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Article

Proton pump inhibitor deprescription: A rapid review

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Proton pump inhibitors (PPI) are drugs that suppress gastric acid secretion. Its use, without support from scientific evidence, can contribute to polypharmacy, lead to drug interactions and, in the long term, cause serious adverse reactions. Studies advise physicians to deprescribe PPI. A rapid review of scientific evidence, also called a rapid systematic review, on the deprescribing of PPI was performed. Evidence searches were performed in the LILACS, Embase, PubMed and NICE evidence databases with the terms "omeprazole", "proton pump inhibitors", "deprescription", "deprescribing". At LILACS these descriptors were also used in Portuguese and Spanish. Of 118 studies identified, four systematic reviews were selected for analysis. Abrupt deprescribing was associated with an increased risk of symptom recurrence. Fear of symptom recurrence is one of the major barriers to patient-related deprescribing. Educational interventions directed at prescribers, pharmacists, and patients are effective strategies in the deprescribing of PPI. Deprescribing process showed to be feasible in different contexts, with different strategies. The process is most effective through actions with educational and guidance materials directed to health professionals and patients, and with the involvement or leadership of the pharmacist.

Keywords: Proton pump inhibitors. Deprescription. Polypharmacy. Drug-related side effects and adverse reactions. Drug interactions.

INTRODUCTION

Proton pump inhibitors (PPI) are drugs that suppress gastric acid secretion by inhibiting the enzyme H+/K+-ATPase, indicated for the treatment of gastric and duodenal ulcers, erosive esophagitis, eradication of H. pylori in combination with antibiotics, prophylaxis of ulcers associated with non-steroidal anti-inflammatory drugs and hypersecretory conditions such as Zollinger-Ellison syndrome. There is no evidence as to the benefit of using PPI for non-ulcer dyspepsia (Wallace, Sharkey, 2012).

For most acid secretion-related illnesses, the duration of PPI treatment varies from two to twelve weeks, but the efficacy, safety profile and tolerability of the drug stimulate long-term use without timely re-evaluation to determine the need for the drug maintenance (Boghossian *et al.*, 2017).

Prolonged use is justified only in the treatment of complications of gastroesophageal reflux disease such as Barrett's esophagus, under hypersecretory conditions such as Zollinger-Ellison syndrome and in patients with erosive esophagitis (Wilsdon *et al.*, 2017). However, according to Reimer *et al.* (2009) the prevalence of long-term treatment is increasing and up to 70% of patients with chronic acid suppression do not have an indication for PPI treatment. The use of PPI has increased over the past decade, with no new indications being added to their use (Haastrup *et al.*, 2014), according to studies conducted in Denmark and the United Kingdom that reveal this increase after 1990 (Pottegård *et al.*, 2016; Othman, Card, Crooks, 2016).

Patient safety is a relevant topic in the health policy agenda, and it is mandatory to consider it even before the effectiveness of medicines. Primary adverse effects associated with short-term use of PPI include headache, diarrhea, constipation, rash and nausea. Prolonged use may trigger drug interactions, such as reducing the antiplatelet effect of clopidogrel, as well as serious adverse effects such

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as pneumonia, hypomagnesemia, vitamin B12 deficiency, *C. difficile* infection, bone fractures, polyp formation (Fohl, Regal, 2011; Ament, Dicola, James, 2012; Chubineh, Birk, 2012), chronic and acute kidney disease, iron deficiency anemia, dementia (Gomm *et al.*, 2010; Schoenfeld, Grady, 2016; Wilsdon *et al*., 2017; Guedes *et al*., 2020).

Adverse effects may be confused with new diseases, leading to the prescription of other medications (Anthierens *et al*., 2010). The chronic use of PPI, as a consequence, contributes to the increase in unnecessary costs for health systems and polypharmacy (Hasstrup *et al*., 2014; Boghossian *et al*., 2017). The increase in prevalence of chronic diseases, multidisciplinary prescriptions and pharmacological choices for health intervention contribute to polypharmacy and expose the elderly population to prescription of potentially inappropriate drugs, with the risk of adverse reactions outweighing the clinical benefits (Gomes *et al*., 2019, Oliveira *et al*., 2012).

