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Urinary incontinence associated with pharmacological treatment of Chronic Obstructive Lung Disease: An integrative review

Incontinência urinária associada ao tratamento farmacológico da Doença Pulmonar Obstrutiva Crônica: Uma revisão integrativa

Incontinencia urinaria asociada con el tratamiento farmacológico de la Enfermedad Pulmonar Obstructiva Crónica: Una revisión integrativa

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease, often associated with smoking. COPD patients have persistent, including urinary incontinence. Therefore, a research has the general objective of knowing the physiological mechanism of urinary incontinence associated with the pharmacological treatment of COPD. As a methodological process, this study is an integrative review that included randomized clinical trials, quasi-experimental intervention studies, cohort and case-control. The selection of studies was carried out in the databases PubMed, SciELO, Science Direct and BVS (Virtual Health Library), published between 2010 and July 2020, in Portuguese and English. Pharmacological classes SABA, LABA, SAMA, LAMA, ICS and iPDE4 were considered to investigate adverse effects and check for the presence of urinary symptoms caused by these drugs. In the results and discussion, 113 articles were identified with the investigated descriptors. After the article selection process, 14 studies resulted: PubMED (13); and Science Direct (1). The pharmacological class related to urinary incontinence identified in this study was that of anticholinergics / antimuscarinics. From this perspective, it can be considered that Urinary Incontinence has a low relationship with the adverse effects of drugs for the treatment of Chronic Obstructive

Pulmonary Disease (COPD). However, as urinary incontinence is not considered a life-threatening problem, it is possible that it has not been included among the adverse events to be explored.
Keywords: Urinary incontinence; Pharmacological treatment; Chronic obstructive pulmonary disease.

Resumo

A Doença Pulmonar Obstrutiva Crônica (DPOC), é uma doença pulmonar, frequentemente associada ao tabagismo. Pacientes com DPOC apresentam sintomas persistentes, incluindo a incontinência urinária. Diante disso, a pesquisa tem como objetivo geral de conhecer o mecanismo fisiológico da incontinência urinária associada ao tratamento farmacológico da DPOC. Como processo metodológico, este estudo trata-se de uma revisão integrativa onde foram incluídos ensaios clínicos randomizados, estudos de intervenção quase-experimentais, coorte e caso-controle. A seleção dos estudos foi realizada nas bases de dados PubMed, SciELO, Science Direct e BVS (Biblioteca Virtual em Saúde), publicados entre 2010 a julho de 2020, nos idiomas português e inglês. Foram considerados as classes farmacológicas SABA, LABA, SAMA, LAMA, ICS e iPDE4 para investigação dos efeitos adversos e verificação da presença de sintomas urinários causados por esses fármacos. Nos resultados e discussão foram identificados 113 artigos com os descritores investigados. Após o processo de seleção dos artigos, resultaram em 14 estudos: PubMED (13); e Science Direct (1). A classe farmacológica relacionada com a incontinência urinária identificada neste estudo foi a dos anticolinérgicos/antimuscarínicos. Nessa perspectiva, pode-se considerar que a Incontinência Urinária tem baixa relação com os efeitos adversos dos medicamentos para o tratamento da Doença Pulmonar Obstrutiva Crônica (DPOC). No entanto, como a incontinência urinária não é considerada um problema com risco de vida, é possível que não tenha sido incluída entre os eventos adversos a serem explorados.
Palavras-chave: Incontinência urinária; Tratamento farmacológico; Doença pulmonar obstrutiva crônica.

