



Use of proton pump inhibitors – part I: Sociodemographic profiles of patients in an internal medicine outpatient clinic of a university hospital, Bahia – Brazil

Bruno Barbosa Góes ¹ and Romário Teixeira Braga Filho ^{2,*}

¹ Faculty of Medicine, Federal University of Bahia.

² Department of Internal Medicine and Diagnostic Support, Faculty of Medicine, Federal University of Bahia.

Open Access Research Journal of Life Sciences, 2022, 04(02), 063–071

Publication history: Received on 08 November 2022; revised on 26 December 2022; accepted on 28 December 2022

Article DOI: <https://doi.org/10.53022/oarjls.2022.4.2.0081>

Abstract

The great effectiveness of proton pump inhibitors [PPIs] in reducing gastric acid secretion is crucial for their wide therapeutic use, overlapping with other antacids such as H₂ receptor antagonists. The main situations in which the use of PPIs is a recommended therapeutic practice are: Gastroesophageal Reflux Disease, prevention and treatment of peptic ulcers associated or not with the use of non-steroidal anti-inflammatory drugs or *Helicobacter pylori* infection. The present analytical-descriptive, observational, cross-sectional study was carried out through the analysis of medical records of patients from the Ambulatory of Internal Medicine of the Ambulatório Professor Francisco Magalhães Neto (Outpatient Clinic) - part of the Complexo Hospitalar Universitário Professor Edgar Santos, Federal University of Bahia, in the year 2016; its main objectives were to outline the clinical profiles of patients using PPIs or not, in addition to the characteristics of the prescriptions, seeking to understand the therapeutic use related to the main morbidities. Regarding the socio-epidemiological profile of the patients studied, it was concluded that the population was characteristically elderly and composed of women; the assessment of the level of formal education was hampered because in most cases there was no specific record; about religion, most of the cases studied had no record, and the most declared was the Catholic Christian; about the functional status most patients declared themselves retired. The clinical profile of the patients, characteristics of the prescriptions, and the general conclusions will be addressed in Part II of this study – in the following article.

Keywords: Proton Pump Inhibitors; Prescription; Patients; Sociodemographic profiles

1. Introduction

Proton pump inhibitors - PPIs - constitute a class of drugs that reduce stomach acid secretion through the basic mechanism of inhibition of the H⁺-K⁺ ATPase enzyme on the gastric parietal cell surface. Among these drugs are listed: omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole, dexlansoprazole and tenatoprazole. These drugs have pharmacokinetic properties with particular aspects, but they have in common the ability to reduce the daily production of gastric acid by up to 95%, for a period of up to 24 hours. [1–3].

PPIs are potent reducers of stomach acid secretion, and so they are excellent therapeutic resources in cases of diseases of the upper digestive tract related to acid secretion, such as peptic diseases and gastroesophageal reflux disease - GERD [3,4]. Histamine receptor antagonists – H₂ – are also good antacid drugs, but PPIs are considered more potent and effective as they act in the final phase of acid secretion. [3,4]

In therapeutic practice, PPIs are used for situations such as: gastroesophageal reflux disease (GERD), peptic ulcers caused by chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), or in association with antibiotics for prevention or treatment of peptic ulcers secondary to infections caused by *Helicobacter pylori*. [2–8] GERD is the most common disorder of digestive tract, and is characterized by being a chronic disease related to the invasion of the

* Corresponding author: Romário Teixeira Braga Filho

esophagus by gastroduodenal contents, with or without tissue damage. The use of PPIs is recommended for treatment of symptomatic patients with endoscopically diagnosed esophagitis; many of the patients with GERD will develop adaptive mechanisms with formation of Barrett's epithelium [2,9–17]. The severity and duration of acid reflux, associated with the incompetence of the injured lower esophageal sphincter, would be in the course of inflammation of the gastroesophageal junction, and also related to the metaplastic process, and the development of Barrett's Esophagus; the latter condition is considered to be the only known precursor lesion of adenocarcinoma of the lower third of the esophagus; hence the importance of treating GERD, either with conservative behavioral measures, with medications such as PPIs, and in some situations with surgery [2,9,11–13,16–24]

