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Problems related to oxygenotherapy in hospitalised adults: a systematic review

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Abstract

Objectives and methods: The objective of this study was to identify problems related to oxygen therapy in hospitalized adults in the literature. The systematic review was developed to identify problems related to oxygen therapy in hospitalised adults and classify them by means of an expert panel using the Pharmaceutical Care Network Europe, version 9.1. **Results:** Of the 2,618 articles initially identified for the systematic review, 18 met the eligibility criteria, of which five were carried out in Australia (5/18; 27.7%), and the most frequent study design was clinical trial (5/18; 27.7%). An analysis by the expert panel identified hyperoxia as the main cause of patients' problems (17/18; 94.4%), and no DRP (drug-related problem) was classified as P1.1 (no treatment effect medication, despite the correct use) or P3.2 (unclear problem or complaint: further clarification is required). Studies show that problems related to oxygen therapy are mostly associated with high doses, often caused by failures in the care process such as errors in prescriptions and failures in administration and monitoring of use. **Conclusions:** the results reinforce the need for the involvement of all members of the multidisciplinary team in the care of patients on oxygen. In addition, the role of the pharmacist in establishing protocols for use with the team, in the standardisation of the system for prescribing medicinal gases, in the validation of medical prescriptions, and in the pharmacotherapeutic follow-up can contribute to the quality and safety of the services provided by health institutions.

Keywords: oxygen inhalation therapy; drug-related problem; systematic review.

Problemas Relacionados à Oxigenoterapia em Adultos Hospitalizados: uma revisão sistemática

Resumo

Objetivos e métodos: o objetivo deste estudo foi identificar na literatura problemas relacionados à oxigenoterapia em adultos hospitalizados. Para tanto, foi desenvolvida uma revisão sistemática visando identificar problemas relacionados à oxigenoterapia em adultos internados e classificá-los por meio de um painel de especialistas utilizando a *Pharmaceutical Care Network Europe* versão 9.1. **Resultados:** dos 2.618 artigos inicialmente identificados na revisão sistemática, 18 atenderam aos critérios de elegibilidade, cinco foram realizados na Austrália (5/18; 27,7%) e o delineamento de estudo mais frequente foi ensaio clínico (5/18; 27,7%). Durante a análise do painel de especialistas foi identificado que a hiperóxia era o problema de saúde ou a causadora dos problemas dos pacientes (17/18; 94,4%), sendo que nenhum PRM foi classificado como P1.1(Nenhum efeito do tratamento medicamentoso, apesar do uso correto) ou P3.2 (Problema ou reclamação pouco claros. Maior esclarecimento necessário). Os estudos demonstram que os problemas relacionados à oxigenoterapia estão associados em sua maioria à dose alta, muitas vezes provocado por falhas no processo assistencial, como erros nas prescrições, falhas na administração e no monitoramento do uso. **Conclusão:** os resultados reforçam a necessidade do envolvimento de todos os membros da equipe multiprofissional no cuidado aos pacientes em uso de oxigênio. Ademais, a atuação do farmacêutico no estabelecimento de protocolos de uso junto à equipe, na padronização do sistema de prescrição de gases medicinais, na validação da prescrição médica e no seguimento farmacoterapêutico pode ser uma estratégia para contribuir com a qualidade e a segurança nos serviços prestados pelas instituições de saúde.

Descritores: Terapia de inalação de oxigênio; Problema relacionado ao medicamento; Revisão sistemática.

Introduction

In Brazil, medicinal gases gained recognition as medicines in 2008, allowing pharmacists to act in various capacities in relation to these inputs, respecting activities related to other professions.[1-3] Similar to other medicines, there are many risks associated with the use of medicinal gases, reinforcing the need for well-trained professionals from the production phase to monitoring for ensuring proper and safe management of these medicines in patient care.[4-9]

Medical oxygen, an important medical gas, is one of the most used therapeutic agents in clinical practice, and has applications in various diseases.[10-12] In the severe form of COVID-19, in which acute respiratory failure is the main manifestation, respiratory support with oxygen is crucial for adequate treatment.[13] Thus, supplemental oxygen delivery is necessary to ensure the maintenance of adequate tissue oxygenation and reduction of cardiopulmonary work in hypoxaemic, breathless, or haemodynamically unstable patients and those under anaesthesia.[10,14] During oxygen therapy, oxygen inhalation occurs at a higher pressure than in ambient air, allowing gas exchange and reducing the effort required to breathe.[15]

However, medical oxygen, when administered incorrectly, can be toxic and have serious consequences. Toxicity depends on factors such as the dose administered, the duration of exposure, and the sensitivity of the individual. The harmful effects of oxygen misuse include tracheobronchitis, interstitial alveolar oedema, depression of mucociliary activity, nausea, anorexia, headaches, and reabsorption atelectasis.[15,4,16] Thus, administration at high doses, in addition to potentially harming patients, harms health services and increases care costs.[4,17]

Medicinal gases, as well as other medications, can pose risks to the patient. Thus, the pharmacist is expected to be committed to performing pharmacotherapeutic monitoring and pharmacovigilance.[6] This can however be a challenge in several countries as the management processes of medicinal gases were previously totally unrelated to the activities of pharmacist, coupled with the scarcity of specialized literature on pharmacists.[18-20]