Resumen

La enfermedad pulmonar obstructiva crónica (EPOC) es una enfermedad pulmonar, a menudo asociada con el tabaquismo. Los pacientes con EPOC tienen incontinencia urinaria persistente, incluida. Por tanto, una investigación tiene como objetivo general conocer el mecanismo fisiológico de la incontinencia urinaria asociado al tratamiento farmacológico de la EPOC. Como proceso metodológico, este estudio es una revisión integradora que incluyó ensayos clínicos aleatorizados, estudios de intervención cuasiexperimentales, de cohortes y de casos y controles. La selección de estudios se realizó en las bases de datos PubMed, SciELO, Science Direct y BVS (Virtual Health Library), publicadas entre 2010 y julio de 2020, en portugués e inglés. Se consideraron las clases farmacológicas SABA, LABA, SAMA, LAMA, ICS e iPDE4 para la investigación de efectos adversos y verificación de la presencia de síntomas urinarios causados por estos fármacos. En los resultados y discusión se identificaron 113 artículos con los descriptores investigados. Tras el proceso de selección de artículos, resultaron 14 estudios: PubMED (13); y Science Direct (1). La clase farmacológica relacionada con la incontinencia urinaria identificada en este estudio fue la de anticolinérgicos / antimuscarínicos. Desde esta perspectiva, se puede considerar que la Incontinencia Urinaria tiene una baja relación con los efectos adversos de los fármacos para el tratamiento de la Enfermedad Pulmonar Obstructiva Crónica (EPOC). Sin embargo, como la incontinencia urinaria no se considera un problema potencialmente mortal, es posible que no se haya incluido entre los eventos adversos que se explorarán.
Palabras clave: Incontinencia urinaria; Tratamiento farmacológico; Enfermedad pulmonar obstructiva crónica.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease, which is characterized by respiratory symptoms and limitations of persistent airflow that is caused by anomalies of the airways and / or alveoli usually caused by an important exposure to particles or harmful gases, caused by an association between small bronchial disease (chronic obstructive bronchitis) and parenchyma destruction (emphysema) (Gold, 2020 & Brazil, 2010).

In COPD there are different risk factors, among which are: smoking (responsible for 80 to 90% of the determinable causes of COPD); home pollution (wood smoke, kerosene); occupational exposure to occupational dust and chemicals; recurrent respiratory infections in childhood; individual susceptibility; childhood malnutrition; and, genetic deficiencies (responsible for less than 1% of cases), such as alpha1 antitrypsin (Gold, 2020).

Currently, based on estimates and epidemiological trends of morbidity and mortality from Chronic Obstructive Pulmonary Disease (COPD), the World Health Organization (WHO) publishes statistics on morbidity and mortality annually for selected causes of death. The Latin American Obstructive Pulmonary Disease Investigation Project (PLATINO) is a population-based epidemiological study whose main objective was to investigate the prevalence of COPD in five major cities

in Latin America. (Nascimento *et al*., 2007 & Moreira *et al*., 2014), while the National Health Survey estimated the prevalence of COPD, as well as the degree to which these conditions limit daily activities (Malta *et al*., 2013).

It is important to note that COPD morbidity can be affected by other concomitant chronic conditions (for example, cardiovascular diseases, musculoskeletal impairment, diabetes mellitus), related to smoking and aging. These conditions can significantly harm the patient's health status, in addition to interfering with the management of COPD and are the main factors of hospitalizations and costs for patients. The single most efficient and cost-effective preventive measure is smoking cessation (Brasil, 2013).

Among the non-pharmacological treatments for COPD, multiprofessional activities include health education, regular physical exercise, pulmonary rehabilitation, a nutritional approach, psychosocial support (for developing anxiety and depression) and home oxygen therapy (Brazil, 2010 & Gold, 2020).

The Latin American COPD Clinical Practice Guide - evidence-based - LatinEPOC-2019 (2020) discusses recommendations for approach and treatment, as well as other guidelines, in its most recent update shows that combined drug therapy should be considered according to the progression and severity of the disease, controlling possible exacerbations (De Oca *et al*., 2020).

The main treatments for COPD are based on bronchodilators (ß2 agonists and anticholinergics) being of short and long duration and Anti-inflammatory drugs (inhaled corticosteroids and phosphodieterase-4 inhibitor). Regarding pharmacological treatments, bronchodilators (BD), often combined with inhaled corticosteroids, are the basis of symptomatic treatment of COPD, with the preferred route of administration being inhalation (Fernandes *et al*., 2017).

Among the most frequent symptoms for Chronic Obstructive Pulmonary Disease (COPD) are chronic cough, sputum production and dyspnea on exertion, aspects that are considered risk factors for Urinary Incontinence, which, together, can contribute to the worsening sensation well-being associated with quality of life, according to a recent review article (Aigon, 2016).

The International Continence Society defines Urinary Incontinence (UI) as any involuntary loss of urine. It is classified as stress incontinence (when there is simultaneous urinary loss on exertion, physical exercise, coughing or sneezing), urgency (when there is an involuntary loss of urine accompanied or immediately preceded by a sudden and uncontrollable urge to urinate, difficult to postpone) or mixed (when there are signs and symptoms of the two types mentioned above) (Burge *et al*., 2017).

The discussion of the study by Burge *et al.* (2017) shows that muscarinic and ß2 adrenergic systems in the airways and bladder are opposed at various levels, including mediator release, receptor signal transduction and receptor regulation, all channeled to functional antagonism at the level of smooth muscle tone. Although there are distinct differences between the airways and the bladder in these interactions, both organs have pathologies characterized by too much muscarinic intake and too little beta-adrenergic. Therefore, the data support the concept of combining muscarinic receptor antagonists and ß2 adrenergic receptor agonists in obstructive airway disease and overactive bladder syndrome (Dale *et al.*, 2014).

