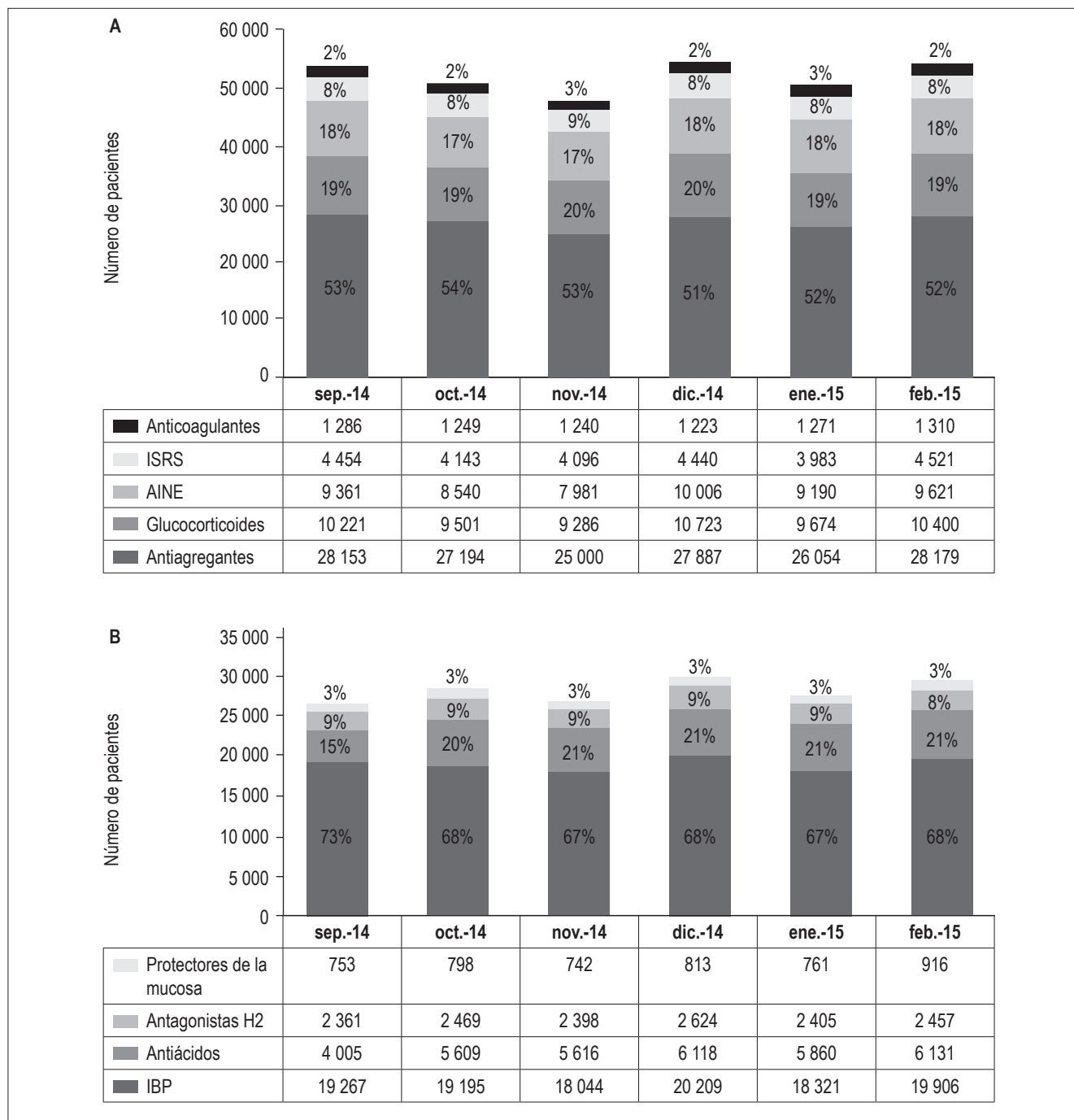
**A**

| | sep.-14 | oct.-14 | nov.-14 | dic.-14 | ene.-15 | feb.-15 |
|---|---|---|---|---|---|---|
| Anticoagulantes | 1 286 | 1 249 | 1 240 | 1 223 | 1 271 | 1 310 |
| ISRS | 4 454 | 4 143 | 4 096 | 4 440 | 3 983 | 4 521 |
| AINE | 9 361 | 8 540 | 7 981 | 10 006 | 9 190 | 9 621 |
| Glucocorticoides | 10 221 | 9 501 | 9 286 | 10 723 | 9 674 | 10 400 |
| Antiagregantes | 28 153 | 27 194 | 25 000 | 27 887 | 26 054 | 28 179 |

