

CHRONIC USE OF PROTON-PUMP INHIBITOR: A NARRATIVE REVIEW

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ABSTRACT

Proton-pump inhibitors (PPIs) are one of the most prescribed therapeutic classes in the world, among them, omeprazole is found in the Brazilian essential drug list. Some research papers show that the short-term use of PPIs can be safe, although its long-term use may cause adverse effects. The present review aimed to gather papers related to the effects of chronic use of PPIs in the literature. It is a narrative review in which the research for data was carried out in the Virtual Health Library in September 2018. The articles selected to compose the sample revealed that PPIs are used empirically for extended period beyond what is recommended and sometimes as self-medication. It is urgent the adoption of strategies by healthcare managers and prescribing professionals of all levels of attention to fight against inadequate prescription and chronic use. Therefore, as a result of that, promoting prevention of damages to the population and unnecessary expenses to the Brazilian public health system.

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INTRODUCTION

The Brazilian Unified Health System (SUS) provides to the population assistance in the primary, secondary and tertiary levels, with the proposal of equitable access. In this context, Primary Health Care (PHC) is still deficient, which overloads other levels of care and causes an increase in costs, of which a large part is with medicines (Castro, 2000). The therapeutic success that must be obtained in the medical treatment of

diseases depends on the fundamentals that guide the selection of the medicine in a scientific and rational way. There are many recommendations that must be taken into consideration when choosing the right medicine. Effectiveness, safety, medication costs, as well as proper prescription and the use of an individual in an appropriate way are some of them. For this reason, clinical decisions and the relationships established between healthcare providers and individuals are determiners for such therapeutic effectiveness (Brasil, 2012). Thus, the participation of several social actors, such as, patients, healthcare providers, legislators, public policy makers, industry, commerce and government is necessary to promote

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the rational use of medicines. Some of the major problems related to drug use are overuse, self-medication and incorrect use (Oenning, Oliveira and Blatt, 2011). Among the most prescribed drug classes in the world, proton-pump inhibitors (PPIs) are among the main ones and are used in the long term due to their high efficacy and relatively low toxicity aspects. Omeprazole is the most prescribed PPI worldwide and is within the Brazilian essential drug list as well as in the World Health Organization's list (Hipólito *et al.*, 2016). The growth of the pharmaceutical industry promotes the arrival of countless drugs to market, all with the promise of solving or relieving diseases. Until then, the use of PPIs is considered to be harmless to humans what justifies the absence of control of its commercialization over-the-counter without the need of a prescription (Lima and Neto Filho, 2014). The use of PPIs for a long period of time can be considered safe according to what some studies indicate but it is necessary medical monitoring (Caricol, 2015). However, other studies address questions about the safety of the continued use of PPIs in the management of gastric acid-associated peptic disease, showing that the recommendation for use should have precise indications and periods established by the prescribers (Hipólito, Rocha and Oliveira, 2016). PPIs are drugs used empirically either by prescription or by self-medication to treat the digestive manifestations of diseases, or to prevent the onset of such symptoms, which can lead to unnecessary costs. Likewise, the usual substitution of omeprazole by new drugs of the class of PPIs is observed, with no evidence of relevant advantages provided by their pharmacokinetic differences (Wannmacher, 2004).

In this way, the irrational use of drugs, besides causing economic losses for the government and/or the individual, it can also cause damages in the sanitary scope, through the adverse reactions. That is why the medical prescription is one of the decisive pillars that must be worked on in the permanent search for the rational use of medicines. For a prescription to be considered appropriate, it should contain as few drugs as possible and they should have the least capacity to provoke adverse reactions, no contraindications, rapid action, appropriate dosage form, simple dosage and for a short time period (Silva Portela *et al.*, 2010). Therefore, this study aimed to gather papers related to the effects of chronic use of PPIs in the literature with a purpose to base the rational prescription and to avoid the perpetuation of empiricism as indication and self-medication.