In view of this, the research has the general objective of knowing the physiological mechanism of urinary incontinence associated with the pharmacological treatment of chronic obstructive pulmonary disease. Given the above, the interest in this integrative review is due to the need to increase research related to adverse events in the treatment of COPD, in order to reduce discomfort for patients with Chronic Respiratory Disease. With the result of this study, although urinary incontinence does not bring fatal risks to the patient, it can guarantee greater safety by assisting in clinical decision-making and in the rational prescription of drugs, minimizing clinical losses and providing the choice of pharmacological treatment that is less harmful to and ensure better quality of life.

2. Methodology

This is an integrative review. According to Mendes *et al.* (2008) and Souza *et al.* (2010) a integrative review is the combination of a broad methodological approach to reviews, allowing the inclusion of experimental and non-experimental studies for an Evidence-Based Practice (EBP), which seeks to solve the problem and complete understanding through taking decision-making, which incorporates the search for the best and most recent scientific evidence.

For the preparation of this integrative review, the methodological procedures divided into six stages were followed:

1) identification of the theme and selection of the hypothesis or research question for the elaboration of the integrative review;
2) establishment of criteria for inclusion and exclusion of studies / sampling or literature search;
3) definition of the information to be extracted from the selected studies / categorization of the studies;
4) evaluation of the studies included in the integrative review;
5) interpretation of results;
6) presentation of the knowledge review / synthesis.

The sample consisted of experimental studies (randomized and controlled clinical trials), quasi-experimental studies (controlled studies before and after) and comparative observational studies (cohorts and case-control), published between 2010 and July 2020, in Portuguese and English. In addition, articles indexed repeatedly in two or more databases were considered only once.

This integrative review excluded theoretical articles, case reports, descriptive studies, cross-sectional studies, conference abstracts, letters to the editor, results and award reports, studies that focused on the assessment of tools, studies in which there are no outcomes associated with adverse effects related to urinary incontinence, studies in pediatric patients, as well as those who did not present the abstract or full text.

As eligibility criteria, studies with patients over 18 were selected; on assessment of adverse effects of the treatment of Chronic Obstructive Pulmonary Disease; in treatments with bronchodilators (ß2 adrenergic agonists and anticholinergics), inhaled corticosteroids, phosphodiesterase-4 inhibitor and their associations; and, related to urinary symptoms (incontinence or retention).

This study was carried out from July to September 2020 and as a study strategy, the search for works was carried out in the databases: PubMed, SciELO (Scientific Electronic Library Online), Science Direct and BVS (Virtual Health Library).