**B**

| | sep.-14 | oct.-14 | nov.-14 | dic.-14 | ene.-15 | feb.-15 |
|---|---|---|---|---|---|---|
| Protectores de la mucosa | 753 | 798 | 742 | 813 | 761 | 916 |
| Antagonistas H2 | 2 361 | 2 469 | 2 398 | 2 624 | 2 405 | 2 457 |
| Antiácidos | 4 005 | 5 609 | 5 616 | 6 118 | 5 860 | 6 131 |
| IBP | 19 267 | 19 195 | 18 044 | 20 209 | 18 321 | 19 906 |

**Figure 2.** Percentage of use by pharmacological group per month in patients with polypharmacy. a) antiulcer drugs; b) gastro-damaging drugs. NSAIDs: nonsteroidal anti-inflammatory drugs, H2: Type 2histamine receptor, PPI: proton-pump inhibitor, SSRIs: selective serotonin reuptake inhibitors.

in patients 65 years and older who had been diagnosed with upper gastrointestinal risks increased the likelihood of prescription of anti-ulcer drugs by 1.1 times (OR: 1.13, 95% CI: 1.01 to 1.27).

## DISCUSSION

B. Guthrie et al. have shown that in the United Kingdom between 1995 and 2010, patients taking 5 to 9 drugs increa-

**Table 1.** Simultaneous treatment with two or more anti-ulcer drugs per month and risk of use in patients with polypharmacy

| Patients with simultaneous use of drugs from two gastroprotective groups | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Drug combinations | Risk of use | Sep 2014 | Oct 2014 | Nov 2014 | Dec 2014 | Jan 2015 | Feb 2015 | Weighted average |
| PPIs and antacids | Decreases absorption of PPI | 1 891 | 2 619 | 2 643 | 2 926 | 2 820 | 2 966 | **2 682** |
| PPIs – mucosa protectors | Decreases absorption of PPI | 380 | 343 | 312 | 364 | 303 | 390 | **348** |
| PPI – H2 antagonists | - | 306 | 268 | 252 | 295 | 279 | 206 | **266** |
| H2 antagonists- antacids | Decreases absorption of Anti-H2 | 181 | 262 | 270 | 306 | 263 | 277 | **264** |
| H2 antagonists- mucosa protectors | Decreases absorption of Anti-H2 | 48 | 40 | 36 | 31 | 33 | 44 | **38** |
| Antacids - mucosa protectors | Decreases efficacy of antacid | 29 | 43 | 46 | 58 | 61 | 59 | **50** |
| **Total** | **2.835** | **3 575** | **3 559** | **3 980** | **3 759** | **3 942** | **3 649** | |

| Patients with simultaneous use of drugs from three and four gastroprotective groups | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Drug combinations | Risk of use | Sep 2014 | Oct 2014 | Nov 2014 | Dec 2014 | Jan 2015 | Feb 2015 | Weighted average |
| PPI - H2 antagonists- antacids | Decreases absorption of PPI and anti-H2 | 77 | 156 | 143 | 166 | 151 | 130 | **142** |
| PPI - antacids - mucosa protectors | Decreases absorption of PPI and efficacy of antacid | 73 | 135 | 143 | 140 | 128 | 156 | **134** |
| PPI - H2 antagonists- mucosa protectors | Decreases absorption of PPI and anti-H2 | 15 | 18 | 8 | 11 | 17 | 20 | **15** |
| H2 antagonists- antacids - mucosa protectors | Decreases absorption of anti-H2 and efficacy of antacid | 7 | 10 | 7 | 8 | 6 | 9 | **8** |
| H2 antagonists- antacids - PPI - mucosa protectors | Decreases absorption of PPI and anti-H2 and efficacy of antacid (general therapeutic failure) | 10 | 15 | 14 | 11 | 14 | 17 | **14** |
| **Total** | **182** | **334** | **315** | **336** | **316** | **332** | **313** | |