This practice is common in the elderly and may be beneficial for treating various diseases, but is associated with increased risks of drug interactions, adverse reactions, falls, iatrogenesis, hospitalizations and mortality (Hilmer, Gnjidic, 2009; Gnjidic *et al*., 2012; Dills *et al*., 2018; Machado *et al*., 2017; Motter *et al*., 2018 e Santos *et al*., 2019).

A population-based study, conducted in primary care in Brazil, observed a 47.4% prevalence of clinically important drug interactions in elderly patients (Obreli *et al*., 2012).

In recent years, the need to reduce over prescription of drugs through an approach called deprescription has been discussed. The term "deprescription" was first mentioned in 2003 in the article*"Deprescribing: Achieving Better Health Outcomes for Older People Through Reducing Medications"*. It is a process planned and supervised by a healthcare professional to reduce, replace or discontinue inappropriate medications to control polypharmacy (Woodward, 2003; Reeve *et al*., 2015). Scott *et al.* (2015, p. 827) define deprescription as "the systematic process of identifying and discontinuing drugs in cases where existing or potential harm outweighs existing or potential benefits (...)". Considers the same principles as starting a prescribed therapy, ie, it is a patient-centered process with shared decision making and monitoring of effects.

Planning this process involves recognizing polypharmacy and knowing the list of drugs used by the patient and their indications, identifying inappropriate drugs, evaluating each one and setting priorities for deprescribing, implementing the strategy, and monitoring withdrawal syndrome, rebound effect, recurrence of the disease and patient´s quality of life (Couteur *et al*., 2011; Reeve *et al*., 2013; Machado *et al*., 2017; Santos *et al*., 2019).

The beneficial consequences of deprescription include the cessation of adverse reactions and drug interactions. It includes also the minimization of future risks, reduced patient and health care costs, improved treatment adherence and patient´s quality of life, and a decreased medication associated errors (Couteur *et al*., 2011).

MATERIAL AND METHODS

A rapid review of the scientific literature on PPI was conducted, with emphasis on deprescription. The rapid review, also called the systematic rapid review, is a secondary study design that has been increasingly used to inform health policies, especially useful for managers and decision makers (Bortoli *et al*., 2017).

The search for scientific evidence was performed in the LILACS, Embase, PubMed and NICE evidence databases on July 7, 2019, without the use of filters. The terms extracted from the Descriptors in Health Sciences - DeHS and the Medical Subject Headings (MeSH) were used. In Embase, PubMed and Nice Evidence, the terms "omeprazole", "proton pump inhibitors", "deprescription" and "deprescribing" were used. The same search strategy was employed in LILACS, however, including also the descriptors in Portuguese and Spanish. The details of the search strategy are in Table I.

The article selection process was performed by the author and discussed with the co-author, starting with reading the titles, followed by reading the abstracts and later the full articles. Inclusion criteria were: Systematic reviews, published in English, Spanish and Portuguese. The selected systematic reviews were evaluated for methodological quality through the Assessment of Multiple Systematic Reviews - AMSTAR 2 instrument

(Shea *et al*., 2017), being applied by the author, followed by discussion with the co-author. The SR were classified as high (13-16/16), moderate (9-12/16), low (5-8/16) and critically low (0-4/16) methodological quality. The data were extracted from the SR by the author in an Excel spreadsheet, containing the following information: author/year, objective, quantity and study designs included, most recent search date, AMSTAR 2 score, intervention studied, participant characteristics, location and countries of achievement, outcomes, barriers to implementation, facilitators of implementation and knowledge gaps (Table II).