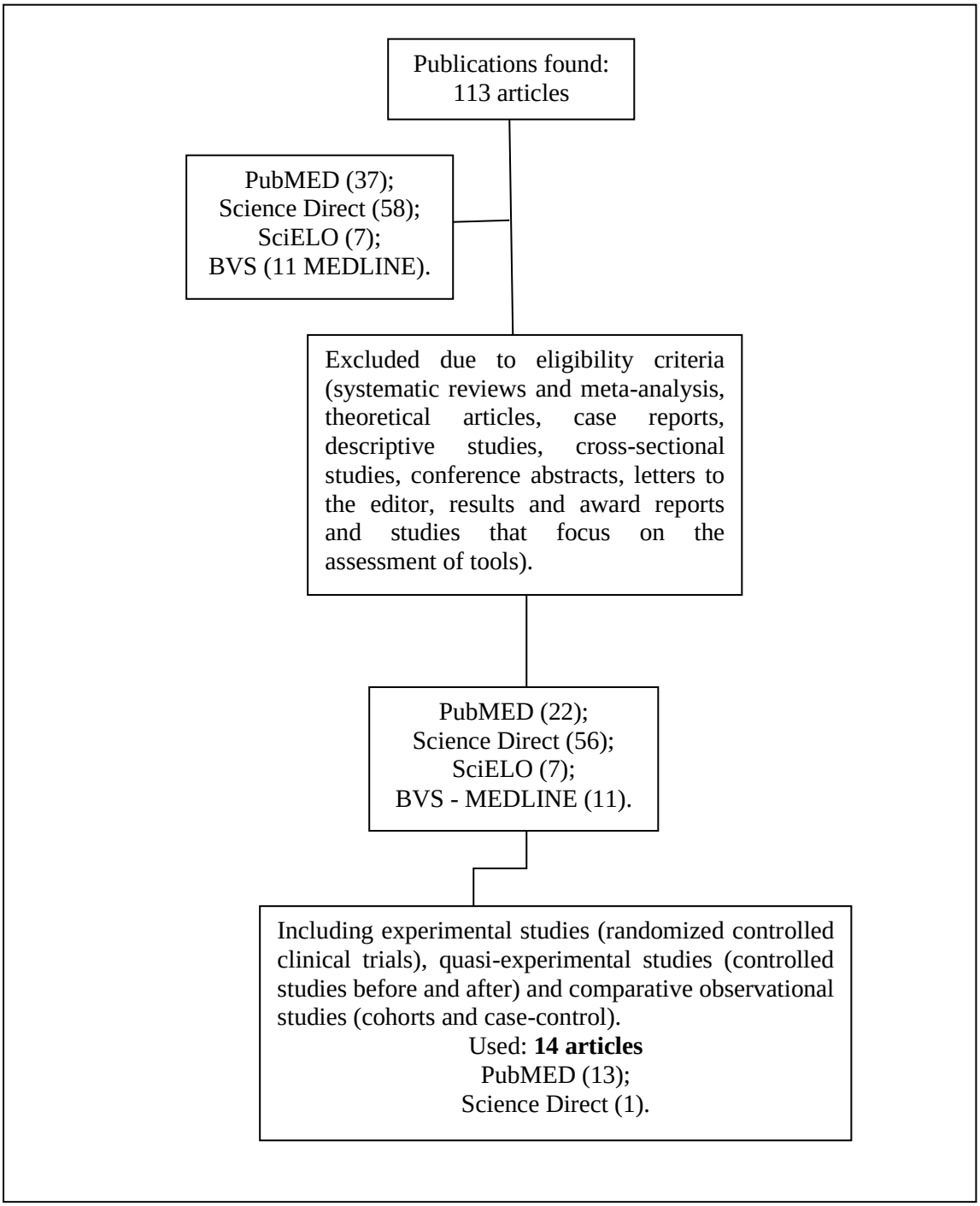
Additionally, a manual search was performed by analyzing the references of the included articles. To identify the articles, the following Medical Subject Headings (MeSH) descriptors were used: “urinary incontinence”, “adverse effect”, “pharmacological treatment”, and “Chronic Obstrutive Pulmonary Disease (COPD)”. To cover the search and group a wider range of publications, each keyword previously described was grouped using the Boolean operator “OR” to its synonyms (for example, “urinary incontinence OR urinary simptoms OR urinary retention”) and subcategories in both languages using MeSH (Medical Subject Headings).

The class and name of bronchodilator drugs (ß2 agonists and anticholinergics / antimuscarinics), Inhaled Corticosteroids and Phosphodiesterase-4 Inhibitor were also included in the search to expand the review. Exclusion was applied according to the eligibility criteria according to the main objective of the present review. For the selection of articles related to the pharmacological treatments available, the manual search of references and the combination of terms in the searches with the drugs described in the literature were also used. The main acronyms used for drugs in this review were: ß2 short-acting (SABA) and long-acting (LABA) agonists; short-acting (SAMA) and long-acting (LAMA) anticholinergics; Inhaled corticosteroids (ICS); and Phosphodiesterase-4 inhibitor (iPDE4).

3. Results and Discussion

The initial search including the descriptors *(((((urinary incontinence) OR (urinary simptoms)) OR (urinary retention)) AND (adverse effect) OR (adverse events)) AND (pharmacological treatment)) AND (Chronic obstrutive pulmonar disease (COPD)))))* identified 113 studies: PubMED (37); Science Direct (58); SciELO (7); BVS (11 MEDLINE), according to Table 1.

Table 1 - Systematization of the selection of studies that made up the sample (2020).



Source: Research data (2020).

After the selection process of the articles, 14 selected studies related to the objective of the study resulted: PubMED (13); Science Direct (1); SciELO (0); e, BVS MEDLINE (0). These being by year of publication: 2011 (1); 2014 (3); 2015 (3); 2016 (1); 2017 (2); e, 2018 (3) (Table 2).

As observed in other studies, the most studied drugs for the symptomatic relief of COPD were used for this review, which are those intended for the treatment of moderate and severe stages of the disease, that is, SABA, LABA, SAMA, LAMA, ICS and iPDE4 (Fernandes *et al*., 2017). Most studies have shown that these drugs, alone or in combination, are effective in relieving COPD symptoms (Menezes *et al.*, 2011). Therefore, these classes were considered for investigating adverse effects and checking for the presence of urinary symptoms caused by these drugs.