In view of the above, the objective of this study was to systematically review the literature to identify problems related to the use of medical oxygen in inhalation therapy in hospitalised adults and classify them according to the Pharmaceutical Care Network Europe method, version 9.1, which defines a drug-related problem (DRP) as an event or circumstance involving drug therapy that truly or potentially interferes with desired health outcomes, thus enabling the instrumentalization of pharmaceutical professionals in clinical practice.[21]

Methods

The first step was the development of the protocol for the systematic review of the topic, followed by the training of participating researchers. Afterward, an active search was performed in PubMed, Web of Science, Scopus, Lilacs, Scopus, Ebsco, Google academic, Cochrane, Embase, Scielo, and Open theses databases, using the English terms, "Oxygen Inhalation Therapy", "Patient Safety", "Drug-Related Side Effects and Adverse Reactions", "Treatment Adherence and Compliance," and "Hospitals" and their synonyms in various combinations, using Boolean operators (AND/OR). Searches were carried out on studies published until 6 June 2019. The terms used were defined by referring to the controlled vocabulary dictionary of the "National Library of Medicine" through the "Medical Subject Headings" (MESH). In addition to the MESH terms, other non-standard terms were used to broaden the search strategy and were selected based on the literature related to the study subject. No date limits were used in the search.

The search terms were organised according to the PICO structure (population, intervention, comparison, and outcome). Comparison (C) was omitted, as the objective was to find a series of studies that presented problems related to the use of oxygen inhalation therapy, without a comparator. Therefore, the research question was, "What drug-related problems can the use of medical oxygen for inhalation therapy cause in hospitalised adult patients?" The terms were searched in all fields of study and were not limited to the title and abstract. The complete search strategy is presented in Supplementary Table 1.

The study selection process was carried out in five stages: (1) search of the defined databases; (2) feeding the Rayyan tool, a web and mobile app for systematic reviews;[22] (3) exclusion of repeated articles; (4) analysis of titles and abstracts of all included articles; and (5) evaluation via careful reading of full texts considered relevant according to the eligibility criteria.

Studies that met the following criteria were considered eligible for inclusion: (1) studies that used oxygen inhalation therapy, (2) studies that involved hospitalised adult patients, and (3) studies that addressed problems related to medication with medical oxygen. The exclusion criteria were as follows: 1) full text unavailable; 2) abstract published in conference proceedings; 3) letter to the editor; 4) literature review; 5) integrative review; 6) scope review; 7) systematic review with or without meta-analysis; 8) overview of systematic reviews with or without meta-analysis; and 9) book chapters. However, year of publication, language, and methodological quality were not used as exclusion criteria.

The analysis of titles and abstracts, as well as the evaluation of full texts, was performed independently by two evaluators; in case of disagreement, a third evaluator was responsible for analysing, judging, and resolving the discrepancy. The analysis of the duplication of studies, with the respective exclusion, as well as the selection of titles and abstracts, was performed using the Rayyan tool. Some studies in which the Rayyan tool did not allow for data import were tabulated and analysed using an Excell® spreadsheet. The kappa coefficient of agreement was applied to assess the interobserver agreement in the evaluation of titles and abstracts, and then in the evaluation of the full text.[23]

After selecting the studies, the data from the articles included were extracted independently by two reviewers using a pre-formatted Microsoft® Excel® spreadsheet. The data extracted were as follows: country in which the study was conducted, study design, sample size, devices used in inhalation therapy, evaluated outcomes, evaluation method, and study limitations. Excerpts from the studies that presented the health problems and the probable DRPs were also extracted and submitted to a panel of experts. Any discrepancies in the data extraction were resolved through consensus. Then, the data was submitted to the expert panel to identify health problems, classify DRPs, and identify possible causes according to the PCNE, version 9.1 (2020) classification.

In parallel, the methodological quality of the included studies was assessed by two independent evaluators, and a third evaluator was responsible for resolving disagreements. The evaluation was carried out using critical assessment tools for systematic reviews proposed by the JBI (checklist for analytical cross-sectional studies, checklist for case reports, checklist for cohort studies, checklist for

quasi-experimental studies, and checklist for randomised controlled trials).[24] In addition, all references from the included studies were evaluated.

After extracting data from the articles, an expert panel was formed to assess and classify medical oxygen-related problems and their causes, according to the PCNE classification. The expert panel was previously defined based on the scoring criteria adapted from Fehring. [25] The invited professionals agreed to participate in the study and responded to an instrument to characterize them.

The panel consisted of five pharmacists with expertise in pharmaceutical care, an individual with a *lato sensu* specialisation, a master, two doctoral students, and a doctor. All participants had more than five years of experience after graduation. The panel's work was mediated by a guest researcher, a doctor with a degree in pharmacy and expertise in pharmaceutical care. The main researcher of the study, present in all the rounds, acted as a consultant. An informed consent form was signed during the first round of discussions. The study was approved by the Research Ethics Committee of the Federal University of Sergipe under the number, CAAE: 22984119.9.0000.5546) under protocol number 3,709,534.

The meeting with the experts was structured as follows: first, the participants were introduced to the topic and the spreadsheet with the extracted data from the studies, which was structured to facilitate the classification of the identified DRPs and their causes. The PCNE basic classification has three primary domains for problems, which are subdivided into seven subdomains, and nine for causes, which are subdivided into 43 subdomains (Supplementary Tables 2 and 3).