Ulcers resulting from chronic use of NSAIDs (as occurs in the treatment of osteoarticular diseases, and in preventive approaches to cardiovascular events) are due to the inhibition of COX-1 which will reduce the potential of the gastric mucosa to produce mucus and bicarbonate; in this way, the interruption of the treatment will be enough for regeneration of the mucosa, but if continuation of treatment with NSAIDs is necessary, the administration of PPIs should be adopted to guarantee the healing of the ulcer and/or the reduction of morbid complications.[7,25–29]. Also in situations of treatment of patients with osteoporosis, when using medications that reduce bone resorption (alendronate, risedronate), it is often necessary to use PPIs together to control the side effects produced by those therapeutic agents[30–32]. *Helicobacter pylori* through its virulence factors - such as bacterial urease that encodes its resistance to hydrochloric acid, proteases and lipases that act on mucus and its own morphology - manages to colonize the epithelial layer of the gastric wall which, due to direct aggression and inflammation in response to the presence of the bacteria, it will be injured and ulcerated; in such a situation the therapy indicated is triple or sequential, with an association of antibiotics (alternatively and combined clarithromycin, amoxicillin, metronidazole, tinidazole, tetracycline or fluoroquinolones) and the use of PPIs [33–39]

In Brazil, in April 2004, through Law nº 10,858, the institution of Popular Pharmacies was implemented, where medicines are made available to patients under treatment and who present a medical prescription, with a 90% discount for the registered population; omeprazole is offered in popular pharmacies at a concentration of 20mg/caps. PPIs are the second most prescribed category of continuous use medications in the United States of America. PPIs are also one of the most prescribed drug classes worldwide, including in Brazil. The side effects associated with the use of PPIs – such as headache, constipation – are usually mild and few in cases of short-term therapeutic use. However, with the high frequency with which they are used in clinical practice for a prolonged period - as in cases of Zollinger-Ellison Syndrome, or GERD - especially if it evolves with erosive esophagitis and Barrett's Esophagus - there are questions from the scientific community about possible side effects that are not yet very well established, especially those related to hypergastrinemia, and development of premalignant lesions[40]. There is also concern in scientific circles about the modification of the human microbiome produced by the chronic use of PPIs, which could facilitate the occurrence of *Clostridium difficile* infections[41,42]. There appears to be a small increased risk of hypomagnesemia in patients on concomitant treatment with PPIs and diuretics[43,44].

The association between chronic use of PPIs and the emergence of anemia due to iron or vitamin B12 deficiency has been investigated [45,46]. A study conducted in Germany found an increased risk of developing dementia in patients using PPIs [47]. Considering the remarkable importance of this class of drugs in clinical practice, and the high frequency with which drugs of this category are used, it is important to carry out a study that seeks to characterize the profile of PPIs prescription in an outpatient service of Internal Medicine of a University Hospital. Such a study can expand the understanding of the morbidity characteristics of these patients, and the medical criteria used in the treatment with PPIs in the scenario of the City of Salvador and the State of Bahia, in view of the broad regional characteristic of the Complexo Hospitalar Universitário Professor Edgard Santos, Federal University of Bahia, Brazil.

2. Material and methods

This descriptive-analytical cross-sectional study was carried out during the period from March 9, 2016 to September 9, 2016, when the available information records about the patients studied were analyzed. The following inclusion criteria were adopted: 1. Patients aged ≥ 18 and ≤ 70 years; 2. Both sexes. Exclusion criteria were: 1. Cases of patients aged < 18 and > 70 years of age; 2. All those records in which the patients were treated/had their care supervised by the researcher and supervisor professor; 3. Cases in which the quality of data collection could be impaired due to spelling illegibility, erasures, or loss of important data such as the variables analyzed in this study. The collected data were recorded in the Statistical Package for Social Sciences software – SPSS – version 17 or later; data were analyzed in relation to measures of frequency, central tendency and dispersion. Regarding ethical aspects, the study was approved by the CEP (Research Ethics Committee) of the Complexo Hospital Universitário Prof. Edgard Santos, under number 1,415,514.