Table 2. Studies selected for review on adverse events related to medications for the treatment of COPD (2010 – 2020).

YEAR	PUBLICATION	TYPE OF STUDY	SAMPLE SIZE AND PREVALENCE	ADVERSE EVENTS
2011	Inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease: a population-based study.	Case control study	Of 565,073 individuals with COPD from the database, 9,432 men and 1,806 women developed acute urinary retention. Men using short- and long-term inhaled anticholinergic medications had a significantly higher risk of AUR compared to monotherapy users (OR, 1.84; 95% CI, 1.25-2.71) or non-users (2.69 ; 1.93-3.76).	Acute urinary retention using anticholinergics.
2014	Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study.	Double-blind, placebo randomized controlled study	1,692 patients with COPD, urinary tract infection as an adverse event of low incidence	Cough, headache, nasopharyngitis, urinary tract infection, back pain, upper respiratory tract infection, diarrhea, muscle spasms, sinusitis, dry mouth, tooth abscess, musculoskeletal pain, oropharyngeal pain, dizziness, insomnia, dyspnoea, nausea, hypertension, constipation, pain in the extremities, vomiting, fatigue, viral gastroenteritis.
	Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study.	Phase 3 study, multicentre, randomized, double-blind study	1,729 patients were included in the safety analysis set	COPD exacerbation, headache, nasopharyngitis, back pain, diarrhea, nausea, upper abdominal pain, arthralgia, respiratory tract infection, hypertension, sinusitis, rhinitis, oropharyngeal pain.
	Efficacy and safety of combining olodaterol Respimat(®) and tiotropium HandiHaler(®) in patients with COPD: results of two randomized, double-blind, active-controlled studies.	Two duplicate, double-blind, randomized studies	2,267 patients were randomized and received treatment in both studies: 1,132 in ANHELTO 1 and 1,135 in ANHELTO 2	Upper respiratory tract infection, bronchitis, nasopharyngitis, flu, urinary tract infection, candidiasis, anemia, headache, dizziness, hypertension, COPD, cough, dysphonia, dyspnoea, dry mouth, diarrhea, constipation, vomiting, nausea, arthralgia, back pain, muscle spasms, chest pain.
2015	Prescription rate of medications potentially contributing to lower urinary tract symptoms and detection of adverse reactions by	Retrospective study of patients through a	5,179 patients used anticholinergic bronchodilator - tiotropium bromide, 129 presented urinary symptoms of	Lower urinary tract symptoms.

	prescription sequence symmetry analysis.	database.	the lower tract..	
	Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial.	Multicenter, randomized controlled double-blind study.	1,945 eligible participants and we randomly assigned 973 to the roflumilast group and 972 to the placebo group	COPD exacerbation, diarrhea, weight loss, nausea, nasopharyngitis, headache, pneumonia, decreased appetite, insomnia, back pain, upper abdominal pain, hypertension.
	Efficacy and safety of fluticasone furoate/vilanterol (50/25 mcg; 100/25 mcg; 200/25 mcg) in Asian patients with chronic obstructive pulmonary disease: a randomized placebo-controlled trial.	Multicenter, randomized controlled double-blind study.	643 patients studied.	Upper respiratory tract infection, nasopharyngitis, COPD, pyrexia, cough, pneumonia, hypertension, oropharyngeal pain, cardiovascular effects, local steroid effects, pneumonia, hypersensitivity, bone disorders, effect on potassium, effect on glucose, eye effects, tremor .
2016	Effect of roflumilast and inhaled corticosteroid/longacting beta2-agonist on chronic obstructive pulmonary disease exacerbations (RE(2)SPOND). A randomized clinical trial.	Randomized clinical trial, phase 4, double-blind, placebo-controlled.	2,352 participants were included in the safety and intention to treat populations (n = 1,178 roflumilast, n = 1,174 placebo), with 48 patients having urinary tract infection.	Diarrhea, decreased weight, headache, pneumonia, upper respiratory tract infection, nausea, nasopharyngitis tract infection, insomnia, flu, hypertension, back pain, decreased appetite.
2017	A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease.	Long-term, randomized, double-blind, placebo-controlled extension study	Of 1322 patients who completed the AUGMENT, 921 signed up and 780 completed the extension. Of these, there was a 4.1% - 8.8% variation in urinary tract infection.	Nasopharyngitis, urinary tract infection and upper respiratory tract infection, diarrhea, headache, cough, nausea, dizziness, back pain, hypertension, flu, anxiety.
	FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease.	Multicenter, phase III, randomized, double-blind, double-simulated, parallel group study	1,810 patients were included in the population, only 1% had urinary retention.	Nasopharyngitis, headache, upper respiratory tract infection, COPD, back pain, arthralgia, pneumonia, pharyngitis, oropharyngeal pain, dizziness, hypertension, dyspnoea, vertigo, cardiovascular effects, anticholinergic syndrome, hypersensitivity, hyperglycemia / diabetes, bone mineral density decreased, eye effects, urinary retention, asthma / bronchospasm.
2018	Long-term safety of tiotropium/olodaterol Respimat® in patients with moderate- to-very severe COPD and renal impairment in the TONADO® studies.	Phase III clinical study, 2 replicates, randomized, double-blind, parallel groups	5,162 patients were treated and 3,100 received the study drugs in commercialized doses. They discuss urinary retention, urinary tract infection and dysuria in kidney patients, but do not describe the presence of incontinence.	Olodaterol: Leg cellulitis, Bronchopneumonia, exacerbation of COPD, oral soft tissue cellulitis, chest tightness, epigastric pain. Tiotropium / olodaterol: Chest pain, upper respiratory tract infection, bronchitis, COPD exacerbation, urinary tract infection, upper respiratory tract infection, headache, dysphagia, insomnia, sweating, tremor.
	Once-daily single-inhaler triple versus dual therapy in patients with COPD.	Randomized, phase 3, randomized, double-blind, parallel	10,355 patients who underwent randomization and received experimental medication (4151 received triple therapy, 4134 received fluticasone-vilanterol	Anticholinergic syndrome, asthma or bronchospasm, cardiovascular effects, lower respiratory tract infection, pneumonia and urinary retention.