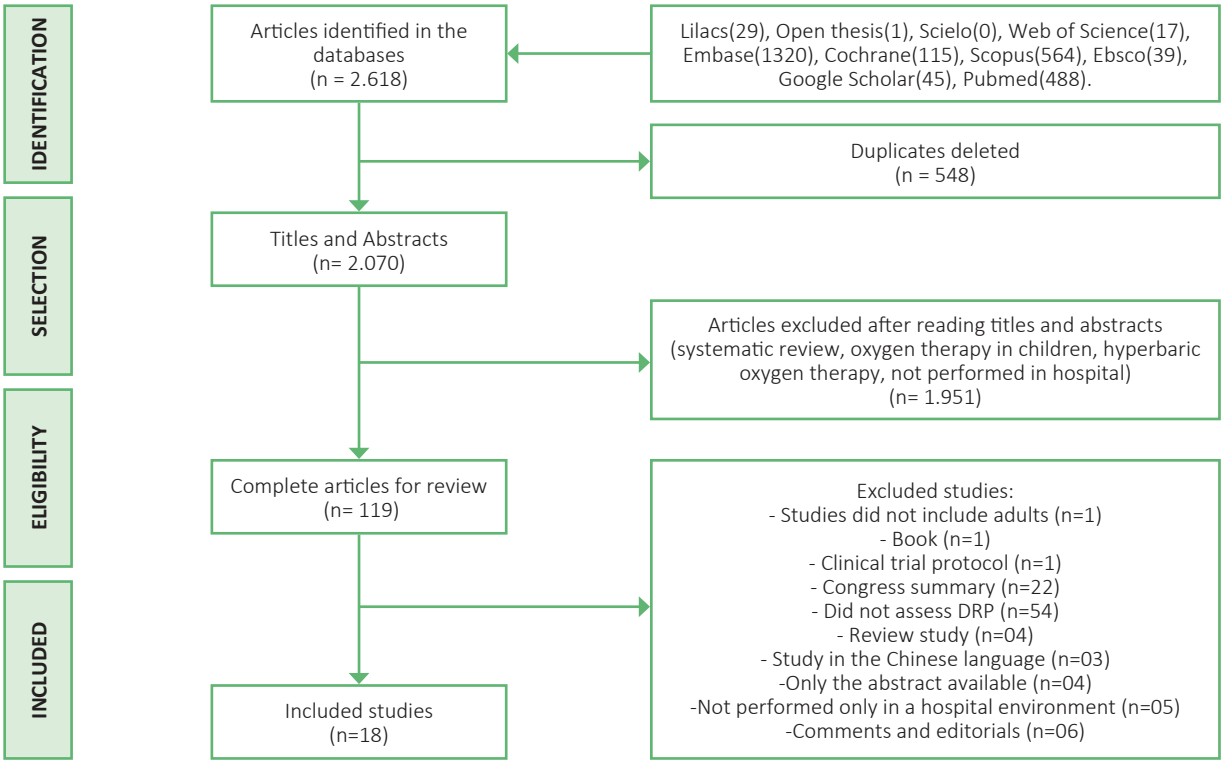
The dynamics of the rounds was as follows: (1) the mediator asked the main researcher to proceed by reading the excerpts of the studies that contained the possible health problem, the possible DRP, and the possible causes. These excerpts were present in the data extraction worksheet that had been made available to all participants along with the PDF file of all studies; (2) the mediator opened the discussion, respecting the order of registration, for each participant to give their opinion; (3) discussion of each item was only concluded after reaching a consensus; (4) the mediator filled in the Microsoft Excel® spreadsheet used to tabulate all the data. Furthermore, the study was conducted using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and the assessment of the methodological quality of systematic reviews (AMSTAR 2).[26,27]

Results

Selection of Studies

The literature search identified 2,618 studies, of which 548 were excluded after analysing duplicates, and 1,951 were excluded after reading the titles and abstracts. At the end of this step, the kappa coefficient of agreement was applied to assess the inter-observer agreement, yielding a value of 0.68 (substantial agreement) and an overall agreement percentage of 84.02%. Further, of the 119 studies selected for full text reading, 18 met the inclusion criteria (Albin *et al*[28], Aakerlund *et al*[29], Kuisma *et al*[30], Gunathilake *et al*[31], Elmer *et al*[32], Jones *et al*[33]; Herren *et al*[34], Kamran *et al*[5], Khoshnood *et al*[35], Lagan *et al*[36], Lazić *et al*[37], Managó *et al*[38], Nehme *et al*[39], Pancioli *et al*[40], Stub *et al*[41], Susanto *et al*[42], Girardis *et al*[43] and Rioseco *et al*[44]). The kappa test was applied again and it showed moderate agreement (0.55) and an overall agreement percentage of 77.31%. Figure 1 illustrates the study selection process.