MATERIALS AND METHODS

In the literature it can be found two categories of review articles: narrative and systematic reviews (Rother, 2007). Narrative reviews are broad publications, adequate for the description and discussion of the development of a given subject, from a theoretical or contextual perspective. According to the same author (2007), they do not indicate the sources of information used, the methodology for searching for references or the criteria used in the evaluation and selection of studies. This type of review is used to describe the highest level of development of a particular subject. It makes possible to acquire and update knowledge about a particular topic in a short period of time (Botelho *et al.*, 2011). The data research was carried out in the Virtual Health Library (VHL) in September 2018. The descriptors used and the results found are placed in Table 1. The VHL offers free access to many database such as LILACS and MEDLINE. VHL is a source of

health information, based on revised medical evidence, dedicated to the synthesis of knowledge for the use of physicians and patients (Neves *et al.*, 2013).

RESULTS

A total of 1,490 articles were found, 362 of these with full text available and 34 in Portuguese. For this study were used articles with full text available in Portuguese language whose titles and abstracts contemplated the interest of the research. There were also used 04 articles in Spanish and 03 articles in English. The literature review was divided into three topics: characteristics and indications of PPIs, effects of chronic use of PPIs and the relation of PPIs with polypharmacy.

Table 1. Descriptors used and the results in the data research at Virtual Health Library

| Descriptors | Results | Complete article available | Portuguese |
|---|---------|----------------------------|------------|
| Proton-pump inhibitor and indications | 02 | 01 | 00 |
| Proton-pump inhibitor and chronic use | 05 | 03 | 01 |
| Proton-pump inhibitor and inadequate use | 00 | 00 | 00 |
| Proton-pump inhibitor and safety | 12 | 05 | 03 |
| Proton-pump inhibitor and polifarmácia | 05 | 04 | 00 |
| Proton-pump inhibitor and polimedicação | 05 | 04 | 00 |
| Proton-pump inhibitor and polypharmacotherapy | 153 | 105 | 01 |
| Omeprazole and indications | 06 | 04 | 04 |
| Omeprazole and Chronic use | 20 | 07 | 04 |
| Omeprazole and inadequate use | 03 | 01 | 01 |
| Omeprazole and safety | 128 | 34 | 09 |
| Omeprazole and polypharmacy | 12 | 09 | 05 |
| Omeprazole and polymedication | 11 | 08 | 04 |
| Omeprazole and polypharmacotherapy | 1.128 | 177 | 02 |
| Total | 1.490 | 362 | 34 |

Source: elaborated by the authors

Table 2. Main indications of PPIs

| Main Indications of PPIs |
|--|
| Peptic ulcer disease |
| Zollinger-Ellison Syndrome |
| Stress ulcer prophylaxis |
| Prevention of NSAID-induced gastroenteropathy |
| <i>Helicobacter pylori</i> eradication |
| High digestive bleeding |
| Gastroesophageal reflux disease (GERD) |
| Esophagitis, Barrett's esophagus |
| Unexplained dyspepsia and functional dyspepsia |
| Eosinophilic esophagitis |
| Pancreatic exocrine insufficiency |

Source: Adapted from Castro, Deprados and Martinez (2016).

Narrative Review

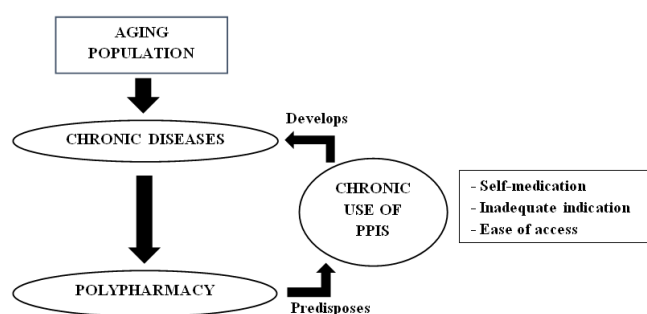
Characteristics and Indications of PPIs: The finding that the enzyme H⁺ / K⁺ Adenosine Triphosphatase (H⁺ / K⁺ - ATPase or próton-pump) constitutes the final stage of acid secretion has led to the development of a class of drugs, the proton pump inhibitors (PPIs). They are used in the treatment