		group, multicentre clinical trial.	furoate and 2070 received umeclidinium-vilanterol). 8, 12 and 9 patients, respectively, presented urinary retention.	
	Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial.	Randomized clinical trial, of parallel groups, double-blind and simulated double, multicentric.	1,532 patients received BDP / FF / G (n = 764) or IND / GLY (n = 768). Urinary disorders, such as dysuria, are listed among adverse effects as rare events	Nasopharyngitis, headache, pneumonia, respiratory tract infection, dyspnoea, back pain, hypertension, cough, heart failure, ischemic heart disease, myocardial infarction, angina pectoris, coronary artery disease, myocardial ischemia, pneumonia, insufficiency cardiac, ischemic heart disease, myocardial infarction, atrial fibrillation, respiratory failure, lung cancer, oral candidiasis, dry mouth, cough.

Fonte: Own authorship (2020).

In this sense, Urinary Incontinence can also be an adverse effect of medications (Battaglia, 2019). To verify the hypothesis that urinary incontinence is related to COPD treatments if it has been reported in studies, the main texts and supplementary materials on COPD treatments were analyzed.

Stimulation of ß2 adrenergic receptors can produce sinus tachycardia at rest and has the potential to precipitate cardiac rhythm disorders in susceptible patients. So, the main adverse effect presented by this class of drugs is exaggerated somatic tremor, which is problematic in some elderly patients treated with higher doses of ß2 agonists, regardless of the route of administration. Although hypokalemia may occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption may be increased in resting conditions in patients with chronic heart failure, these metabolic effects decrease over time (that is, they show tachyphylaxis). Mild drops in partial oxygen pressure (PaO2) may occur after administration of SABAs and LABAs, but the clinical significance of these changes is uncertain (Gold, 2020).

Inhaled anticholinergic drugs are poorly absorbed, which limits the problematic systemic effects seen with atropine. The extensive use of this class of agents in a wide range of doses and in clinical settings has shown them to be very safe. The main side effect is the dryness of the mouth. Some patients who use ipratropium report a bitter, metallic taste. A small unexpected increase in cardiovascular events has been reported in patients with COPD regularly treated with ipratropium bromide (Gold, 2020).

In a large long-term clinical trial in patients with COPD (Tashkin et al., 2008), tiotropium added to other standard therapies had no effect on cardiovascular risk. The rate of anticholinergic side effects for drugs in this class appears to be low and generally similar. The use of solutions with a face mask for inhalation can precipitate acute glaucoma, probably as a direct result of contact between the solution and the eye (Gold, 2020).