Figure 1. Flow diagram of identification of studies



Characteristics of the studies

The articles were published between 1992 and 2018, with 83.3% (15/18) published in English. These studies were conducted in America, Europe, and Oceania. Five studies were conducted in Australia (Gunathilake *et al*[31], Kamran *et al*[5], Nehme *et al*[39], Stub *et al*[41] and Susanto *et al*[42]). The number of participants ranged from 1 to 638 (Herren *et al*[34] and Nehme *et al*[39]). Regarding the methodological design of the included studies, six were randomised clinical trials (Girardis *et al*[43], Kuisma *et al*[30], Stub *et al*[41], Jones *et al*[33], Khoshnood *et al*[35] and Nehme *et al*[39]), six were cross-sectional studies (Albin *et al*[28], Pancioli *et al*[40], Susanto *et al*[42], Kamran *et al*[5], Lazić *et al*[37]and Rioseco *et al*[44]), two were cohort studies (Elmer *et al*[32] and Aakerlund *et al*[29]), three were quasi-experimental studies (Gunathilake *et al*[31], Lagan *et al*[36] and Managó *et al*[38]) and one was a case report (Herren *et al*[34]). The methodological designs were not discussed in four of the studies, necessitating discussions among researchers to define the classification of the design and to enable the assessment of methodological quality (Aakerlund *et al*[29], Lagan *et al*[36], Managó *et al*[38], Rioseco *et al*[44]).

In all the studies, the pharmacist was not cited as a professional participant in the process of care-taking for patients using oxygen, except in that by Rioseco *et al* [44] in which the authors cited the pharmacist, Carl Wilhelm Scheele, a Swedish-German pharmaceutical chemist who in 1773 had discovered "fire gas," a gas capable of increasing combustion. Credit for the discovery of oxygen is given to English chemist, Joseph Priestley. It was discovered in 1774 with the name, dephlogisticated air and, later, the French chemist, Antoine Lavoisier, gave it the name, oxygen.[45]

As for the devices used for oxygen administration, the studies contemplated the most diverse possible, including mechanical ventilation (Elmer *et al*[32], Girardis *et al*[43] and Rioseco *et al*[44]), mask with non-rebreathing reservoir or Hudson (Aakerlund *et al*[29], Gunathilake *et al*[31], Herren *et al*[34], Kuisma *et al*[30], Lagan *et al*[36], Susanto *et al*[42] and RIOSECO *et al*[44]), face mask (simple) (Albin *et al*[28], Nehme *et al*[39] and Stub *et al*[41]), nasal catheter (cannula) (Aakerlund *et al*[29], Gunathilake *et al*[31], Herren *et al*[34], KUISMA *et al*[30], LAZIĆ *et al*[37], STUB *et al*[41], SUSANTO *et al*[42] and RIOSECO *et al*[44]), venturi mask (GUNATHILAKE *et al*[31], MANAGÓ *et al*[38] and RIOSECO *et al*[44]), high-flow nasal cannula (JONES *et al*[33]), Oxymask® (KHOSHNOOD *et al*[35]), and binasal tube (nasal catheter type glasses) (LAZIĆ *et al*[37]). None of the studies had the term "drug-related problem" or DRP in their text. The characteristics of the included studies are summarised in Table 1.

Table 1. Characteristics of the studies included in the systematic review (Continued)

nº	Reference	Country	Design	Sample size	Average age of participants (years)	Device used in inhalation therapy	Evaluated outcomes	Evaluation methods	Limitation of studies
1	Aakerlund *et al.*(1994)	Denmark	*	24	68 (29-84)	Hudson mask Nasal catheter (internal tube diameter 8 mm)	Delirium	Pulse oximetry Postoperative delirium was assessed using confusion assessment method (CAM) and DSM-III-R diagnostic criteria.	Not described
2	Albin *et al.*(1992)	USA	Cross-sectional	274	Not described	Face mask	Oxygen Saturation	Pulse oximetry	Not described
3	Elmer *et al.* (2015)	USA	Cohorte	170	60 (54-66)	Mechanical ventilation	Decreased survival Neurological damage	Measure of PaO_2, Fi, and PaO_2:Fi. SOFA scale (cardiopulmonary dysfunction). FiO_2 AUC .(pulse oximetry and arterial gasometry)	Use of a single hyperoxemia marker (PaO2) without taking into account the underlying physiological dysfunction; No evaluations were carried out in subsequent time points.
4	Gunathilake *et al.* (2014)	Australia	Prospective pre- and post-intervention audit.	82 (pre- intervention) 77 (post- intervention)	72,7 ± 14,7 (pre- intervention) 73,6 ±12,4 (post-intervention)	Nasal cannula Hudson mask Venturi mask	Hypercapnia Respiratory failure Saturation above target	Pulse oximetry	Short time of study
5	Herren *et al.*(2017)	Switzerland	Case report	1	72	Non-rebreathing mask with an oxygen reservoir bag attached Nasal cannula	Respiratory acidosis	Arterial gasometry Capnography	Not described