of gastrointestinal disorders. It is also known that many different drugs, such as H2 receptor antagonists, also promote the inhibition of acid secretion in the stomach (Braga, Silva and Adams, 2011). However, the PPIs are considered to be more effective by blocking the final acid secretion step. The PPIs cause the suppression of gastric acid secretion by specific inhibition of the proton-pump on the secretory surface of the gastric parietal cell. It reduces in 95% of a daily gastric acid production. There is a defined evidence to the efficacy of these drugs in the treatment of manifestations and complications of peptic disease and gastrointestinal reflux disease (Wannmacher, 2004). Nowadays, there are seven drug of this class. Among them, only six are available over-the-counter in Brazil: omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole and tenatoprazole, while dexlansoprazol is not available yet (Braga, Silva and Adams, 2011). PPIs are indicated for the treatment of the following conditions: Peptic ulcer associated with *Helicobacter pylori*, dyspeptic symptoms related to the continuous use of non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid, non-ulcer dyspepsia, gastroesophageal reflux disease and reflux esophagitis. In addition to these indications, PPIs are also part of *Helicobacter pylori* eradication schemes. For treatment of most of these conditions, a brief time, usually weeks, is usually necessary (Hipolito, Rocha and Oliveira, 2016).

Table 3. Main effects of prolonged use of PPIs

| Main effects of prolonged use of PPIs |
|--|
| Proliferative changes in the gastric mucosa |
| Increased risk of fracture |
| Deficiency of iron and magnesium (hypomagnesaemia) |
| Decreased absorption of calcium and vitamin B12 |
| Increased intestinal infections |
| Increased risk of community-acquired pneumonia |
| Cognitive decline (dementia) |
| Acute interstitial nephritis |

Source: data research.



Source: designed by the authors

PPIs are particularly indicated in patients with hypergastrinemia, Zollinger-Ellison syndrome and duodenal peptic ulcers refractory to H2 antagonists. However, there is no established evidence of benefit of its use to prevent recurrence of ulcers and other gastrointestinal lesions induced by NSAIDs because the results of the studies are more divergent (Wannmacher, 2004). In *Helicobacter pylori* positive patients, the associated use of PPIs and antibiotics increases the chance of therapeutic success in peptic disease. This drug efficacy of peptic disease has provided a considerable reduction in the need for a surgical approach, which is reserved for ulcer complications or patients refractory to clinical treatment (Wannmacher, 2004). According to Wannmacher (2004) for gastro esophageal reflux disease, there is evidence of the effectiveness of PPIs in relieving heartburn

and regurgitation. Treatment for this condition is intended to attenuate symptoms, to heal lesions, and to prevent relapses and complications. PPIs only have a likely benefit in dyspepsia when manifests with heartburn and regurgitation. Regarding to the prophylaxis of stress ulcer, the use of limited PPIs for patients undergoing intensive therapy and the presence of risk factors for peptic ulcer: previous history of ulcer, acute renal failure, liver cirrhosis, coagulopathy, shock, severe sepsis, multiple organ failure, need for mechanical ventilation, head trauma, neurosurgery or burns (Castro, Deprados and Martínez, 2016). In addition, other indications considered acceptable for the prevention of stress ulcer are: severe respiratory acidosis and use of corticosteroids (Ribeiro *et al.*, 2014). For upper gastrointestinal bleeding (UGIB) caused by peptic ulcer with a high risk of rebleeding, after endoscopic treatment, continuous venous infusion of PPI was effective against placebo. For the prophylaxis of gastroenteropathy by NSAIDs, the use of PPIs is indicated in patients with a history of peptic ulcer, older than 60 years, severe co morbidities, high NSAID dose, concomitant use of another NSAID acetylsalicylic acid (ASA), concomitant use of anticoagulants, antiplatelet agents or glucocorticoids. The indication of PPIs for the prevention of gastroenteropathy by NSAIDs is probably the one that causes most confusion among prescribers (Castro, Deprados and Martínez, 2016). Despite the lack of important clinical results, the use of PPI is recommended for patients with unprotected and functional dyspepsia, for several reasons, among them: PPIs are drugs with few side effects besides benefiting patients poorly classified as functional dyspepsia who present with ulcer disease peptic. In eosinophilic esophagitis, PPIs are useful for differential diagnosis with GERD and eosinophilic esophagitis responsive to PPI. For exocrine pancreatic insufficiency, the association of PPI with the enzymatic treatment increases the pH, which consequently decreases lipase degradation (Castro, Deprados and Martínez, 2016). The table 2 summarizes the main indications of PPIs.