TABLE I - Search strategies in scientific literature databases

BASE	DATE	STRATEGY	NUMBER OF ARTICLES
LILACS	07/07/2019	(Desprescrições OR Deprescriptions OR Deprescripciones OR Deprescrição OR Deprescrições OR Desprescrição) AND ("Parte superior do formulário Inibidores da Bomba de Prótons" OR "Proton Pump Inhibitors" OR "Inhibidores de la Bomba de Protones")	0
PUBMED	07/07/2019	((("Proton Pump Inhibitors"[Mesh] OR Inhibitors, Proton Pump)) OR ("Omeprazole"[Mesh] OR Prilosec OR Omeprazole Sodium OR Sodium, Omeprazole OR H 168-68 OR H 168 68 OR H 16868 OR Omeprazole Magnesium OR Magnesium, Omeprazole)) AND ("Deprescriptions"[Mesh] OR Deprescription OR Deprescribing)	43
EMBASE	07/07/2019	('proton pump inhibitor'/exp OR 'omeprazole'/exp) AND 'deprescription'/exp AND [embase]/lim	42
NICE evidence	07/07/2019	(deprescription OR deprescribing) AND ("proton pump inhibitors" OR omeprazole)	33
TOTAL			118

TABLE II - Characteristics of the included studies

Systematic Review	**Deprescribing versus continuation of chronic proton pump**	**Effectiveness of interventions to deprescribe inappropriate proton pump inhibitors in older adults**	**Patient barriers to and enablers of deprescribing: A systematic review**	**Deprescribing medications for chronic diseases management in primary care settings: A systematic review of randomized controlled trials**
Author, year	Boghossian et al. (2017)	Wilsdon *et al*. (2017a)	Reeve *et al.* (2013)	Dills *et al.* (2018)
Objective	To determine the effects associated with long-term deprescription of PPI therapy in adults compared with chronic daily use (28 days or more).	To determine the effectiveness of interventions to reduce inappropriate use of PPI in the elderly.	To identify barriers and enablers that may influence the patient's decision to discontinue medication use (ME).	To evaluate the result of deprescription in reducing the amount of ME and controlling chronic medical and mental conditions compared with standard treatment in the non-terminal adult population.

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Study designs and quantity	Prospective open multicenter randomized trial (n = 4). Prospective randomized double-blind multicenter trial (n = 2).	Randomized controlled trials (n = 6) (one specific for PPI), prospective uncontrolled cohort (n = 8), interrupted time series (n = 2), pre and post-intervention audits (n = 3), retrospective uncontrolled cohort (n = 1), multicenter prospective cohort without control (n = 1).	Qualitative: Semi-structured interview (n = 11). -Focus group (n = 2). Qualitative (mixed): - Open answers (n = 1), semi-structured interview (n = 5), open and closed answers (n = 1). Quantitative: - Research (n = 1).	Randomized clinical trials (n = 58).
Latest search date	November 2016	January 2017	August 2011	December 2016
AMSTAR 2	Methodological quality assessment: high	Methodological quality assessment: moderate	Methodological quality assessment: moderate	Methodological quality assessment: moderate
Intervention in detail	Deprescription: - On demand regarding the continuous use of PPI in outpatients (average 48 to 57 years) with moderate GERD and mild esophagitis. Abrupt compared to continued use of PPI in outpatients (age> 18 years /average 73 years) with mild to moderate esophagitis	Discharge counseling (n = 1), outpatient clinics with focus on deprescription (n = 2), education for doctors and pharmacists (n = 5), academic detailing (n = 2), geriatrician management (n = 5) or revision of ME (n = 6). -Deprescription of PPI: a) Evidence-based educational material (leaflets) provided to physicians, pharmacists and patients. b) Academic detailing: teaching sessions. c) Deprescription by a geriatrician.	Semi - structured interview, focus group, questionnaire survey. Boath and Blenkinsopp (1997) n = 20 and Grime *et al.* (2001) n = 82: Qualitative research with semi - structured interviews in the United Kingdom report barriers and enablers for PPI deprescription.	To refine the amount of ME: Educational interventions: Training of health professionals -Specific interventions: Educative targeted at high-risk patients individually on the management of chronic diseases and the inappropriate use of ME in an inpatient, outpatient and long term care settings. - Mixed intervention (prescriptive and patient specific). PPI deprescription: mixed educational interventions.
Participants	Participants (n = 1758) between 48 and 57 years old. One study (Pilotto 2003) included participants aged 65 old and older (average age 73 years old). All participants were outpatient and had non-erosive reflux disease or milder degrees of esophagitis (LA grade A or B).	Participants with a median age of 65 years old on inadequate PPI use.	Participants (n = 1310) in use or recently suspended use of ME.	Non-terminal adults 18 years old and older
Place	Morgan 2007: 23 canadian locations. Pilotto 2003: 16 italian centers. Van der Velden 2010: 23 general practices of the central and eastern Netherlands. Bour 2005: 41 french hospitals (exact undisclosed locations). Janssen 2005: 58 centers (29 in Germany, 12 in France, 11 in Switzerland and 6 in Hungary). Bayerdörffer 2016: 61 sites (Austria, France, Germany, South Africa and Spain).	Hospitals and community or elderly care facilities.	Not informed.	Ambulatory, assisted living environments and nursing home.
Countries	Canada, Italy, the Netherlands, France, Germany, Switzerland, Hungary, Austria, South Africa and Spain.	Australia, New Zealand, USA, England, Wales, Scotland, Ireland, France, Switzerland, Germany, Netherlands and Israel.	United States, United Kingdom, Australia, Israel, Netherlands, Sweden.	Finland, Spain, United States, New Zealand, Canada, Sweden, Belgium, Germany, Australia, Israel, United Kingdom, France, Ireland, Norway, Netherlands, Denmark, Brazil.