Table 1. Characteristics of the studies included in the systematic review (Continued)

nº	Reference	Country	Design	Sample size	Average age of participants (years)	Device used in inhalation therapy	Evaluated outcomes	Evaluation methods	Limitation of studies
6	Jones *et al*. (2016)	New Zealand	Clinical trial	303	74,6 +/- 15,6 (intervention) e 72,216,8 (control)	HFNC (Humidified high-flow nasal cannula) Hudson mask Venturi mask Nasal prongs	Need to switch to non-invasive or invasive ventilation Mortality Pneumothorax Subcutaneous emphysema Apnea	Glasgow Coma Score by CO_2 Accumulation (Quiz)	With the write-offs (exclusions) it was not possible to reach the sample initially planned.
7	Kamran *et al*. (2018)	Australia	Cross-sectional	65	69 +/- 19	Various devices	Adequate saturation for the clinical situation	Gasometry Analysis of medical records	Retrospective data collection with lapses in annotations and consequent data loss
8	Khoshnood *et al*. (2018)	Sweden	Clinical trial	95	64	Oxymask ™ (high-flow Oxygen)	Myocardial salvage index Size of the infarction.	Cardiac magnetic resonance Troponin	Involved only two hospitals Several patients were lost because they did not perform the resonance.
9	Kuisma *et al*.(2006)	Finland	Randomized clinical trial	28	63	Hudson mask Nasal catheter	Serum levels of NSE and S-100 (markers of neuronal injury) 30 min, 24h and 48h after ROSC (return to spontaneous circulation)	Arterial gasometry Dosage of S-100 and NSE Monitoring with pulse oximetry	Did not assess post-discharge survival This is considered a preliminary or pilot study.
10	Lagan *et al*. (2013)	England	*	100 (2010) 100 (2012) 105 (2013)	61±16 57±20 52±20	High flow oxygen therapy (Mask with reservoir)	Target saturation	Pulse oximetry Arterial gasometry	Unable to involve paramedics in the educational program
11	Lazić *et al*. (2008)	Serbia	Uncontrolled analytical study	93	60,8±9	Nasal cannula Nasopharyngeal catheter	Increase in PCO_2	Arterial gasometry	Not described
12	Managó *et al*. (2011)	Argentina	*	223 (phase 1) 251 (phase 2)	65,70 ± 2,45 (phase 1) .67,70 ± 2,86 (phase 2)	Campbel mask with Venturi system	Economic Compliance with the clinical protocol Functional Independence	Pulse oximetry	Not described
13	Nehme *et al*. (2016)	Australia	Descriptive analysis of data from a multicentre, prospective, randomised, controlled trial	638	62,7 ± 12,3	Face mask	Increased myocardial injury Time of hospitalization.	Laboratory measurement of Ck and troponin I	It was a descriptive analysis of a clinical trial The trial did not blind the professionals who treated with oxygen The Fi of O_2 and PaO_2 was not recorded.

Table 1. Characteristics of the studies included in the systematic review (Continued)

nº	Reference	Country	Design	Sample size	Average age of participants (years)	Device used in inhalation therapy	Evaluated outcomes	Evaluation methods	Limitation of studies
14	Pancioli *et al*. (2002)	USA	Retrospective study	167	61	Not described	Days of unnecessary oxygen use Cost	Analysis of medical records based on criteria proposed in the literature.	As this is a retrospective study of data, some criteria for oxygen use in the medical records may have been missing and the cost measurement may have failed.
15	Stub *et al*. (2015)	Australia	Clinical trial (multicentric)	441	63.0± 11.9 (intervention) 62.6±13.0 (control)	Face mask Nasal cannula	Primary: size of myocardial infarction Secondary: recurrent myocardial infarction, cardiac arrhythmia and myocardial infarction size assessed by cardiac magnetic resonance at 6 months.	Laboratory measurement of troponin I (cTnI) and CK (creatine kinase).	Treatment allocation was not blinded to paramedics, patients and medical staff
16	Susanto *et al*.(2015)	Australia	Retrospective audit	150	75 +/- 8,7	Hudson mask Nasal cannula	Hypercapnia and its complications	Pulse oximetry Arterial gasometry	retrospective study small sample Some data missing.
17	Girardis *et al*.(2016)	Italy	Randomized clinical trial	434	63 (51-74) conservative therapy; 65 (52-76) conventional therapy	Mechanical ventilation	Primary: ICU mortality Secondary: hospital mortality, failure in another organ during the ICU stay, new infection during the ICU stay, surgical re-approach, hours free from mechanical ventilation, length of stay in the ICU and length of hospital stay.	Quis Laboratory measurement of creatinine and bilirubin Gasometry.	Open-label single center study Small sample
18	Rioseco *et al*. (2017)	Chile	*	381	62,2 (20-100)	Nasal prong Mechanical ventilation Mask with reservoir Venturi mask	Compliance with clinical protocol	Analysis of medical records Pulse oximetry Arterial gasometry	Small number of participating patients

Abbreviations: USA- United States of America; Fi – Inspired fraction; CPAP- Continuous Positive Airway Pressure; NIV – Non-invasive ventilation; AUC – Area under the curve; PaO2 – Partial Pressure of Oxygen.

Classification of Drug-Related Problem

After four rounds of discussion, the experts completed the identification of actual and potential health problems, the classification of DRPs identified in the studies, and analysis of their causes. Among the problems proposed by the PCNE classification, two were not identified in the studies included in this review, P1.1 (no effect of drug treatment, despite correct use) which is related to the "effectiveness" domain, and P3.2 [problem or unclear complaint (o). Further clarification is required (should only be used as an escape)] which is related to the "others" domain, as shown in Table 2.