The table of supplementary material on serious adverse events from the study on tiotropium carried out by Tashkin *et al.* (2008) cited by Battaglia *et al.* (2019), reported the item "renal and urinary disorders". However, the authors did not specify the type of "urinary disorder" and did not observe any statistically significant difference in the incidence rate of renal and urinary disorders between the tested drug (tiotropium) and the placebo group.

A study by Hashimoto *et al*. (2015) on prescriptions that potentially contribute to lower urinary tract symptoms done with 17,824 patients, identified inhaled tiotropium as the only respiratory (inhalant) drug prescribed for COPD, causing urinary tract symptoms (urinary retention). In addition, the number of patients with symptoms of the urinary tract and prescription of other respiratory drugs was less than ten. Given the large sample size of this study, it can be assumed that the probability that inhaled respiratory drugs will cause UI is quite low. Unfortunately, this study did not include oral medications for COPD.

In the case-control study carried out by Stephenson *et al.* (2011) investigated individuals with COPD being treated with inhaled anticholinergic and the risk of urinary retention. The result of this study, urinary incontinence was identified as one of the risk factors of patients who developed acute urinary retention and highlights that doctors should inform patients of the possible connection between urinary symptoms and use of inhaled respiratory medication to ensure that urinary changes (for example, incomplete urination, urinary incontinence and decreased urine flow).

Randomized (ANHELTO 1 and ANHELTO 2), double-blind, controlled studies that evaluated the efficacy and safety of the combination of olodaterol and tiotropium in patients with COPD, also investigated the incidence of adverse events, demonstrating urinary tract infection as one of them, with low incidence, but did not point out incontinence as an adverse event (Zuwallack, 2014).

Thus, the TONADO study on long-term safety of tiotropium and olodaterol in patients with moderate to very severe COPD with renal failure, showed that tiotropium is predominantly excreted by the kidneys, while olodaterol is mainly metabolized by the liver and its metabolites excreted in the stool, then the safety profile was investigated in patients with renal failure in a safety analysis, where they concluded that, of these patients, there was a low incidence of potential anticholinergic effects in general, including urinary retention, urinary tract infection and dysuria (Laforce, 2018) but it does not describe the presence of urinary incontinence.

Thus, the multicenter clinical trial that assesses the efficacy and safety of fixed dose combinations of aclidinium bromide and formoterol fumarate compared to individual components and placebo in patients with COPD, did not bring any adverse events related to urinary symptoms (Singh *et al.*, 2014).

In another randomized, double-blind, placebo-controlled study, with a long-term extension of the efficacy, safety and tolerability of fixed dose combinations of the same formulation or monotherapy in the treatment of COPD, brings urinary tract infection as an adverse event of low incidence, but also does not report the presence of urinary incontinence (D'urzo, 2017).

Regarding inhaled corticosteroids, there is a high quality of randomized clinical trials that corticosteroids are associated with a higher prevalence of oral candidacy, hoarse voice, bruising on the skin, diabetes, fractures, cataracts, mycobacterial infection (including tuberculosis) and pneumonia, however, little evidence of urinary risks. In studies of patients with moderate COPD, or ICS alone or in combination with a LABA, the risk of pneumonia was not increased, but by other factors such as smoking, age over 55, history of exacerbations or previous pneumonia (Gold, 2020).

Thus, another randomized, placebo-controlled study, which traces the efficacy and safety of the association of an inhaled corticosteroid with a long-acting ß2 agonist (LABA) (fluticasone and vilanterol furoate) in Asian patients with COPD, brought more adverse events with cardiovascular effects and pneumonia, with no urinary effects (Zheng, 2015).

However, two studies by Lipson and collaborators (2017 and 2018), both on triple combination therapy with long-acting ß2 Agonist (LABA) + Long-acting anticholinergic (LAMA) + Inhaled corticosteroids (fluticasone furoate, umeclidinium and vilanterol), reported urinary retention in <1% of patients treated with umeclidinium.

However, another study on triple therapy with beclomethasone dipropionate, formoterol fumarate and glycopyrronium reported dysuria as a serious treatment-related adverse event. This information is also included in the summary of product characteristics for each inhaled drug, in which urinary disorders, such as dysuria, are listed among adverse effects as rare events (Papi *et al*., 2018).

On the phosphodiesterase-4 inhibitor, the most frequent adverse effects are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disorders and headache. Adverse effects appear to occur early during treatment, are reversible and decrease over time with continued treatment. In controlled studies, an average unexplained weight loss of 2 kg has been observed and monitoring of weight during treatment is recommended, in addition to avoiding treatment with roflumilast in

patients with low weight. Roflumilast should also be used with caution in patients with depression according to recommendations (Gold, 2020).