Effects of chronic use of proton-pump inhibitors

Recent studies have shown the relationship between the chronic use of these drugs with proliferative changes of the fundal mucosa and the gastric body. Although there are controversies regarding this relationship, they have already been described in large studies where there was no statistical difference between the groups. The time of treatment with IBPs required to cause proliferative changes in the gastric mucosa has not yet been determined because it is very variable in the literature (Souza Menegassi *et al.*, 2010). Omeprazole at usual doses ranging from 20 to 40 mg/day is able to inhibit more than 90% of the 24-hour acid secretion in most patients, which makes many of these patients almost acaloric. Because of that therapeutic potency, the doubts about the safety of its long-term use multiply themselves (Lima and Neto Filho, 2014). Nowadays the question arose that the use of PPIs could lead to malabsorption of calcium by bones with consequent osteoporosis and an increased risk of fractures, especially in the hip. Although the data presented are not uniform, some studies show that there is a small but significant association between the use of PPIs and the risk of fractures. However, clinical significance has not been demonstrated because the risk is low. Nevertheless, the Food and Drugs Administration (FDA) suggested that the IBP insert should indicate a possible risk of fracture with its use (Braga, Silva and Adams, 2011). Although it is not possible to establish the causal association, the use of PP is associated with an

increased risk of bone fracture. With the available evidences, it is not recommended to discontinue treatment with PPI to avoid bone fractures, but an adequate prescription should be stimulated and the search for a minimal effective dose (De-La-Coba *et al.*, 2016). The mechanisms by which PPIs cause deleterious effects on bone mass include decreased calcium and vitamin B12 absorption (Pinto *et al.*, 2011). Another explanation is the inhibition of the proton-pump of the osteoclasts, which causes interference in the bone metabolism (Arai and Gallerani, 2011). Other current studies show that exaggerated use of PPIs is directly linked to iron and magnesium deficiency, which in turn is related to increased vulnerability to pneumonia, intestinal infections. There are also some studies that relate the chronic use of some PPIs to depression (Lima and Neto Filho, 2014). In general terms it can be stated that PPIs are a safe pharmacological class with mostly mild adverse effects, such as headache, constipation, diarrhea, dyspepsia and rashes. No cases of cancer or carcinoid tumors related to prolonged use of PPI have been reported (De-La-Coba *et al.*, 2016).