3. Results and discussion

3.1. About the Socio-Demographic Profile

The medical records were studied according to the methodology described, and 256 cases were selected according to established criteria; as a methodological adjustment, the option of including cases without an upper age limit was adopted, so that there was no significant loss in the sample number.

In the studied sample, a predominant frequency of elderly people was found; the mean age was 64.76 years, with a bimodal frequency of 63 and 64 years of age. This finding highlights the importance of characterizing the clinical profile, given the known great sensitivity of the older population to complications of a chronic-degenerative nature.

Table 1 Statistical analysis on the age* of patients at last clinical appointment

Number of patients	254
No registry	2
Mean	64.76
Mode	64/63
Standard deviation	10.963
Minimum	16
Maximum	106

*age in years

Table 2 Number of patients by age groups

Age group (in years)	Count	Percent
No registry	2	0.78
Age < 20	1	0.39
Age ≥20 and <30	1	0.39
Age ≥30 and <40	3	1.17
Age ≥40 and <50	14	5.47
Age ≥50 and <60	49	19.14
Age ≥60 and <70	111	43.36
Age ≥70 and <80	54	21.09
Age ≥80 and <90	19	7.42
Age ≥90 and <100	1	0.39
Age >100	1	0.39
Total	256	100

It was observed that the number of patients aged ≥ 50 and < 80 years of age, in cumulative frequency, make up 83.59% of the total sample; It is also noteworthy that 72.65% of the patients were in the age range greater than 60 years of age, characterizing a typically elderly population sample; this aspect is relevant when considering that it is a population that, from an epidemiological point of view, has a greater number of chronic morbidities, such as chronic degenerative diseases.

Discussion about skin color and race in epidemiological studies in Brazil is a difficult task, due to classification difficulties[48]. It was observed that in almost 1/3 [31.3%] of the analyzed cases there was no record of skin color; however, in line with the frequency described in the general reference population, 32.4% of the cases were categorized as black, and 26.6% as brown, making an accumulated frequency of about 59% among blacks and browns.

Data on the gender of the patients studied are summarized in the following table:

Table 3 Gender informed in medical records

Gender	Count	Percent
Male	55	21.5
Female	201	78.5
Total	256	100

The data are in accordance with the national experience in Brazil, which refers to the predominant presence of the female public in outpatient services; in the case under study, this prevalence was 78.5%. A study carried out in a state in the South Region revealed a situation in which female patients presented a higher frequency of self-report of morbidities, attributed to a behavior of seeking health services motivated by the perception/report of health problems, this behavior being more characteristic of the female gender[49]. In addition to drawing attention to the evident need for a service with a differentiated strategy for the care of the male public, the study also reflects on the need for planning care in a more comprehensive format for the specificities presented by female patients in the outpatient context (climacteric/menopause, overweight, thyroid diseases, osteoporosis, anxiety/depressive disorders, etc.); women are the predominant gender in the public that most seeks medical visits[50].

As for the level of education reported in the medical records, the data are illustrated in the table below:

Table 4 Level of education of patients according to medical records

	Count	Percent
No registry	218	85.2
Incomplete elementary level	12	4.7
Complete high school	12	4.7
Complete elementary level	8	3.1
Incomplete high school	4	1.5
Complete graduation	2	.8
Total	256	100

As for the level of education reported in the medical records, these are relevant data when it is known that many of the information passed on to patients - prescription, dietary and physical activity guidance, etc - are more effective when there is a knowledge structure capable of allowing effective communication. A study revealed that a higher level of education and participation in physical activities had an impact on the level of satisfaction in a population of elderly people in a city in the interior of São Paulo[51].