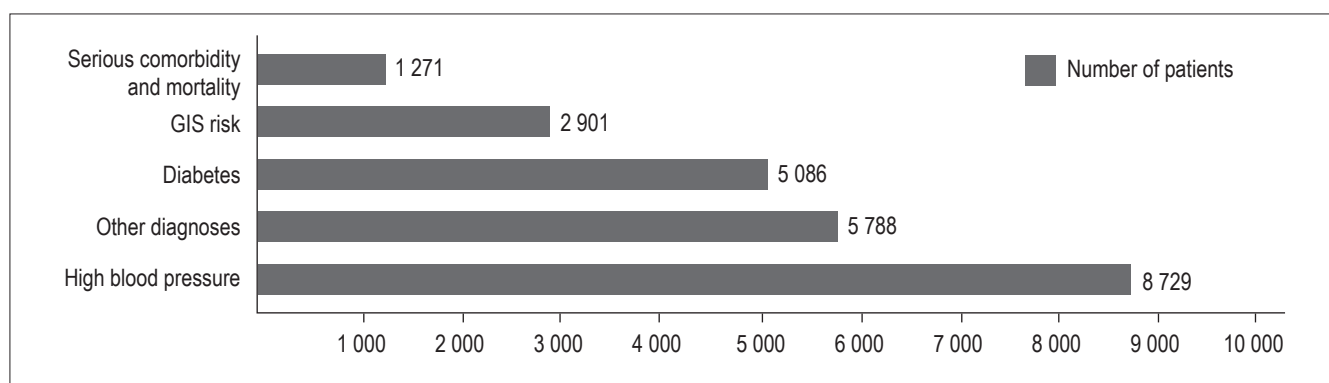H2: Type 2histamine receptor, PPI: proton-pump inhibitor



**Figure 3.** Diagnoses associated with prescription of anti-ulcer drugs in patients with polypharmacy. Severe comorbidity: septicemia, cancer, hepatitis, chronic renal failure, trauma and severe burns; Diabetes: diabetes mellitus types 1 and 2; HBP: high blood pressure; Other diagnoses: other diagnoses that do not justify the use of anti-ulcer agents; GIS risk: gastritis, duodenitis, esophagitis, gastric ulcers, duodenal ulcers, peptic ulcers, gastro-jejunal ulcers; gastroesophageal reflux disease, esophageal, gastric and duodenal varices, and cancers of the upper gastrointestinal tract.

**Table 2.** Association between prescription of anti-ulcer agents and factors that justify their prescription (age ≥65 years, consumption of two or more gastrolesive agents and diagnosis of upper gastrointestinal risk)

| Factors justifying gastroprotection | OR | 95% CI | LS |
|---|---|---|---|
| Age ≥ 65 years | 0.89 | 0.86-0.92 | +++ |
| Diagnosis of UGIT risk | 0.98 | 0.90-1.07 | +++ |
| Prescription of two or more gastroprotective agents | 0.88 | 0.85-0.91 | |
| Age ≥65 years and diagnosis of UGIT risk | 0.34 | 0.31-0.38 | +++ |
| Age ≥ 65 years and prescription of 2 or more gastrolesive drugs | 1.19 | 1.13-1.24 | +++ |
| Diagnosis of UGIT risk and prescription of 2 or more gastrolesive drugs | 0.98 | 0.88-1.10 | +++ |
| Age ≥ 65 years, diagnosis of UGIT risk and prescription of 2 or more gastrolesive drugs | 1.13 | 1.01-1.27 | + |
| **Levels of significance (LS)** | +++ = 0 ++ = 0,001 + = 0,01 | | |

**OR:** Odds Ratio, **CI**: Confidence Interval, **LS:** Level of significance, the lower the level of significance the greater the veracity of the confidence interval, **UGIT:** Upper gastrointestinal tract

sed from 9.7% to 16.3%, patients taking 10 to 14 drugs from 1.5% to 4.7 %, and patients taking 15 or more drugs increased from 0.2% to 1.1%. (18) These figures correlate well with the PI found in this study: 18.9% for five or more drugs, 2.1% for ten or more drugs, and 0. 2% for 15 or more drugs. As in this study, D. Qato et al. found that the ages of 30% of the patients with polypharmacy were 65 years or over. (19) One out of five drugs used by these patients may be inappropriate. (20) In addition, A Eiras et al. have shown that patients with polypharmacy are four times more likely to use inappropriate medications than are other patients. (21) this puts them at increased risk of adverse drug reactions. (22) The population of this study has a high probability of polypharmacy and of inappropriate drug use between the ages of 50 and 70 years.

