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Use of proton pump inhibitors – part II: Clinical profiles of patients and characteristics of the prescriptions of proton pump inhibitors in an internal medicine outpatient clinic of a university hospital, Bahia – Brazil

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Abstract

Worldwide, proton pump inhibitors are one of the most prescribed long-term drug categories. PPIs are considered important therapeutic options in several clinical situations, with emphasis in peptic diseases – associated or not with Helicobacter Pylori infection – and Gastroesophageal Reflux Disease; the latter is a frequent clinical condition, and can result in adaptive mechanisms such as Barrett's Epithelium, considered a premalignant lesion for adenocarcinoma of the lower third of the esophagus. Due to the frequency of chronic use of PPIs, and the possibility of side effects not yet fully established, the present study was carried out in an Internal Medicine Outpatient Clinic of a University Hospital of the Federal University of Bahia. The sociodemographic profile evidenced in the first part of the study – previous article – showed a prevalence of elderly and predominantly female population; the conclusions of this article – second part of the study – revealed the most frequently diagnosed clinical conditions were those that are risk factors for illness and death from cardiovascular causes such as systemic arterial hypertension, diabetes mellitus, dyslipidemia; obesity; osteoporosis and osteoarthritis also appear in a relevant way. Regarding clinical conditions related to the digestive system, gastroesophageal reflux disease, sliding hiatal hernia, esophagitis/gastritis, "epigastric discomfort" and "abdominal pain" are more frequently recorded in the group of patients using PPIs than in those not using the medication. It is proposed to carry out new studies that can assess and establish criteria for prescribing, monitoring and preventing side effects from the long-term use of prescribed drugs.

Keywords: Proton Pump Inhibitors; Patients; Clinical profiles; Characteristics of prescriptions

1. Introduction

For a better understanding by the reader, some information contained in the most essential parts of the theoretical foundation described in the previous article – the first part of this study – will be presented again in this 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].

In clinical practice, Gastroesophageal Reflux Disease – GERD – and peptic ulcers, associated or not with the presence of Helicobacter Pylori, are relatively frequent situations. GERD is the most common disorder of the digestive tract, characterized by being a chronic condition in which gastroduodenal contents invade the esophagus. Many patients with GERD will develop adaptive conditions with the formation of Barrett's epithelium - which is recognized as a precursor lesion of adenocarcinoma of the lower third of the esophagus. As they are considered efficient reducers of stomach acid secretion, PPIs are excellent therapeutic options in clinical situations involving diseases of the upper digestive tract,

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such as peptic diseases and gastroesophageal reflux disease – GERD [2–5]. In the United States, PPIs are the second most prescribed category of long-term medications. All over the world - including in Brazil - PPIs are one of the most prescribed drug classes. Side effects related to the use of PPIs - such as headache and constipation - are generally mild and few in short-term treatments.; however, taking into account the high frequency with which these medications are used in clinical practice for a prolonged period of time, the scientific community investigates the possibility of side effects not completely established, with relevance to hypergastrinemia or the development of premalignant lesions [6]. There is also a concern among scholars about a possible modification of the microbiome as a consequence of the chronic use of PPIs, which could facilitate the occurrence of Clostridium difficile infections [1,7]. There also appears to be a slight increased risk of hypomagnesemia in those patients on concomitant treatment with PPIs and diuretics [8,9]. Scholars have investigated whether or not there is an association between chronic PPIs use and anemia due to iron or vitamin B12 deficiency [10,11]. In Germany, researchers carried out a study that showed an increased risk of developing dementia in patients using PPIs[11]. Considering the high frequency with which PPIs are used in clinical practice[12,13], it is important to carry out a study that seeks to characterize the clinical profile and prescription characteristics of this important category of medications, in an outpatient care service of a University Hospital. This study aims to expand the understanding of the morbidity characteristics of these patients, the medical criteria used in the treatment with PPIs in a scenario of the City of Salvador in the State of Bahia, in view of the regional characteristics presented by the consultations performed at the Complexo Hospitalar Universitário Professor Edgard Santos, Federal University of Bahia, Brazil.

This descriptive-analytical and cross-sectional study was carried out from March 9 to September 9, 2016, when informations from patient records were analyzed. This study was carried out as a final paper for the first author's graduation in Medicine, with the second author being the Advisor and Supervisor Professor of this scientific activity. The inclusion criteria were as follows: 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.