Table 2. Characteristics of patients, health problems and drug-related problems and their causes in the studies included in the systematic review (Continued)

Patient characteristics, health problems, DRPs and their causes						
nº	**Author**	**Clinical characteristics of the patients studied and/or care failures identified.**	**Health problem (HP)**	**Potential health problems - PHP**	**DRP**	**Causes**
1	Aakerlund, L.P. *et al*. ,1994	Postoperative patients receiving low-dose oxygen had delirium (assessed by CAM or confusion assessment method). At the time of diagnosis of delirium, patients were not using the devices or treatment had not been instituted. All patients received routine postoperative care, except oxygen therapy.	Postoperative delirium associated with hypoxemia	_	P1.2	C9.1
2	Albin, R.J., *et al*., 1992	Clinical and surgical patients using oxygen On the first assessment day more than 50% of patients were not using their oxygen delivery devices.	HP1 (hypoxemia SaO2<92)	_	P1.2	C3.1
		There was monitoring of the treatment, but the change in the flow in the prescription or chart was not verified. Failed monitoring of oxygen usage.	HP2 (hypoxemia SaO2<92)	_	P1.2	C9.1
		Prescribing excessive oxygen concentrations. Prescription of oxygen without clinical need.	_	PHP1 (hyperoxia)	P2.1	C3.2
		Arbitrary use of oxygen outside the ICU. Low doses prescribed keeping patients hypoxemic. Low patient compliance. Physicians were slow to change the administered dose after information on the titration results.	_	PSP2 (hyperoxia)	P3.1	C1.2
3	Elmer, J. *et al*., 2015	Patients with cardiac arrest assessed using the SOFA score (validated measure of organ dysfunction) and assessed using the PCAC (clinical prediction tool that stratifies post-arrest patients by risk of subsequent death or neurological deterioration based on clinical characteristics during the first 6 h after the return of spontaneous circulation or ROSC).	HP1 (Baseline cardiopulmonary dysfunction in the first 24 hours)	_	P2.1	C3.2
			HP2 (Neurological dysfunction)	_	P2.1	C3.2
		They were also evaluated by PaO2 and its relationship with FiO2. Greater oxygen exposure in the initial 24 hours was strongly associated with the presence of baseline cardiopulmonary dysfunction, but not associated with deterioration in lung compliance or gas exchange in the first 48 h after the return of spontaneous circulation. Despite the absence of an association with change in lung function, higher levels of inhaled oxygen were independently associated with decreased survival and worsening neurologic outcomes. At extreme levels, high oxygen exposure was associated with decreased survival to discharge, likely related to worsening neurological damage. The study suggests avoiding prolonged exposure to a FiO2 > 0.75 in the initial post-initial stop period.	HP2 (Neurological dysfunction)	_	P2.1	C3.2
4	Girardis, M. *et al*., 2016	Patients in a medical-surgical intensive care unit. Patients were randomly assigned to receive oxygen therapy to maintain PaO2 between 70 and 100mmHg or arterial oxyhemoglobin saturation (SpO2) between 94% and 98% (conservative group) Others to receive treatment as per standard ICU practice (allow PaO2 values to rise to 150mmHg or SpO2 values between 97% and 100% (conventional control group). Despite suggestions of potential harm from unnecessary oxygen therapy, critically ill patients spend substantial periods in a hyperoxemic state.	HP01 (Hyperoxia)	_	P2.1	C3.2

Table 2. Characteristics of patients, health problems and drug-related problems and their causes in the studies included in the systematic review (Continued)

Patient characteristics, health problems, DRPs and their causes						
nº	**Author**	**Clinical characteristics of the patients studied and/or care failures identified.**	**Health problem (HP)**	**Potential health problems - PHP**	**DRP**	**Causes**
5	Gunathilake, R. *et al*., 2014	Clinical and surgical patients on oxygen due to cardiorespiratory arrest, heart failure, pulmonary infection and pulmonary vascular disease. Patients with respiratory conditions that predispose to hypercapnia and who were receiving oxygen therapy were having oxygen saturation above the recommended target (SpO2 88-92%) at the time of the audit. According to the study, inadequate oxygen administration can result in serious damage and therefore oxygen must be prescribed specifying target saturation, device and initial flow rate as a minimum standard for patient safety.	_	PHP1 (Respiratory hypercapnia)	P2.1	C3.2/ C3.5 / C9.2
6	Herren, T. *et al*, 2017	72-year-old Caucasian male with severe chronic obstructive pulmonary disease. Admitted for worsening dyspnea and an oxygen saturation of 81% as measured by pulse oximetry. The study highlights that anti-rebreathing masks (with oxygen reservoir bags) should be used with caution, by experienced medical personnel, and with an appropriately high oxygen flow of 10-15 L/minute. It also highlights that arterial blood gases should be analyzed regularly for the early detection of an increase in the partial pressure of carbon dioxide in arterial blood in patients with chronic obstructive pulmonary disease and hypoxia. It is noteworthy that these patients are most safely managed using a nasal cannula with an oxygen flow of 1–2L/minute or using a simple face mask with an oxygen flow of 5L/minute.	HP01 (Carbon dioxide narcosis)	_	P2.1	C9.2
7	Jones, P. *et al*, 2016	Adult subjects with hypoxia and tachypnea. HFNC has not been shown to reduce the need for mechanical ventilation in the emergency department for individuals with acute respiratory distress compared with standard therapy (although it is safe and may reduce the need for intensified oxygen therapy within the first 24 hours of admission). Some patients had dry mouth and nose.	HP01 (Secura na boca e nariz)	_	P2.1	C9.3
8	Kamran, A. *et al*., 2018	Patients seen in the emergency department of a hospital and in a clinical ward. Patients using oxygen with failures throughout the process. Continued treatment without proper reassessment. Wrongly prescribed target range. Lack of documentation of oxygen weaning. Medical record filled out incorrectly. Lack of saturation result before starting oxygen use. No prescription. High and low doses prescribed promoting risk of toxicity and hypoxia.	_	PHP01 (hypoxia) PHP02 (Hyperoxia)	P1.2 P2.1	C3.1/ C3.5/ C9.1 C3.2/ C3.5/ C42 / C9.1
9	Khoshnood, A. *et al*., 2018	Using cardiac magnetic resonance (CMR), the study evaluated the effects of supplemental O2 in patients ST-segment elevation myocardial infarction (STEMI) accepted for acute treatment percutaneous coronary intervention - PCI. No effect of high-flow oxygen compared to room air on ischemia size prior to PCI, myocardial salvage, or the size of the resulting infarction. Supplemental O2 was given only to patients with Saturation up to 90%. Results support the safety of withholding supplemental oxygen in normoxic and stable STEMI patients. Empirical evidence is now accumulating in support of current recommendations that patients with suspected acute coronary syndrome should only receive supplemental O2 if hypoxia is present, dyspnea or signs of heart failure.	_	PHP01 (Hyperoxia)	P3.1	C1.2