B. Guthrie et al. also evaluated the association between the number of drugs taken and the probability of serious drug interactions. They found that 80.8% of patients taking 15 or more drugs had potential for serious drug interactions. (18) Other studies have found an association between polypharmacy and risk of hospitalization but have found that survival rates are no higher than those for patients who use fewer drugs. (2, 23 - 25) For this reason, the 49 patients in our study who were taking 20 drugs of more had high probabilities of serious drug interactions and hospitalization. The PI found by A. Eiras of 23.9% was very close to the 22.3% PI found in this study. (23) Antiulcer drugs were prescribed to 31.8% of those patients. (23) Despite similar PIs, our study showed higher levels of anti-ulcer drug use (40%). PPIs were the most frequently employed. This follows recommendations for use of omeprazole as first-line prophylaxis for drug induced ulcers to reduce the risk by 50%. (10, 11)

Highlighting just how debatable the treatment received by 300 patients of three or more prescriptions of anti-ulcer medications, there are no guidelines or studies that advocate or justify the prophylactic use of various anti-ulcer medications at the same time. This treatment does not involve an additional benefit to the patient, but does result in increased risk of serious drug interactions, adverse drug reaction, hospitalizations and other therapeutic failures from modification of the absorption of other drugs and increased gastric pH. (26) The interactions of PPIs or H2-blockers may persist even after use of the drugs is suspended because of the long half-lives of these drugs (6-8 hours for ranitidine and more than 72 hours for omeprazole). (26) In addition, simultaneous use of aluminum-containing antacids with sucralfate, which also contains aluminum, has the potential for increased toxicity. (27)

Gastroprotection reduces morbidity and mortality from long-term ASA and NSAID use. (28) L. Ibanez et al. have reported that 14.5% of cases of upper gastrointestinal tract bleeding occur in patients taking antiplatelet agents. Incidence of acetylsalicylic acid (ASA) usage at low doses is 50.6 cases/million/year. (29) The reported incidence of upper gastrointestinal tract bleeding due to usage of NSAIDs significantly greater: 152 cases/million/year. (30) In our study, 31% of the patients on antiplatelet therapy but only 10% of the patients using NSAIDs received gastroprotective agents. This shows possible under-utilization and is consistent with other studies that have observed underutilization of gastric protection in patients using NSAIDs. (11, 31) There were justifications for the use of anti-ulcer drugs for only 12% of patients using gastrolesive drugs according to the existing transactional information and established prescriptin criteria. (10, 11) This could support the conclu-

sion that those who need gastroprotection do not receive it while those who do not need it, do receive it.

Twenty-four percent of patients with polypharmacy who were gastroprotected had no diagnoses that justified the use of gastroprotective drugs in their transactional data, and only 12% had diagnoses of upper gastrointestinal pathologies in the database. This percentage is well below those reported in epidemiological studies which show a prevalence of acid-peptic disease of 41% and a prevalence of gastroesophageal reflux of 23%. (32, 33) This finding may be associated with the improper registration of diagnoses by the prescribing physicians. Clearly, the quality of the results of this study depends on the quality of the transactional records. Therefore, it may well be that the number of patients with diagnoses or histories of upper gastrointestinal pathologies that justify the use of gastroprotective agents may have been underestimated due to the absence of diagnoses in the database.

P. Santiestevea et al. found that 28.2% of patients who had been prescribed NSAIDs in Barcelona were not receiving adequate gastroprotection. (34) This is similar to the observation in our study of 35% inadequate gastroprotection. This result represents 75 million Colombian pesos monthly. No significant associations between prescription of gastroprotection and factors that justify their prescription were found, leaving open the possibility that anti-ulcer medications are explained by polypharmacy per se and not upper gastrointestinal risk factors. It is therefore recommended that patients using more than one gastrolesive agent who have gastrointestinal risk factors be given gastroprotection regardless of whether or not there is polypharmacy.

There are several tools that support the optimization of medication and reduction of prescriptions. These include the STOPP and Beers criteria (35) within the framework of pharmaceutical care and interventions. They have been shown to reduce the average number of drugs prescribed by 53% (RR: 0.47) with improved clinical results and of patient quality of life. (36)

The main limitation of this study is the quality of the source of information. There is the possibility that medical diagnoses and patient histories have been poorly recorded and do not show underlying diseases and chronic patients. This may have led to underestimation of the number of patients who require gastroprotection. In addition, the lack of information about adverse drug reactions and therapeutic failures as well as of clinical outcomes of patients whose gastric protection was not adequate, either by excess or defect, are other limitations of this study. Nevertheless, the findings here open the door to future research regarding the association between polypharmacy and gastric protection as well as research into the consequences of inadequate gas-

tric protection for patient quality of life, healthcare costs, and the financial impact on the health care system.

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