The first part of this study - presented in the previous article - outlined as conclusions about the sociodemographic profile of the patients the information as follows: they were 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. Regarding the functional situation, most patients – more than half – were listed as retired – in line with the predominant age group. These sociodemographic findings will be considered in terms of the possible association with the clinical profile of the patients - central focus of this second part of the study -, as will be discussed in detail below.

2. Results and discussion

Table 1 Weight (Kg), Height (m) and BMI (kg/m^2) of the patients studied

	Weight (kg)	**Height (m)**	**BMI (kg/m^2)**
Count /Percent	175 / 68.36%	172 / 67.19%	167 / 65.23%
No registry	81 / 31.64%	84 / 32.81%	89 / 34.76%
Average	70.97	1.56	29.02
Mode *	68	1.65	22.67
Standard deviation	14.97134	0.08491	5.33169
Minimum	36.7	1.4	14.52
Maximum	128	1.83	44.82

* Multiple mode; the lowest value is referred

The weight (in kilograms – kg) presented by the patients, the height (in meters – m), and the body mass index - BMI – (kg/m2), according to the notes in the medical records are illustrated in the table

An average BMI of 29.02 was found, close to the obesity range, which gives a predominant characteristic of overweight to the population group studied.

Metabolic Syndrome is an important risk factor for illness and death from cardiovascular causes, especially cerebrovascular events and coronary heart disease, with an increase in mortality. Obesity and high blood pressure are - among others - important factors in the development of metabolic syndrome [14]. Abdominal circumference was a variable in the research whose descriptive analysis was not performed due to lack of records in the medical records (among the cases studied, only one case had a record of the patient's abdominal circumference).

Still regarding the clinical profile, see below the data relating to the blood pressure records of the patients studied.

Table 2 Recorded blood pressure* of the patients studied

	N	Minimum	Maximum	Average	Standard Deviation
Systolic Blood Pressure	234	96	220	135.02	18.616
Diastolic Blood Pressure	234	50	120	81.27	11.266

*in mmHg

Expanding the understanding of blood pressure data, in 65.2% of the patients studied the diagnosis of Hypertension was present as the first option among the listed diagnoses.

Table 3 Diagnostics listed as first option and with frequency ≥2 times

Diagnosis 01	Frequency	Percent	Valid percent	Accumulated percent
Hypertension	167	65.2	66.5	66.5
Diabetes Mellitus	21	8.2	8.4	74.9
Dyslipidemia	11	4.3	4.4	79.3
Chagas disease	5	2.0	2.0	81.3
hypothyroidism	3	1.2	1.2	82.5
osteoporosis	3	1.2	1.2	83.7
osteoarthritis	2	.8	.8	84.5
Cataract	2	.8	.8	85.3
Obesity	2	.8	.8	86.1
Rheumatic valvulopathy	2	.8	.8	86.9
Metabolic syndrome	2	.8	.8	87.6
Other less frequent diagnoses	31	12.4	12.4	100
Total	251	98.0	100	100
Missing	5	2.0		
Total	256	100.	100	100

In relation to the diagnoses listed, for the standardization of the analysis, the first 5 diagnoses related to each patient were selected, due to the great diversity of the cited diagnoses; in order to facilitate understanding and analysis, only those diagnoses that appeared with frequency ≥2 times were selected (when analyzing diagnosis 01), with frequency ≥3 times (when analyzing diagnosis 02) and with frequency ≥4 times (when analyzing diagnoses 03, 04 and 05).

The above tables illustrate the information.

In relation to the above data, the participation of the first three clinical conditions, reflected in the diagnoses, stands out: Arterial Hypertension, Diabetes Mellitus and Dyslipidemia, which are factors usually present in the Metabolic Syndrome condition, an important risk factor for illness and death from cardiovascular causes [14–20].

Table 4 Diagnosis listed as second choice and with frequency ≥3 times

Diagnosis 02	Frequency	Percent	Valid percent	Accumulated percent
Diabetes Mellitus	69	27.0	27.7	27.7
Dyslipidemia	47	18.4	18.9	46.6
Hypertension	30	11.7	12.0	58.6
Obesity	8	3.1	3.2	61.8
Metabolic syndrome	7	2.7	2.8	64.7
Hypothyroidism	5	2.0	2.0	66.7
Osteoporosis	4	1.6	1.6	68.3
Asthma	4	1.6	1.6	69.9
Chagas disease	3	1.2	1.2	71.1
Overweight	3	1.2	1.2	72.3
Osteopenia	3	1.2	1.2	73.5
Altered fasting blood glucose	3	1.2	1.2	74.7
Herniated disc	3	1.2	1.2	75.9
GERD	3	1.2	1.2	77.1
Other less frequent diagnoses	57	22.9	22.9	100
Total	249	97.3	100	100
Missing	7	2.7		
Total	256	100		