Regarding the declared religion, the information is illustrated in the table below:

Table 5 Religion of the studied patients as informed in the medical records

	Count	Percent	Accumulated percent
No registry	112	43.8	43.8
Catholic Christian	84	32.8	76.6
Protestant Christian	51	19.9	96.5
Spiritist	4	1.6	98.1
Undefined Christian	3	1.2	99.3
Candomblecist	1	.4	99.7
Agnóstic	1	.4	100
Total	256	100	

In this aspect, the lack of specific records on religion in about 43.8% of the cases stands out; the cumulative frequency between the unrecorded cases, and those declared as Catholic Christians and Protestant Christians, made up a total of 96.5% of the cases; in the State of Bahia, with a predominantly black and mestizo population, with cultural habits of predominant African origins, it is a point of reflection that there is only one case described as a Candomblecist religion. A study reveals the importance of deepening reflections and research on the knowledge of the existing interfaces between religion/spirituality and cardiovascular diseases, since the existence of a relationship between cardiovascular risk factors (mainly lifestyle habits) and personal beliefs is known[52].

As for origin, it was observed that about 78.5% of the cases studied came from the Capital itself – the city of Salvador; 10.9% came from other municipalities in the Metropolitan Region of Salvador; these two situations, added to the cases with no record of origin [8.6% of the cases], make up an accumulated percentage of 95.7% of the cases studied. In a much less expressive percentage [4.3%], some patients came from other cities in the interior of the state.

As for the functional (work) situation, the data are illustrated in the table below:

Table 6 Functional status of the patients studied

	Count	Percent	Accumulated percent
Retired	138	53.9	53,9
No registry	59	23.0	76,9
In activity	54	21.1	98.0
Pensioner	4	1.6	99.6
Social Security Benefit	1	.4	100
Total	256	100	

In line with the data relating to the predominance of the typically elderly age group, 53.9% of the patients were defined as retired; added to the cases without records [23%], these retirees make up an accumulated percentage of 77%; about 1/5 [21.1%] of the patients reported work activity at the time of the medical consultation.

Because there is no pre-formatted standardization of the records of the professions, and the excessive number of denominations for the activities reported, in addition to the fact that most patients are listed as retired, a descriptive analysis of frequencies of the various activities/professions is not presented.

4. Conclusion

The population studied showed socio-demographic conditions that characterized the public of patients treated as: predominantly female [78.5%], elderly age group (average 64.76 years), skin color mostly described as black or brown. Most of the patients came from Salvador or municipalities in the Metropolitan Region of Salvador;

There was a lack of records on the education and religion of the patients, conditions that are important for the knowledge of the assistant team, for a better understanding of the perceptions, understandings, and ethical-spiritual values of the patients, which may interfere with their participation in care. with one's own health.

Regarding the functional situation, most patients – more than half – were listed as retired – in line with the predominant age group. These sociodemographic data will be analyzed in accordance with the clinical profile data that will be addressed in the second part of this study, in the following article.

Compliance with ethical standards

Acknowledgments

The authors would like to thank the team of the Ambulatório Professor Francisco Magalhães Neto, who diligently assisted them in separating and making available the medical records to collect the necessary data.

Disclosure of conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of ethical approval

The study was approved by the Ethics Committee of Complexo Hospital Universitário Professor Edgard Santos, Federal University of Bahia, and was conducted in accordance with the principles of Ethics in Research and the Declaration of Helsinki.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Statement of informed consent

The study did not involve information about any individual e.g. case studies; survey; interview etc.; therefore, no use of informed consent was necessary. Regarding ethical aspects, the study was approved by the CEP – Comitê de Ética em Pesquisa (Research Ethics Committee) of the Complexo Hospital Universitário Professor Edgard Santos, under number 1,415,514