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Outcomes and Results	Primary outcomes: lack of symptom control = return of symptoms or inadequate relief, use of ME (including PPI) and cost (no report). Secondary outcome: Positive result (no report), all negative results or adverse withdrawal event (exception: gastrointestinal symptoms) and participant satisfaction. The six studies measured the lack of symptom control and analyzed data separately for on demand deprescription and abrupt discontinuation. 1) On demand prescription vs. PPI continuous therapy: Bour 2005 and Janssen 2005 evaluated treatment failure. Bayerdörffer 2016; Morgan 2007; Van der Velden 2010 assessed inadequate symptom relief: 16.3% of participants in the on demand prescription group experienced lack of symptom control versus 9.2% in continuous treatment (RR 1.71, 95% CI 1.31 to 2.21). Bayerdörffer 2016; Bour 2005; Janssen 2005 evaluated the number of PPI tablets: Reduction of use of 3.79 PPI tablets/week (95% CI -4.73 to -2.84). Bayerdorffer 2016 assessed adverse withdrawal events: 15 participants (5%) developed esophagitis with on demand deprescription compared to none with continued use of PPI. Bayerdörffer 2016; Bour 2005; Janssen 2005; Morgan 2007; Morgan 2007; Van der Velden 2010) assessed participant satisfaction (unwillingness to continue and inadequate symptom relief). Participants using on demand PPI showed greater dissatisfaction compared to participants using continuous PPI (15.8% with demand versus 8.8% with continuous; RR 1.82, 95% CI 1.26 to 2.65). 2) Abrupt desprescription vs. continuous PPI therapy: Pilotto 2003 assessed treatment failure: Abrupt deprescription has been associated with an increased risk of return of gastrointestinal symptoms. Pilotto 2003 evaluated adverse withdrawal events: 69.6% of participants with a history of esophagitis relapsed with abrupt discontinuation compared with 20.4% with continuous treatment (RR 3.41, 95% CI 1.91, 6.09).	Studies with effective interventions (n = 6). Inconclusive studies (n = 11), ineffective studies (n = 4). Effective interventions for PPI: Roughead *et al.* and Pratt *et al.*: PPI specific with educational material for physicians, pharmacists and patients: a) Increase of 0.6%/month in the low dose prescription rate and increase to 0.9% per month after 20 months (p = 0.007). b) Decrease of 8.47% in the prescription rate (95% CI –13.72 to –3.21%) compared to the rate without intervention. c) Increase of 1.57% in the rate of use of low dose PPI (95% CI 0.71-2.44%). - Clyne *et al.* 2015 and 2016 reported the intervention of "scholarly detailing ": Pharmacist visit to clinics to discuss potentially inappropriate prescriptions, ME review, and the algorithm. The adjusted OR of continuing to receive an inadequate PPI in the intervention group compared to the group increased from 0.3 at six months to 0.4 after one year of study. Michalek *et al.* and Wehling *et al.* reported deprescription by geriatricians and use of FORTA to guide prescribing.	Barriers reported by patients: Disagreement with deprescription, deprescription process, negative influencers, fear and others. Enablers: Agreement to discontinue the medication, deprescription process, positive influencers, antipathy to ME, others. Influence of the pharmacological class. - Barriers to the deprescription of PPI: Belief in the benefit of the drug for the clinical condition, unwillingness to try alternatives, fear of the return of the clinical condition or the return of symptoms and bad experiences with previous deprescriptions. - Enablers for the deprescription of PPI: Fear of adverse effects, possibility of restarting medication use, influence of primary care physician, and cost of medication.	Primary outcome: Successful deprescription. Statistically significant reduction in ME burden between the intervention group (IG) and the control group (CG). More than 50% of patients tolerated drug deprescription compared with the control. Secondary outcome: Adverse effects related to the drug or chronic condition. - Deprescription of PPI: a) Zwisler *et al.* 2015 (n = 171), randomized, double-blind, placebo-controlled study: Highest deprescription rate was 27% of participants. b) Clyne *et al.* 2015: Successful deprescribing (dose reduction to maintenance level in 50% of patients) with patient-specific pharmacist-related educational intervention for prescribers, related to potentially inappropriate medication (PIM) 20% of cases: suspension of use. Indication of alternative therapy: 11% unchanged behaviour: 20%.