In randomized clinical trials with roflumilast, Martinez *et al.,* (2015) and Martinez *et al.,* (2016), urinary incontinence has not been listed as an adverse effect related to this oral medication.

Acute urinary retention, on the other hand, is a medical emergency that can cause serious complications. Previous studies have reported that the mortality rate of elderly men with acute urinary retention is twice that of ordinary men. The total mortality of men with acute urinary problems is 9.5% in men between 45 and 54 and above 85 years of age, the retention rate of the elderly is between 45.4%. Acute urinary retention is usually related to the presence of prostate disease. However, some drugs are known to be associated with urinary retention, including antipsychotics, tricyclic antidepressants, calcium channel antagonists and anticholinergic drugs (Loke *et al*., 2013).

Urinary incontinence is a common clinical condition and its incidence increases with age and alcohol consumption. It can occur for several causes, including medication, which can cause or exacerbate urinary incontinence, the most common being: alpha-adrenergic agonists; Alpha blockers (doxazosin, tamsulosin); Angiotensin-converting enzyme inhibitors (ramipril, lisinopril); Caffeine; Cholinesterase inhibitors (donepezil, rivastigmine); Diuretics (hydrochlorothiazide, furosemide); Anticholinergic drugs; Opioids (codeine, morphine, tramadol); and, Sedatives and hypnotics, (benzodiazepines, zopiclone) (Alexander *et al*., 2015).

Studies of Silva *et al*. (2019) and Burge *et al*. (2017) point out that the chronic cough itself, secondary to COPD is a risk factor for the development of urinary incontinence. However, urinary incontinence has other risk factors that can influence such as age, sex, polymedication, drug interaction and, also, can be an adverse effect of medications (Battaglia *et al*., 2019).

In a Brazilian study on the frequency of cough in patients with COPD and urinary loss, of the 30 individuals evaluated, 11 (36.7%) indicated having urinary loss. The majority being women, overweight, aged 60 years or over (Silva *et al*., 2019).

Anticholinergic drugs are used to treat urgent urinary incontinence (or overactive bladder syndrome) and can act on smooth muscle muscarinic receptors of which there are five types: M1 to M5. Type M2 causes bladder relaxation during filling and M3 mediates bladder contraction, so the interaction between these receptors contributes to bladder hyperactivity symptoms. Therefore, revision of medications is essential, as anticholinergic medications can increase incomplete emptying of the bladder, which should be avoided (Alexander *et al*., 2015).

Chronic obstructive pulmonary disease (COPD) and urinary bladder dysfunction, such as overactive bladder syndrome, are typically seen as unrelated conditions. However, both affect hollow organs and are characterized by an imbalance between contractile and relaxing smooth muscle stimuli. In addition, the sympathetic and parasympathetic nervous systems play important roles in both cases, although sympathetic innervation can be scarce. Consequently, antagonists of muscarinic receptors and agonists of ß -adrenergic receptors are important therapeutics for both organ systems (Dale *et al.*, 2014).

A non-pharmacotherapeutic approach that we must take into account is physiotherapeutic care. A comparative study done with a group of women with COPD and others with healthy women, both with urinary incontinence, shows the result of this action, with regard to dealing with UI in patients with COPD without accusing the pharmacological treatment of such a reaction. This study highlighted the importance of this problem, especially for women, due to the fact that they are the most recurrent public with urinary incontinence, which can be caused by several factors, such as pregnancy, age and obesity (Silva *et al*., 2019).

The result of the study by Burge et al. (2017) shows that although there is a low relationship between the treatment of COPD and the triggers of urinary incontinence, specialized physical therapy intervention has reduced urinary incontinence in a

large part of the experimental public and highlights the need for immediate referral for evaluation, education and treatment in a clinic specialized in continence.

4. Final Considerations

Research discusses the need to increase pharmacovigilance studies and investigate adverse events related to the treatment of chronic respiratory diseases. In this sense, it was possible to study whether urinary incontinence and related symptoms are associated with a possible adverse event in the treatment of COPD.

In this perspective, after analyzing the studies, it can be considered that Urinary Incontinence has a low relationship with adverse effects of drugs for the treatment of Chronic Obstructive Pulmonary Disease (COPD). The pharmacological class that could be identified in this study as a low consideration for urinary incontinence is that of anticholinergic / antimuscarinic drugs. Although occasional urinary symptoms have been reported in the studies, more concrete clinical trials are needed to prove a true causal relationship. However, as urinary incontinence is not considered a life-threatening problem, it is possible that it has not been included among the adverse events to be explored.

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