References

- [1] Seto CT, Jeraldo P, Orenstein R, Chia N, DiBaise JK. Erratum: Prolonged use of a proton pump inhibitor reduces microbial diversity: Implications for *Clostridium difficile* susceptibility [Microbiome, 4, [2016]: 10]. DOI 10.1186/s40168-016-0158-1. Microbiome. 2016;4:1–11.
- [2] Funk LM, Zhang JY, Drosdeck JM, Melvin WS, Walker JP, Perry KA. Long-term cost-effectiveness of medical, endoscopic and surgical management of gastroesophageal reflux disease. Surg [United States] [Internet]. 2015;157[1]:126–36. Available from: <http://dx.doi.org/10.1016/j.surg.2014.05.027>
- [3] Chen WC, Li Y Da, Chiang PH, Tsay FW, Chan HH, Tsai WL, et al. Comparison of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist in the Prevention of Recurrent Peptic Ulcers/Erosions in Long-Term Low-Dose Aspirin Users: A Retrospective Cohort Study. Biomed Res Int. 2014;2014.
- [4] Asaoka D, Nagahara A, Matsumoto K, Hojo M, Watanabe S. Current perspectives on reflux laryngitis. Clin J Gastroenterol. 2014 Dec 1;7:471–5.

- [5] Mandaliya R, DiMarino AJ, Cohen S. Survey of findings in patients having persistent heartburn on proton pump inhibitor therapy: Persistent heartburn. *Dis esophagus*. 2016;29[1]:27–33.
- [6] De Souza TF, Artifon ELDA, Mestieri LHM, Reimão SM, Aires FT, Bernardo WM, et al. Systematic review and meta-analysis of endoscopic ablative treatment of Barrett's esophagus. *Rev Gastroenterol Peru*. 2014;34[3]:217–24.
- [7] Lim H, Kim J, Baik G, Park J won, Kang H, Moon S, et al. Effect of low-dose PPI on preventing upper gastrointestinal bleeding in chronic kidney disease patients receiving aspirin. *J Gastroenterol Hepatol*. 2014 Sep 1;30.
- [8] Chuah S-K, Tai W-C, Lee C-H, Liang C-M, Hu T-H. Quinolone-Containing Therapies in the Eradication of *Helicobacter pylori*. *Biomed Res Int*. 2014 Aug 28;2014.
- [9] Butt AK, Hashemy I. Risk factors and prescription patterns of gastroesophageal reflux disease: HEAL study in Pakistan. *J Pak Med Assoc [Internet]*. 2014 Jul;64[7]:751–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25255580>
- [10] Jang WS, Shin HP, Lee J Il, Joo KR, Cha JM, Jeon JW, et al. Proton pump inhibitor administration delays rebleeding after endoscopic gastric variceal obturation. *World J Gastroenterol [Internet]*. 2014 Dec 7;20[45]:17127–31. Available from: <https://pubmed.ncbi.nlm.nih.gov/25493026>
- [11] Cho SY, Choung RS, Saito YA, Schleck CD, Zinsmeister AR, Locke GR, et al. Prevalence and risk factors for dysphagia: a USA community study. *Neurogastroenterol Motil [Internet]*. 2015 Feb;27[2]:212–9. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/nmo.12467>