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Implementation barriers	Abrupt deprescription was associated with an increased risk of symptom recurrence.	Deprescription processes without involvement between physician and patient.	Need for drug: - Belief in the benefit of ME for the clinical condition (PPI and others), hope for future benefits, psychological well-being, unwillingness to try alternatives (PPI and others), desire to increase the dose of the drug, skepticism in the suspension recommendation. - Fear: Return of clinical condition, return of symptoms (PPI and others), withdrawal effects, non-specific fears (PPI and others). - In the process of deprescription: Lack of support, unknown or conflicting information, need for adequate time. - Influences: From primary care physician, relatives and friends, bad experiences with previous withdrawals (PPI and others). - Other: Pragmatism, resistance to change, habit, unwillingness.	Adverse results, worsening clinical condition and exacerbation of chronic diseases. Interventions can be costly, intensive and ongoing.
Implementation enablers	Possible reduction in the number of tablets if on demand deprescription is tolerated.	Evidence-based educational interventions, "scholarly detailing" involving pharmacist visits and geriatrician-led deprescriptions.	Need for medication: - Presence of adverse effects, fear of adverse effects (PPI and others), belief that medication is not necessary, finding of ineffectiveness, fear of dependence, acceptance of alternative treatment option, uncertainty about need of treatment continuity, insecurity about the doctor who started the treatment. - Deprescription process: Possibility of restarting the use of medication (PPI and others), monitoring of primary care physician and other services, family support, factors related to cessation of stress. - Influences: Primary care physician (PPI and others), other influences. - Dislike: Psychological benefits, aversion to drug use, inconvenience, including cost (PPI and others), ME are unnatural, stigma. - Other: Absence of fear.	Pharmacist's intervention in the educative actions with the doctor and the patient, and in the specific recommendations in patient's treatment.

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Knowledge Gaps	Best strategy for deprescription: Inconclusive. Comparison of continuous therapy deprescription methods in populations with other gastrointestinal disorders (results limited to people with gastroesophageal reflux disease (GERD) presenting with NERD or mild esophagitis), broadening of population characteristics and extension of the mean follow-up after one year, cost-benefit analysis of adverse events of ME withdrawal and positive events of ME withdrawal and comparison of deprescribing outcomes in people with high-grade EE (erosive esophagitis).	Overcome knowledge barriers regarding inadequate PPI prescribing. Uncertainty whether PPI deprescription translates into better clinical outcomes. Discussion of strategies for deprescription (abrupt discontinuation, dose reduction, gradual reduction or use on demand).	Proposal of deprescription for specific age groups, studies of deprescription with other classes of ME, evaluation of results regarding patient-centered deprescription.	Not informed

RESULTS

The searches allowed to identify 118 studies, of which six SR were considered eligible and four were selected, according to the selection process presented in Figure 1.