Table 2. Characteristics of patients, health problems and drug-related problems and their causes in the studies included in the systematic review (Continued)

Patient characteristics, health problems, DRPs and their causes						
nº	**Author**	**Clinical characteristics of the patients studied and/or care failures identified.**	**Health problem (HP)**	**Potential health problems - PHP**	**DRP**	**Causes**
12	Lazić, Z. *et al*., 2008	Patients with severe chronic respiratory failure (CRF) undergoing oxygen therapy were analyzed.	HP01 (hypercapnia)	_	P2.1	C3.2
		Risks that must be taken into account during this therapy are: unpredictable increase in carbon dioxide in the blood, carbonarcosis, respiratory acidosis and coma.	_	PHP01 (Carbonarcosis)	P2.1	C3.2
		The effect of oxygenation was controlled by measuring PaO2 and PaCO2 in arterial blood samples.	_	PHP02 (Respiratory acidosis)	P2.1	C3.2
		Most of the patients studied (89.4%) had chronic obstructive pulmonary disease (COPD).	_	PHP03 (Coma)	P2.1	C3.2
		Looking at the group of subjects as a whole, the application of oxygen led to an increase in PaO2, but also to an increase in PaCO2.				
		Controlled oxygen therapy in patients with severe respiratory failure greatly reduces the risk of an undesired increase in PaCO2, but does not completely exclude it.				
13	Managó, M.J. *et al*., 2011	The study evaluated patients after cardiac surgery, CHF, pneumonia, stroke, AMI, acute pulmonary edema, liver transplantation and others.	_	PHP01 (Hypoxia)	P1.3	C6.4
		The days of oxygen therapy use in the period before the study days they averaged 4.1 and in the period when a protocol was used the average was 2.7.	_	PHP02 (Hypoxia)	P1.2	C6.2
		The application of oxygen therapy has the same demands as surveillance of any other medication.	_	PHP03 (Hyperoxia)	P2.1	C4.2/ C6.3
		It was found that 87.39% showed inadequate application.				
		59.50% of patients were using oxygen as needed.				
		40.50% of the patients were not receiving oxygen despite having a medical indication.				
		At the first moment of the study, 87.39% of the evaluations, the flow of oxygen administered did not match the FIO2 defined in some patients.				
		The study showed that among patients who were using a Campbell mask (venturi) 18.55% were using the correct flow of oxygen, 44.50% had a flow greater than that indicated by the manufacturer's technical specifications and 36, 95% received a flow lower than these specifications.				
14	Nehme, Z. *et al*., 2016	The study evaluated patients with myocardial infarction after follow-up ST elevation (STEMI).	HP01 (Increased myocardial injury)	_	P2.1	C3.3/ C4.2
		Every 100 L of oxygen exposure was associated with 1.4% (95% CI, p<0.001) and 1.2% (95% CI, p<0.001) increase in mean peak cTnI (troponin) and CK (creatine kinase), respectively.				
		Our results suggest that incremental exposure to supplemental oxygen in the first 12 h after STEMI is associated with a significant increase in myocardial injury.				
		These observations suggest that increases in myocardial injury relative to oxygen exposure are cumulative over the duration of treatment, and not necessarily related to the administration of oxygen at reperfusion.				
		Supplemental oxygen therapy may increase myocardial damage after ST-elevation infarction (STEMI).				
15	Pancioli, A.M. *et al*., 2002	The study evaluated patients with ischemic stroke on supplemental oxygen (who were not intubated).	_	PHP01 (Hyperoxia)	P3.1	C1.5
		Using a literature-based list of criteria for the use of supplemental oxygen, only 45.6% of days of oxygen use were justified in our ischemic stroke population.	_	PHP02 (Hypoxia)	P1.3	C1.2
		This study demonstrates that oxygen therapy is commonly given to ischemic stroke patients with no clear indication, and opportunities exist for substantial resource conservation.				
		When more than half of all oxygen use cannot be considered clinically justified by a set of comprehensive and inclusive criteria, there is significant hope for a potential decrease in oxygen use and the resources involved for these patients.				