- [12] Trad KS, Simoni G, Barnes WE, Shughoury AB, Raza M, Heise JA, et al. Efficacy of transoral fundoplication for treatment of chronic gastroesophageal reflux disease incompletely controlled with high-dose proton-pump inhibitors therapy: A randomized, multicenter, open label, crossover study. *BMC Gastroenterol*. 2014;14[1]:1–12.
- [13] Hold it! Are you taking your reflux meds correctly? PPIs for heartburn and GERD are effective--but only when used according to directions. *Johns Hopkins Med Lett Health After 50 [Internet]*. 2014 Oct 14;26[10]:3. Available from: https://www.unboundmedicine.com/medline/citation/25306565/Hold_it!_Are_you_taking_your_reflux_meds_correctly_PPIs_for_heartburn_and_GERD_are_effective--but_only_when_used_according_to_directions.
- [14] Drews G, Rudolph F, Martinenko O, Kühne P, Schreiber J. [The Influence of Laparoscopic Fundoplication on Reflux-Associated Cough]. *Zentralbl Chir [Internet]*. 2016 Oct;141[5]:545–51. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25377517>
- [15] Johnson DA, Le Moigne A, Hugo V, Nagy P. Rapid resolution of sleep disturbances related to frequent reflux: effect of esomeprazole 20 mg in two randomized, double-blind, controlled trials. *Curr Med Res Opin [Internet]*. 2015 Feb 1;31[2]:243–50. Available from: <https://doi.org/10.1185/03007995.2014.991818>
- [16] Powell J, O'Hara J, Wilson JA. Are persistent throat symptoms atypical features of gastric reflux and should they be treated with proton pump inhibitors? *BMJ Br Med J*. 2014;349.
- [17] Yasawy MI, Randhawa MA. GERD is becoming a challenge for the medical profession: is there any remedy? *Hepatogastroenterology [Internet]*. 2014 Sep;61[134]:1623–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25436353>
- [18] Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal reflux disease. *Gastroenterol Rep [Internet]*. 2015 Feb 1;3[1]:41–53. Available from: <https://doi.org/10.1093/gastro/gou061>
- [19] Akiyama J, Alexandre L, Baruah A, Buttar N, Chandra R, Clark AB, et al. Strategy for prevention of cancers of the esophagus. *Ann N Y Acad Sci [Internet]*. 2014 Sep;1325[1]:108–26. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/nyas.12529>
- [20] Furuta K, Kohata Y, Fujiwara Y, Sugimoto M, Uotani T, Yamade M, et al. Intra-gastric pH following single oral administrations of rabeprazole and esomeprazole: Double-blind cross-over comparison. *J Clin Biochem Nutr*. 2014 Nov 1;55:178–83.
- [21] Iurenev GL, Sirota NA, Dicheva DT, Bitkova EN, Maev I V. [Role of psychological correction in the combination treatment of patients with gastroesophageal reflux disease]. *Ter Arkh [Internet]*. 2014;86[8]:42–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25306743>
- [22] Dall'Olmo L, Fassan M, Dassie E, Scarpa M, Realdon S, Cavallin F, et al. Role of Proton Pump Inhibitor on Esophageal Carcinogenesis and Pancreatic Acinar Cell Metaplasia Development: An Experimental In Vivo Study.