Because gastric acidity plays the role of protective barrier against infections of the upper gastrointestinal tract, hypochlorite has been associated with increased intestinal infections and respiratory infections caused by microaspiration. Infections with *Campylobacter* and *Salmonella* acid-sensitive bacteria were associated with the use of PPIs. Several epidemiological studies have linked the use of PPIs to the increased risk of community-acquired pneumonia, especially in the first few days of prescription (Castro, Deprados and Martínez, 2016). In a recent case-control study it has been described that PPIs besides being widely used for the treatment of gastrointestinal diseases are also potentially involved in cognitive decline. The mechanism of PPIs responsible for the development of dementia has not yet been elucidated. One possible explanation would be that PPIs cross the blood-brain barrier and lead to increased levels of β -amyloid in the brain by modulating its degradation and increasing the formation of anomalous aggregates of TAU protein. Associated with this, malabsorption of vitamin B12 and other nutrients due to prolonged hypochloridation may be implicated in cognitive decline (Viegas and Nabais, 2017). Renal insufficiency caused by acute interstitial nephritis (AIN) is a known complication of omeprazole use (Cotta *et al.*, 2012). Both recent and previous use of a proton pump inhibitor was associated with a significantly increased risk of NIA (Blank *et al.*, 2014). The mechanism of drug-induced AIN is still unknown, although an immunological mechanism is suspected. AIN is a complication associated with the entire group of PPIs and not just omeprazole. Therefore, it is important that health care providers be vigilant about this complication, because accurate and attenuated diagnosis along with drug withdrawal can prevent life-threatening renal failure (Harmark *et al.*, 2007). Potentially serious adverse reactions of PPIs include AIN and hypomagnesemia. Although rare, AIN can lead to kidney damage in the long term. Hypomagnesemia may occur after chronic use of a PPI and its monitoring is especially indicated when the patient has risk factors for arrhythmias or is on digoxin (Woods, 2017). A study on the safety of omeprazole and duration of treatment found that 60% of the patients surveyed exceeded the time of treatment with omeprazole to treat GERD and that 4.5% of the elderly patient was using omeprazole in high doses over a long period (over a year). Another observation made was that more than half of the patients evaluated (53.2%) did not remember their doctor's

guidelines regarding the duration of treatment with omeprazole (Caricol, 2015). The table 3 summarizes the main effects of chronic use of PPIs.

Relation of proton-pump inhibitors with polypharmacy

Polymedication, also known as polypharmacy or polypharmacotherapy, means the simultaneous and continuous use of drugs for several pathologies and symptoms by the same person. This is an increasingly common practice in the elderly, which increases the possibility of adverse drug reactions, toxicity, drug interactions and decreased adherence to treatment (Rosa and Camargo, 2014). Another definition for polypharmacy is the use of five or more medications by the same individual. Such occurrence has increased significantly in recent years, its cause is multifactorial. However, chronic diseases and clinical manifestations due to aging may be considered as the main reasons for the polypharmacy (Secoli *et al.*, 2010). The use of multiple drugs, self-medication and irrational use of medications may co-operate with disease risks and complications, and the elderly population is the group most vulnerable to these risks. In general words, elderly people make use of omeprazole uncontrolled, and precisely because of the high prevalence of chronic diseases in this age group, polypharmacy is favored. In this population using multiple medications, the risks of interactions and adverse effects related to the use of omeprazole can be increased when used as self-medication, for long periods of time and polypharmacy (Pimenta *et al.*, 2016). Polypharmacy is one of the main risk factors for the emergence of drug interactions and adverse drug reactions. Drug interaction occurs when the effects of one drug are altered by the presence of another, and may be beneficial (increased efficacy) or harmful (decreased efficacy). Among the therapeutic regimens of higher prevalence and with a greater chance of causing drug interactions, the association between opioid and antiulcer agents is highlighted. These are represented by ranitidine and omeprazole as inhibitors of the enzyme system of opioids, which promotes increased bioavailability and toxicity (Melgaço *et al.*, 2011).

In a study of the use of antiulcer drugs in a population of elderly people in a Brazilian capital, it was observed that the PPIs were the subclass of most used drugs, besides observing the marked presence of polypharmacy (Schroeter, 2008). The consumption of drugs for symptoms of the digestive tract observed in research may be related to the need to alleviate these symptoms of the gastric mucosa caused by excessive use of medications as a consequence of polypharmacy (Silveira, Dalastra and Pagotto, 2014). PPIs are usually prescribed for inadequate reasons and for a period of time that most often goes beyond what is established. The considerable increase in its use in recent years has instigated concerns regarding its dispensable prescription, associated cost and potential risks (Ribeiro *et al.*, 2014). What is observed is that polypharmacy is strictly related to the aging of the population, with the consequent and high prevalence of chronic conditions, as well as the ease of access to the use of PPIs. Figure 1 explains the relationship between polypharmacy and chronic use of PPIs, as interpreted by the authors of this paper.