Once again, the prominence of the diagnoses Diabetes Mellitus, dyslipidemia and Systemic Arterial Hypertension is highlighted, all present in the first three positions as clinical conditions of diagnosis 01; as mentioned above, these three clinical conditions are important risk factors for illness and death from cardiovascular causes, as defined in the case of Metabolic Syndrome [14–20]

Once again, the presence of dyslipidemia, obesity, diabetes mellitus and systemic arterial hypertension is observed as the four most frequent conditions, corroborating the prevalence of risk factors for illness and death from cardiovascular causes, as defined for the clinical condition Metabolic Syndrome; this is especially important considering the population studied, predominantly made up of elderly women[14–20]

Table 5 Diagnosis listed as a third choice and with frequency ≥4 times

Diagnosis 03	Frequency	Percent	Valid percent	Accumulated percent
Dyslipidemia	61	23.8	25.8	25.8
Obesity	16	6.3	6.8	32.6
Diabetes Mellitus	13	5.1	5.5	38.1
Hypertension	9	3.5	3.8	41.9
Osteoporosis	9	3.5	3.8	45.8
Overweight	6	2.3	2.5	48.3
Allergic rhinitis	6	2.3	2.5	50.8
Osteoarthritis	5	2.0	2.1	53.0
Glaucoma	5	2.0	2.1	55.1
GERD	5	2.0	2.1	57.2
Gastritis	4	1.6	1.7	58.9
Asthma	4	1.6	1.7	60.6
Osteopenia	4	1.6	1.7	62.3
Other less frequent diagnoses	89	37,7	37,7	100
Total	236	92.2	100	100
Missing	20	7.8		
Total	256	100		

Table 6 Diagnosis listed as fourth option and with frequency ≥4 times

Diagnosis 04	Frequency	Percent	Valid percent	Accumulated percent
Dyslipidemia	16	6.3	7.8	7.8
Obesity	13	5.1	6.4	14.2
Overweight	10	3.9	4.9	19.1
Osteoarthritis	8	3.1	3.9	23.0
Osteopenia	7	2.7	3.4	26.5
Chronic kidney failure	6	2.3	2.9	29.4
Diabetes Mellitus	5	2.0	2.5	31.9
Cataract	5	2.0	2.5	34.3
Glaucoma	5	2.0	2.5	36.8
Psoriasis	5	2.0	2.5	39.2
Hypothyroidism	4	1.6	2.0	41.2
Mild constipation	4	1.6	2.0	43.1
Herniated disc	4	1.6	2.0	45.1
Labyrinthitis	4	1.6	2.0	47.1
Other less frequent diagnoses	104	51	51	100
Total	204	79.7	100	100
Missing	52	20.3		
Total	256	100		

Then, the pattern of occurrence of risk factors for illness and death from cardiovascular causes (dyslipidemia, obesity/overweight), components usually present in the clinical condition Metabolic Syndrome is repeated. [14–20]

Table 7 Diagnosis listed as fifth option and with frequency ≥4 times

Diagnosis 05	Frequency	Percent	Valid percenta	Accumulated percentage
Obesity	15	5.9	10.0	10.0
Dyslipidemia	9	3.5	6.0	16.0
Osteoarthritis	7	2.7	4.7	20.7
Osteoporosis	6	2.3	4.0	24.7
GERD	6	2.3	4.0	28.7
Glaucoma	5	2.0	3.3	32.0
Osteopenia	5	2.0	3.3	35.3
Thyroid nodule	4	1.6	2.7	38.0
Labyrinthitis	4	1.6	2.7	40.7
Other less frequent diagnoses	89	59,3	59,3	100
Total	150	58.6	100	100
Missing	106	41.4		
Total	256	100		

Confirming the previous pattern, the diagnostic conditions of obesity and dyslipidemia were found in the first two positions, important components of the Metabolic Syndrome, with their implicit risks for illness and death from cardiovascular causes. [14–20]; then, important clinical conditions for the older age group - osteoporosis/osteoarthrosis with their potential for functional limitation and reduced quality of life[21–23]; and in the fifth position, GERD appears, a frequent clinical condition, which has implications for quality of life, and association with the need for treatment with PPIs [24,25]. Also, the significant prevalence of diseases of bone metabolism (osteopenia/osteoporosis), which often require the prescription of specific drugs (alendronate, rizedronate), whose side effects may require the addition of PPIs to the prescription, (and the latter are also possibly related to deleterious effects on bone metabolism), are relevant issues in clinical practice [26–28]

3. Analysis of the Use of IBP

Central theme of this study, the frequency with which patients who receive care at the Internal Medicine outpatient clinic were prescribed PPIs is illustrated below.