- Mukaisho K, editor. PLoS One [Internet]. 2014 Nov 21;9[11]:e112862. Available from: <https://dx.plos.org/10.1371/journal.pone.0112862>
- [23] Nguyen TH, Thrift AP, Ramsey D, Green L, Shaib YH, Graham DY, et al. Risk Factors for Barrett's Esophagus Compared Between African Americans and Non-Hispanic Whites. *Am J Gastroenterol* [Internet]. 2014 Dec;109[12]:1870–80. Available from: <https://journals.lww.com/00000434-201412000-00009>
- [24] Simonka Z, Paszt A, Géczi T, Ábrahám S, Tóth I, Horváth Z, et al. Comparison of surgical patients with gastroesophageal reflux disease and Barrett's esophagus. *Magy Sebészet [Hungarian J Surgery]* [Internet]. 2014 Oct 1;67[5]:287–96. Available from: <https://akjournals.com/doi/10.1556/maseb.67.2014.5.1>
- [25] Choi H-G, Jeon J-Y, Kwak SS, Kim H, Jin C, Im Y-J, et al. Pharmacokinetic comparison study of a combination containing 500 mg of Naproxen and 20 mg of Esomeprazole: a randomized, single-dose, 2-way crossover, open-label study in healthy Korean men. *Clin Ther.* 2015;37 1:83–93.
- [26] Lanás Á, Carrera-Lasfuentes P, Arguedas Y, García S, Bujanda L, Calvet X, et al. Risk of Upper and Lower Gastrointestinal Bleeding in Patients Taking Nonsteroidal Anti-inflammatory Drugs, Antiplatelet Agents, or Anticoagulants. *Clin Gastroenterol Hepatol* [Internet]. 2015;13[5]:906–912.e2. Available from: <https://www.sciencedirect.com/science/article/pii/S1542356514016206>
- [27] Henriksson K, From J, Strateli G. Patient-reported adherence to coprescribed proton pump inhibitor gastroprotection in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis patients using nonsteroidal anti-inflammatory drugs. *Patient Prefer Adherence* [Internet]. 2014 Nov;1611. Available from: <http://www.dovepress.com/patient-reported-adherence-to-coprescribed-proton-pump-inhibitor-gastr-peer-reviewed-article-PPA>
- [28] Marlicz W, Łoniewski I, Grimes DS, Quigley EM. Nonsteroidal Anti-inflammatory Drugs, Proton Pump Inhibitors, and Gastrointestinal Injury: Contrasting Interactions in the Stomach and Small Intestine. *Mayo Clin Proc* [Internet]. 2014 Dec;89[12]:1699–709. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0025619614007125>
- [29] Tandon VR, Chandail V, Khajuria V, Gillani Z. Gastrointestinal bleed induced by a fixed dose combination of rabeprazole and diclofenac sodium. *Indian J Pharmacol* [Internet]. 2014;46[5]:555–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/25298591>
- [30] Tanaka M, Itoh S, Yoshioka T, Yamashita K. The Therapeutic Effectiveness of the Coadministration of Weekly Risedronate and Proton Pump Inhibitor in Osteoporosis Treatment. *J Osteoporos.* 2014;2014.
- [31] Cegieła U, Pytlik M, Folwarczna J, Miozga R, Piskorz S, Nowak D. Exercise prevented the lansoprazole-induced reduction of anti-osteoporotic efficacy of alendronate in androgen deficiency rats. *Acta Pol Pharm* [Internet]. 2014;71[3]:485–95. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25265829>
- [32] Jo Y, Park E, Ahn SB, Jo YK, Son B, Kim SH, et al. A Proton Pump Inhibitor's Effect on Bone Metabolism Mediated by Osteoclast Action in Old Age: A Prospective Randomized Study. *Gut Liver* [Internet]. 2015 Sep 23;9[5]. Available from: <http://www.gutnliver.org/journal/view.html?doi=10.5009/gnl14135>
- [33] Gisbert JP, Romano M, Molina-Infante J, Lucendo AJ, Medina E, Modolell I, et al. Two-week, high-dose proton pump inhibitor, moxifloxacin triple Helicobacter pylori therapy after failure of standard triple or non-bismuth quadruple treatments. *Dig Liver Dis* [Internet]. 2015 Feb;47[2]:108–13. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1590865814007543>
- [34] Ince AT, Tozlu M, Baysal B, Şentürk H, Arıcı S, Özden A. Yields of dual therapy containing high-dose proton pump inhibitor in eradication of H. pylori positive dyspeptic patients. *Hepatogastroenterology* [Internet]. 2014;61[133]:1454–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25436324>
- [35] Gisbert JP. [Diseases linked to Helicobacter pylori infection]. *Gastroenterol Hepatol* [Internet]. 2014 Sep;37 Suppl 3:40–52. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0210570514700822>
- [36] Peng Y-C, Huang L-R, Shyu C-L, Cheng C-C, Ho S-P. Interaction of omeprazole and Helicobacter pylori-induced nuclear factor-κB activation and mediators in gastric epithelial cells. *J Chinese Med Assoc* [Internet]. 2014;77[11]:567–72. Available from: <https://www.sciencedirect.com/science/article/pii/S1726490114001816>
- [37] Nagata N, Niikura R, Sekine K, Sakurai T, Shimbo T, Kishida Y, et al. Risk of peptic ulcer bleeding associated with Helicobacter pylori infection, nonsteroidal anti-inflammatory drugs, low-dose aspirin, and antihypertensive