DISCUSSION

In the present study, it was found that PPIs constitute a widely prescribed class of drugs. The research papers analyzed showed the characteristics, indications, effects of chronic use

and the relationship of polypharmacy with this class of drugs. The strict relationship between polypharmacy, the elderly population and chronic diseases was also observed. The high percentage of PPIs prescribed without a justified indication and the differences found between primary and specialized care leads to the assumption that there is a lack of prophylactic indications and a lack of coordination between the different levels of care, whose solution would be the creation of protocols of conjunct actions (Burgos Lunar *et al.*, 2006). PPIs have been used empirically often by prescription or self-medication, and for the treatment of digestive manifestations or prophylaxis of the onset of symptoms. The prescription of omeprazole or any other PPI, outside the established indications, is considered a prescription error, and its use should be limited to the duration of treatment defined according to guidelines. Therefore, the term "continuous use", which is frequent in the prescriptions, is imprecise and does not have a rational therapeutic basis because it does not indicate the duration of treatment (Braga, Silva and Adams, 2014). PPIs are known as effective, safe and with few adverse effects and for these reasons are widely sold out.

However, in only a few specific situations its long-term use is justified, such as in GERD requiring maintenance treatment, in the prophylaxis of benign duodenal and gastric ulcers associated with NSAIDs and in Zollinger-Ellison syndrome (Viegas and Nabais; 2017). When the use of PPIs is prolonged, the renewal of the prescription should occur every three or six months by re-prescription and evaluation of the patient regarding the therapeutic effect and appearance of adverse effects. In order to make the deprescription of the PPI, it is necessary to reconsider the reasons that led to prescription, contraindications and differences. This is a process that can result in dose modification, substitution or suspension of the drugs (Braga *et al.*, 2014). The indiscriminate prescription of PPIs may be due to the characteristics of this class of drugs, which are their high efficiency and low toxicity. However, studies warn of the risks associated with prolonged use of PPIs, which involve risks to the health and quality of life of people. For this reason, prescribing professionals should consider the risk-benefit when necessary prolonged use of these drugs. Similarly, surveillance should be performed for signs and symptoms related to the adverse effects of prolonged use of PPIs (Hipolito, Rocha and Oliveira, 2016).

The strategy to rationalize the use of medicines, including PPIs, is the fundamental factor for efficient and quality clinical care, based on compliance with the recommendations of the guidelines and protocols elaborated with scientific evidence (Ponce and Esplugas, 2013). Regarding to the deprescription, for this act it is necessary to evaluate the risks and benefits of the medication considered, which should be based on criteria of need and psychosocial aspects. In order to have adherence and acceptance of the patient's prescribing, the physician should emphasize the relevance of this process and emphasize that it is a reversible condition (Braga *et al.*, 2014). Thus, the importance of health professionals in promoting the rational use of medicines is evidenced in the sharing of information to the population about the risks related to the use of PPIs, mainly omeprazole, due to their ease of access (Hipolito, Rocha and Oliveria, 2016). For this, we need the implementation of strategies for population education, in order to promote early adherence and thus avoid the banalization of the use of PPIs (Braga *et al.*, 2014). However, discontinuation of long-term omeprazole therapy should be carefully considered. It is

feasible to interrupt the treatment if it is followed by a physician, and in those patients who use it without a clear indication, the reduction or interruption can be safely performed (Hipolito, Rocha and Oliveira, 2016). PPIs are often misused and continued without the support of scientific evidence. The pharmacological characteristics of this class, ease of access and distribution, disregard for indications, aging of the population and lack of follow-up of therapy are some of the factors favoring widespread chronic use. It is imperative to adopt strategies in all levels of attention to combat inadequate prescription and chronic use in order to prevent damages to the population.

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