Table 8 Frequency of use of PPIs among patients treated at the Internal Medicine Outpatient Clinic of the Complexo Hospital Universitário Professor Edgard Santos, Federal University of Bahia.

	Frequency	Percent	Accumulated percent
No	159	62.1	62.1
Yes	97	37.9	100
Total	256	100	

It was observed that approximately 40% of the patients studied had a prescription for the use of PPIs. Among these, the most prescribed drug was omeprazole (see table 19 below), which is understandable due to the free dispensation in the network of Popular Pharmacies of the Unified Health System (Sistema Único de Saúde – SUS).

Table 9 Types of PPIs used among patients receiving care at the Internal Medicine Outpatient Clinic of the HUPES Complex

	Frequency	Percent	Accumulated percent
No use	159	62.1	62.1
Omeprazole	85	33.2	95.7
Omeprazole / Pantoprazole	7	2.7	98.4
Pantoprazole	2	.8	99.2
Omeprazole/Lansoprazole	2	.8	99.6
Unidentified PPI	1	.4	100
Total	256	100	

About the frequency of use of PPIs according to gender, among patients seen at the Internal Medicine Outpatient Clinic of the Complexo Hospital Universitário Professor Edgard Santos, it can be concluded that the frequency of women among the patients studied (201) compared with the frequency of men (55), shows a prevalence ratio of 78.5%/21.5% = 3.65; the frequency of PPI use among women (77) compared to the frequency of PPIs among men, shows a prevalence ratio of 38.31%/36.36% = 1.05, which does not seem to represent a difference with significant statistical significance; that is, although the female gender is predominant in the population of patients seen, it does not seem that gender is an important variable in the definition of the use of PPIs.

Regarding the performance of Upper Digestive Endoscopy – UDE - prior to the introduction of PPIs, records were found in 43 patients among the 97 using the medication (some of these with several procedures performed on different occasions), which makes up a percentage of 44.32% of patients undergoing the diagnostic procedure.

- 08 UDE procedures reported sliding hiatal hernia, associated or not with gastritis and/or esophagitis; in 01 case, there was a description of distal esophageal ulcer;

- 62 UDE procedures reported esophagitis, and/or gastritis, and/or duodenitis, in 24 cases the erosive aspect was described; in 05 procedures the presence of duodenal ulcer was reported, in 02 occasions with signs of activity and/or bleeding; on 09 occasions the presence of H pylori was described; in 01 case, an extensive area of intestinal metaplasia in the gastric epithelium was reported.

Considering the six diagnostic formulations registered for the patients studied, and most likely associated with pathologies of the digestive tract that could justify the prescription of PPIs, the frequency of these diagnoses and their possible relation with the prescription of PPIs, are discussed below.

When listed as the first diagnoses, from the first to the fifth choice, the following clinical conditions were likely to be associated with the use of PPIs:

As a first diagnostic option: the diagnosis of epigastric discomfort occurred once, without the use of PPIs; the diagnosis gastritis occurred once, and the prescription of PPIs was observed. The conditions GERD, esophagitis, abdominal pain, sliding hiatal hernia, did not occur as the first diagnostic option.

As a second diagnostic option, the diagnosis of GERD was present 03 times, at the same time that the prescription of PPIs was observed; the diagnosis of gastritis was present once, with concomitant use of PPIs. The other clinical conditions – epigastric discomfort, esophagitis, abdominal pain, sliding hiatal hernia, did not occur as a second diagnostic option.

As a third diagnostic option, GERD occurred 5 times, and PPIs were used all these times; gastritis occurred 4 times, all times there was also the use of PPIs; sliding hiatal hernia occurred once, with concomitant use of PPIs; the other conditions – epigastric discomfort, esophagitis and abdominal pain – did not occur as third diagnostic options.