- drugs: A case-control study. *J Gastroenterol Hepatol* [Internet]. 2015 Feb;30[2]:292–8. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/jgh.12805>
- [38] Freedberg DE, Lebowitz B, Abrams JA. The Impact of Proton Pump Inhibitors on the Human Gastrointestinal Microbiome. *Clin Lab Med* [Internet]. 2014 Dec;34[4]:771–85. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0272271214000833>
- [39] Pellicano R, Ribaldone DG, Saracco GM, Leone N, De Angelis C, Arrigoni A, et al. Benefit of supplements in functional dyspepsia after treatment of *Helicobacter pylori*. *Minerva Gastroenterol Dietol* [Internet]. 2014 Dec;60[4]:263–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25384804>
- [40] Song H, Zhu J, Lu D. Long-term proton pump inhibitor [PPI] use and the development of gastric pre-malignant lesions. *Cochrane Database Syst Rev*. 2014 Dec 3;12.
- [41] Seto CT, Jeraldo P, Orenstein R, Chia N, DiBaise JK. Prolonged use of a proton pump inhibitor reduces microbial diversity: implications for *Clostridium difficile* susceptibility. *Microbiome* [Internet]. 2014 Nov 25 [cited 2022 Jul 29];2[1]. Available from: <https://go-gale.ez10.periodicos.capes.gov.br/ps/i.do?p=AONE&sw=w&issn=20492618&v=2.1&it=r&id=GALE%7CA541259420&sid=googleScholar&linkaccess=fulltext>
- [42] Freedberg D, Lebowitz B, Abrams J. The Impact of Proton Pump Inhibitors on the Human Gastrointestinal Microbiome. *Clin Lab Med*. 2014 Dec 1;34.
- [43] Biyik M, Solak Y, Ucar R, Cifci S, Tekis D, Polat İ, et al. Hypomagnesemia Among Outpatient Long-Term Proton Pump Inhibitor Users. *Am J Ther* [Internet]. 2017 Jan;24[1]:e52–5. Available from: <https://journals.lww.com/00045391-201701000-00008>
- [44] Zipursky J, Macdonald EM, Hollands S, Gomes T, Mamdani MM, Paterson JM, et al. Proton Pump Inhibitors and Hospitalization with Hypomagnesemia: A Population-Based Case-Control Study. Strom BL, editor. *PLoS Med* [Internet]. 2014 Sep 30;11[9]:e1001736. Available from: <https://dx.plos.org/10.1371/journal.pmed.1001736>
- [45] Shikata T, Sasaki N, Ueda M, Kimura T, Itohara K, Sugahara M, et al. Use of Proton Pump Inhibitors Is Associated With Anemia in Cardiovascular Outpatients. *Circ J* [Internet]. 2014;79[1]:193–200. Available from: https://www.jstage.jst.go.jp/article/circj/79/1/79_CJ-14-0582/_article
- [46] Hashimoto R, Matsuda T, Chonan A. Iron-deficiency Anemia Caused by a Proton Pump Inhibitor. *Intern Med* [Internet]. 2014;53[20]:2297–9. Available from: https://www.jstage.jst.go.jp/article/internalmedicine/53/20/53_53.2743/_article
- [47] Haenisch B, von Holt K, Wiese B, Prokein J, Lange C, Ernst A, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. *Eur Arch Psychiatry Clin Neurosci* [Internet]. 2015 Aug 24;265[5]:419–28. Available from: <http://link.springer.com/10.1007/s00406-014-0554-0>
- [48] Travassos C, Laguardia J, Marques PM, Mota JC, Szwarcwald CL. Comparison between two race/skin color classifications in relation to health-related outcomes in Brazil. *Int J Equity Health* [Internet]. 2011;10[1]:35. Available from: <http://equityhealth.biomedcentral.com/articles/10.1186/1475-9276-10-35>
- [49] Mendoza-Sassi RA, Béria JU. Gender differences in self-reported morbidity: evidence from a population-based study in southern Brazil. *Cad Saude Publica* [Internet]. 2007 Feb;23[2]:341–6. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-311X2007000200010&lng=en&tlng=en
- [50] Boing AF, Matos IB, Arruda MP de, Oliveira MC de, Njaine K. [Prevalence of medical visits and associated factors: a population-based study in Southern Brazil]. *Rev Assoc Med Bras* [Internet]. 56[1]:41–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20339785>
- [51] Inouye K, Pedrazzani E. Educational status, social economic status and evaluation of some dimensions of octogenarians' quality of life. *Rev Lat Am Enfermagem*. 2006 Nov 30;15 Spec No:742–7.
- [52] Lucchese FA, Koenig HG. Religion, spirituality and cardiovascular disease: research, clinical implications, and opportunities in Brazil. *Rev Bras Cir Cardiovasc*. 2013;28 1:103–28.