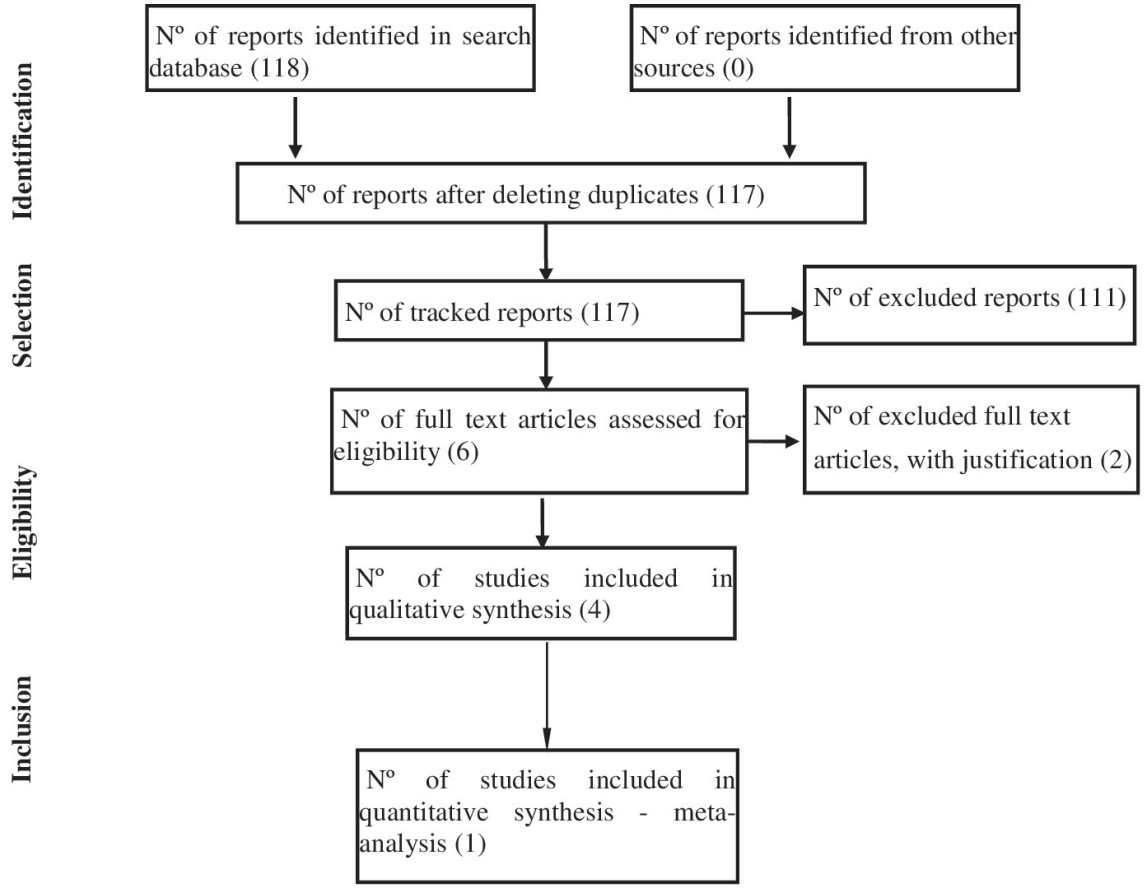

FIGURE 1 - Study selection flow chart

The systematic reviews of Page *et al*., 2016 and Malhotra *et al*., 2018 were excluded because they did not contemplate the objectives of this study. Of the four SR included, one is of high methodological quality and the others of moderate quality.

Two of the included systematic reviews specifically address PPI (Boghossian *et al*., 2017; Wilsdon *et al*., 2017) to determine the effects (Boghossian *et al*., 2017) and effectiveness of interventions (Wilsdon *et al*., 2017) associated with deprescribing. The third analyzed barriers and facilitators that influence the patient in the decision to deprescribe (Reeve *et al*., 2013) and the fourth evaluated the result of deprescription in reducing the amount of medication and controlling medical conditions (Dills *et al*., 2018).