As the fourth diagnostic option, the GERD condition occurred on four occasions, and on all of them PPIs were used; gastritis was a diagnosis listed in one case, in which PPI was used; epigastric discomfort occurred in 02 situations, and the use of PPIs occurred in only one of them, in a proportion of 50%; esophagitis was a diagnosis listed in one situation, in which the use of PPIs was also verified; the conditions abdominal pain and sliding hiatal hernia were not listed as the fourth diagnostic hypothesis.

As the fifth diagnostic option, the GERD condition occurred in 6 situations, and in four of them there was concomitant use of PPIs - in a proportion of 66.66% - and in 2 of them there was no use of these medications; the clinical conditions gastritis, epigastric discomfort and abdominal pain occurred once each, and in all of them there was concomitant use of PPIs; the clinical conditions esophagitis and sliding hiatal hernia did not occur as a fifth diagnostic option.

From the above discussion, it can be considered that the pathologies related to the digestive tract and registered as diagnoses in the first five positions were more prevalent among patients with PPI prescriptions than among those without them, with a prevalence ratio of 7, 25 times; GERD occupied more than half of the occurrences (16/29), which is in agreement with the literature, which points out gastroesophageal reflux disease as a clinical challenge usually faced with measures to correct eating habits associated with the use of PPIs [25]

As for the time of use of PPIs, the arrangement in written records, associated with lack of records or imprecision of information, both hampered the analysis of the variable; however, there was a suggestion that an important portion of the patient population has a prolonged use of this medication; this is interpreted from the lack of information about the suspension of the medication, and its appearance in another observation in the medical record. However, from what was observed, it can be concluded that the average time of PPI use was 4.6 years; with a median of 3.5 years, a standard deviation of 4.26731, a variance of 20.244, an amplitude of 23.95, a minimum of 0.4 years, and a maximum of 23.99 years.

Although the statistical information is imprecise due to the variability of the records, the information that a considerable number of patients have a relatively prolonged period of PPI use raises concerns about the possibility of a higher incidence of side effects that are particularly worrisome given the age group - predominant in the population studied -, and the nature of the chronic-degenerative diseases present in this population.

From the above data, it can be concluded that in addition to the high prevalence of PPIs use in outpatients, there is a frequency of prolonged use that demands further studies, given the relevance of the issue, and the possibility of related adverse side effects.

4. Conclusion

There were difficulties in carrying out this study because the electronic medical record was not available at that time. As demonstrated in the previous article – the first part of this study – the sociodemographic conditions of the population studied revealed the predominant female gender (78.5%), elderly age group (average 64.76 years), skin color mostly described as black or brown. Regarding the functional situation, most patients (more than half) were listed as retired – in line with the predominant age group; the average BMI of 29.03kg/m2 – characterized as overweight with a tendency to obesity. As for the most frequently diagnosed clinical conditions, those that are risk factors for illness and death from cardiovascular causes were relevant – including as components of the Metabolic Syndrome: systemic arterial hypertension, diabetes mellitus, dyslipidemia, are the most expressive. Obesity, osteoporosis and osteoarthritis also appear in a relevant way, which are, in the medium and long term, conducive to discomfort and disability, with a reduction in quality of life. Regarding the clinical conditions diagnosed with reference to the digestive system, gastroesophageal reflux disease, sliding hiatal hernia, esophagitis/gastritis, “epigastric discomfort” and “abdominal pain” are more expressive; these clinical conditions were more frequently recorded in the group of patients using PPIs than in those not using the medication (7.25-fold prevalence ratio); this is in agreement with the magnitude of GERD in clinical practice, and as a determinant of PPI prescription. Associated with the prevalence of the use of PPIs under medical prescription, the duration of the medication use is noteworthy, which leads to the consideration of the need to adopt protocols for the use of PPIs in Internal Medicine Outpatient Service, which can evaluate the relationship between benefits and risks of adverse effects. It is proposed to carry out other studies – mainly using the greater precision of information provided by the electronic medical record tool – that routinely assess criteria for prescribing PPIs, and mechanisms for monitoring and preventing possible adverse effects from their chronic use.

Compliance with ethical standards

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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.

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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. 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

[2] 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.

[3] 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. Surgery. 2015 Jan 1;157[1]:126–36.