Boghossian *et al*. (2017) analyzed the effects of two strategies (n=1758): on demand PPI deprescription in patients aged 48 to 57 years old with moderate gastroesophageal reflux disease and mild esophagitis, and abrupt deprescription in patients ≥ 65 years old with mild to moderate esophagitis compared to continuous use (28 days or more). In the on-demand deprescription, 16.3% of participants had return of gastrointestinal symptoms or inadequate relief versus 9.2% in continuous use (RR 1.71; 95% CI 1.31 to 2.21). Fifteen participants in the intervention group developed esophagitis compared to none in the control group. There was a reduction in use on average, of 3.79 tablets of PPI/week (95% CI -4.73 to -2.84). The use of PPI on demand caused greater dissatisfaction among participants compared to the control group, respectively 15.8% and 8.8% (RR 1.82; 95% CI 1.26 to 2.65). Abrupt deprescription was associated with an increased risk of symptom recurrence, with relapse in 69.6% of participants with a history

of esophagitis compared with 20.4% of those with continuous PPI use (RR 3.41; 95% CI 1.91 to 6.09).

Wilsdon *et al*. (2017) reported effective and targeted interventions to promote high-dose-reduced PPI deprescription through educational material (leaflets) prepared on the basis of scientific evidence directed to physicians, pharmacists and patients who were in different programs and periods in Australia. The number of low-dose prescriptions increased by 0.6% per month and after 20 months increased to 0.9% per month (p = 0.007). In one of the studies reviewed, these interventions were rated as useful or very useful by 81% of physicians, 95% of pharmacists and 72% of patients.

Reeve *et al*. (2013) studied 1310 participants who were taking or recently discontinuing use of drugs, in order to identify barriers and facilitators that may influence the patient's decision to deprescribe. Two qualitative studies analyzed were conducted in the United Kingdom and cite as barriers to PPI deprescription: Belief in the benefit of the drug for the clinical condition, unwillingness to try alternatives, fear of the return of the clinical condition or the return of symptoms and poor experiences with previous deprescription. On the other hand, the fear of adverse effects, the possibility of restarting the use of the medication, the influence of the primary care physician and the cost of the medication were cited as facilitators of the PPI deprescription.

Dills *et al*. (2018) included adult participants over 18 years old to evaluate the outcome of deprescribing in reducing the amount of medication and in controlling medical conditions. Pharmacist-led educational interventions on symptom management and prescription, directed at prescribers and patient-directed educational interventions on inappropriate drug use resulted in a reduction in PPI dose to maintenance dose in 50% of patients.

DISCUSSION

This review has limitations inherent in the design of a rapid review, such as fewer databases searched, selection processes and data extraction not performed independently, focusing on systematic reviews. On the other hand, this type of review has the advantage of providing timely answers to the demands of managers in the daily routine of health services.

Deprescription is a process that begins prior to the formal act of prescribing a change in conduct. For the deprescription process to be developed effectively and safely, barriers must be considered by both doctors and patients. Confidence in drug therapy for cure or remission of symptoms, limited time for consultation with the healthcare professional, fear of discontinuation of therapy initiated by another prescriber, market influences, lack of communication between prescribers, disagreement between professionals and patients regarding the strategy for deprescription, lack of knowledge in the management of deprescription are barriers experienced by prescribers. In addition, patient resistance to discontinuation or replacement of therapy for fear of symptom recurrence, reporting of unsuccessful experiences of others and pressure from family and community to continue drug use should be considered (Reeve *et al*., 2013; Boghossian *et al*., 2017; Wilsdon *et al*., 2017; Dills *et al*., 2018). Patient education about the risks and benefits of drug therapy, a structured process of drug withdrawal, monitoring and support facilitate deprescription (Dills *et al*., 2018).

Boghossian *et al*. (2017) demonstrated that abrupt deprescription was associated with an increased risk of recurrence of gastric symptoms. In the case of PPI, deprescription may be performed with abrupt discontinuation, use on demand until relief of gastric symptoms, use of a lower dose or alternative therapy such as histamine-2 receptor antagonists (Thompson *et al*., 2018). Despite gaps in the scientific literature regarding agreement on the best strategy for deprescription, considering the clinical effects, the gradual on demand or dose-reduction process of PPI is more effective in controlling the recurrence of gastric symptoms compared to an abruptly withdrawal. (Katz, Gerson, Vela, 2013; Haastrup *et al*., 2014; Farrell *et al*., 2017). According to Reimer *et al*. (2009) abrupt withdrawal of PPI after 8 weeks of treatment may cause rebound acid hypersecretion in healthy adults. In a qualitative study, patients reported that they would use PPI at low or on demand doses (Grime, Pollock**,** 2002).

It is very important to take these findings into account, as the fear of recurrence of gastric symptoms,

associated with an increased risk of abrupt withdrawal, is one of the main barriers to deprescription, in addition to the belief in the benefit of the drug, unwillingness to try alternatives, bad experiences with previous deprescriptions processes and costs. Patients consider the use of PPI for clinical treatment necessary, value the control of gastric symptoms and the quality of life provided by their use and point this class of drugs as the most effective for this purpose (Spijker-Huiges, Winters, Meyboom-De Jong, 2006; Farrell *et al*., 2017; Thompson *et al*., 2018). In the study by Spijker-Huiges, Winters, Meyboom-De Jong (2006) 68% of patients reported that they would not accept the return of any symptoms after deprescription.

Systematic reviews by Wilsdon *et al*. (2017) and Dills *et al*. (2018) showed that information directed to physicians, pharmacists and patients through educational actions involving teaching materials and explanatory content on the promotion of rational use of medicines, as well as guides and algorithms, guide the conduct in the deprescription process. Based on the awareness of health professionals about prescribing and symptom management, the deprescription process can be relied on through the use of tools for guidance (Walsh *et al*., 2016; Farrell *et al*., 2017).

In partnership with groups from other countries, Brazilian investigators performed the translation and cultural adaptation of deprescribing algorithms developed by the Canadian Deprescribing Network (Caden) for various drugs, including PPI (Sbrafh, 2020).

According to Thompson *et al*. (2018) physicians are also afraid of the return of adverse effects in the face of deprescribing, so a strategy to guide deprescribing should include the identification, evaluation and prioritization of drugs in relation to the potential for risk, in a shared way between doctors and pharmacists. The time limitation on primary care physicians imposed by the routine of the service, however, implies the lack of reevaluation of continuous use medications (Thompson *et al*., 2018).

In the midst of a process that involves technical knowledge, established care routines and patients' anxieties, the experiences and expectations should be considered and discussed as a component for the shared development of the best strategy for deprescribing. The adverse effects of long-term PPI use worry patients in inverse proportion to the degree of satisfaction with symptom control and the costs incurred to maintain treatment (Chey, Mody, Izat, 2010). According to studies (Farrell *et al*., 2017; Thompson *et al*., 2018), patients agree to discuss over prescription, are willing to decrease PPI use, and information exchange is important in this process. The patient is interested in understanding what is, how effective is, what actions and options are considered in view of the different outcomes, especially the occurrence of symptom recurrence and the possibility of resumption of PPI treatment. In the study by Smeets *et al*. (2009), patients considered the clarification of their involvement, the reasons for the deprescription, and the possibility of symptom recurrence to be of greater importance in the deprescription process.

In this sense, the inclusion of the pharmacist in health teams and their involvement in actions related to the promotion of rational use of medicines, educational actions to provide patient education and review of the list of medicines used, becomes increasingly relevant. This includes also monitoring symptoms in a shared and complementary manner to the physician (Farrell *et al*., 2017); and reducing indiscriminate drug use and health system costs (Bundeff, Zaiken, 2013).

The studies included in this review were conducted in Europe, the United States and the Middle East and show that deprescription is feasible in different contexts with different strategies. The findings of the systematic reviews indicate that the process is most effective through actions with educational and guiding materials directed to health professionals and patients, with the involvement or leadership of the pharmacist. There were no studies conducted in Brazil on PPI deprescription, however, at the care level, the factors implicated in greater effectiveness and the actors involved are generally common to health systems, yet adaptations may be necessary to adapt to the local reality.

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