[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] Savarino V, Marabotto E, Zentilin P, Furnari M, Bodini G, De Maria C, et al. The appropriate use of proton-pump inhibitors. Minerva Med [Internet]. 2018 Oct;109[5]. Available from: https://www.minervamedica.it/index2.php?show=R10Y2018N05A0386

[6] 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 [Internet]. 2014 Dec 2;[12]:CD010623. Available from: https://doi.wiley.com/10.1002/14651858.CD010623.pub2

[7] Freedberg D, Lebwohl B, Abrams J. The Impact of Proton Pump Inhibitors on the Human Gastrointestinal Microbiome. Clin Lab Med. 2014 Dec 1;34.

[8] 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

[9] 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

[10] 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

[11] 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

[12] Spechler SJ. Proton Pump Inhibitors. Med Clin North Am [Internet]. 2019 Jan;103[1]:1–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0025712518300920

[13] Dharmarajan TS. The Use and Misuse of Proton Pump Inhibitors: An Opportunity for Deprescribing. J Am Med Dir Assoc [Internet]. 2021 Jan;22[1]:15–22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1525861020309890

[14] Denys K, Cankurtaran M, Janssens W, Petrovic M. Metabolic syndrome in the elderly: an overview of the evidence. Acta Clin Belg [Internet]. 64[1]:23–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19317238

[15] Bener A, Zirie M, Musallam M, Khader YS, Al-Hamaq AOAA. Prevalence of Metabolic Syndrome According to Adult Treatment Panel III and International Diabetes Federation Criteria: A Population-Based Study. Metab Syndr Relat Disord [Internet]. 2009 Jun;7[3]:221–30. Available from: http://www.liebertpub.com/doi/10.1089/met.2008.0077

[16] Franco G, Scala L, Alves C, França G, Cassanelli T, Jardim P. Metabolic Syndrome in Patients with High Blood Pressure in Cuiaba - Mato Grosso State: Prevalence and Associated Factors. Arq Bras Cardiol. 2009 Jul 1;92:437-442,456.

[17] Petri Nahas EA, Padoani NP, Nahas-Neto J, Orsatti FL, Tardivo AP, Dias R. Metabolic syndrome and its associated risk factors in Brazilian postmenopausal women. Climacteric [Internet]. 2009 Jan 19;12[5]:431–8. Available from: http://www.tandfonline.com/doi/full/10.1080/13697130902718168

[18] Lin C-C, Liu C-S, Li C-I, Lin W-Y, Lai M-M, Lin T, et al. The relation of metabolic syndrome according to five definitions to cardiovascular risk factors - a population-based study. BMC Public Health [Internet]. 2009 Dec 23;9[1]:484. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-9-484

[19] Rigo JC, Vieira JL, Dalacorte RR, Reichert CL. Prevalence of metabolic syndrome in an elderly community: comparison between three diagnostic methods. Arq Bras Cardiol [Internet]. 2009 Aug;93[2]:85–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19838483

[20] Zhang Y, Hong J, Gu W, Gui M, Chen Y, Zhang Y, et al. Impact of the metabolic syndrome and its individual components on risk and severity of coronary heart disease. Endocrine [Internet]. 2009 Oct 18;36[2]:233–8. Available from: http://link.springer.com/10.1007/s12020-009-9214-y

[21] Edwards MH, Dennison EM, Aihie Sayer A, Fielding R, Cooper C. Osteoporosis and sarcopenia in older age. Bone [Internet]. 2015 Nov;80:126–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25886902

[22] Masud T. 08 Evidence Base for Treatment of Osteoporosis in Older People. Age Ageing [Internet]. 2019 Dec 20;48[Supplement_4]:iv3–iv3. Available from: https://academic.oup.com/ageing/article/48/Supplement_4/iv3/5682092

[23] Weston JM, Norris E V., Clark EM. The Invisible Disease. Qual Health Res [Internet]. 2011 Dec 2;21[12]:1692–704. Available from: http://journals.sagepub.com/doi/10.1177/1049732311416825

[24] Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal reflux disease. Gastroenterol Rep [Internet]. 2015;3:41–53. Available from: https://academic.oup.com/gastro/article/3/1/41/2910183

[25] Yasawy M, Randhawa M. GERD is Becoming a Challenge for the Medical Profession: is there any Remedy? Hepatogastroenterology. 2014 Sep 1;61:1623–6.

[26] 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 [Internet]. 2014;2014:1–5. Available from: http://www.hindawi.com/journals/jos/2014/607145/

[27] 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

[28] Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: screening and treatment strategies. Ther Adv Musculoskelet Dis [Internet]. 2014 Oct 11;6[5]:185–202. Available from: http://journals.sagepub.com/doi/10.1177/1759720X14546350