Table 2. Characteristics of patients, health problems and drug-related problems and their causes in the studies included in the systematic review (Concluded)

Patient characteristics, health problems, DRPs and their causes						
nº	**Author**	**Clinical characteristics of the patients studied and/or care failures identified.**	**Health problem (HP)**	**Potential health problems - PHP**	**DRP**	**Causes**
16	Rioseco, S. *et al*., 2017	The study evaluated inpatients on oxygen. Most hospitalized with respiratory system problems or with cardiovascular disease. A fixed dose was indicated in 75% of cases and 50% had an oximetry value as a target. Patients were identified in O2 treatments that was not indicated at all, or in use of suboptimal or supraoptimal doses due to lack of control or adequate registration. 100% of patients in the emergency ward were receiving a different dose than indicated in their records. The indication for O2 administration was given by a physician by 88.5%. 3.8% of patients were using it but did not have any records in their medical records or prescriptions.	HP01 (Hyperoxia)	_	P2.1	C3.2/ C3.5/ C5.2/ C9.1
			_	PHP02 (Hypoxia)	P1.2	C3.1/ C3.5/ C5.2/ C9.1
17	Stub, D. *et al*, 2015	The study evaluated patients with ST-segment elevation myocardial infarction. Oxygen therapy in these patients was associated with a larger myocardial infarction size assessed at 6 months. There was an increase in the rate of recurrence of myocardial infarction in the oxygen group compared to the no oxygen group (5.5% versus 0.9%; P = 0.006) and an increase in cardiac arrhythmia frequency. Oxygen is commonly given to patients with ST-segment elevation myocardial infarction, despite studies that suggest a possible increase in myocardial injury as a result of coronary vasoconstriction and increased oxidative stress.	HP01 (Increased cardiac arrhythmia)	_	P3.1	C1.2
			HP02 (Increased recurrence of infarction)	_	P3.1	C1.2
			HP03 (Increased myocardial injury)	_	P3.1	C1.2
18	Susanto, C. *et al*., 2015	The study evaluated patients with chronic obstructive pulmonary disease. Administration of oxygen is a common medical intervention for emergency management of COPD exacerbations. High flow oxygen is often given. Based on current guidelines, most patients did not require initial oxygen supplementation as the mean oxygen saturation was ≥88%, or could have been managed with a lower FiO2. This study showed that a diagnosis of COPD was not necessarily appreciated as being a relative contraindication to high flow oxygen supplementation. Non-invasive ventilation was required in 53 patients. Seven patients were admitted to the intensive care unit and 10 patients died. Hypercapnia was seen in 71 patients. The lack of recognition of a pre-existing diagnosis of COPD may be responsible for the high number of episodes of uncontrolled oxygen administration. Current recommendations suggest an inspired oxygen level (FiO2) <0.28, aiming at saturation (SpO2) of 88–92% until arterial blood gas is available.	HP01 (Hypercapnia)	_	P2.1	C3.2
			HP01 (Hypercapnia)	_	P3.1	C1.2

Table 3 presents the problems identified in this review, classified according to the PCNE, version 9.1. Table 4 presents the causes or possible causes of the real and potential problems identified in the studies examined in this review, according to PCNE, version 9.1.

A tabela 4 apresenta as causas ou possíveis causas dos problemas reais e potenciais identificados nos estudos desta revisão de acordo com o PCNE versão 9.1.

Quality Assessment

Based on the methodological analysis, two studies met the criteria for the instruments proposed by the JBI Systematic Reviews. Six articles (6/7) met between 76.92% and 100% of the checklist criteria for randomized clinical trials (GIRARDIS *et al*[43], KUISMA *et al*[30], STUB *et al*[41], JONES *et al*[33], KHOSHNOOD *et al*[35] and NEHME *et al*[39]), four articles (4/6) met 87.5% of the checklist criteria for cross-

sectional studies (PANCIOLI *et al*[40], SUSANTO *et al*[42], RIOSECO *et al*[44], KAMRAN *et al*[5]), two articles (2/3) met 77.77% of the checklist criteria for quasi-experimental studies (GUNATHILAKE *et al*[31] and MANAGÓ *et al*[38]), two articles (2/2) met 90.90% of the checklist criteria for cohort studies (AAKERLUND[29] and ELMER *et al*[32]) and one article (1/1) met 100% of checklist criteria for case studies (HERREN *et al*[34]). Tables 5, 6, 7, 8, and 9 show this assessment.

Table 3. DRPs identified in the studies of this review according to the PCNE classification V9.1.

DRP		N(%)
P1 Treatment effectiveness	P1.2 Effect of drug treatment not optimal	7 (17,95)
	P1.3 Untreated symptoms or indication	2 (5,13)
P2 Treatment safety	P2.1 Adverse drug event (possibly) occurring	23 (58,97)
P3 Others	P3.1 Unnecessary drug-treatment	7(17,95)

Table 4. Causes of DRPs identified in the studies in this review according to the PCNE Classification V9.1.

Causes			N(%)
Prescribing & drug selection	1 Drug selection	C1.1 Inappropriate drug according to guidelines/formulary	1(1,61)
		C1.2 No indication for drug	7(11,29)
		C1.5 No or incomplete drug treatment in spite of existing indication	1(1,61)
	3 Dose selection	C3.1 Drug dose too low	5(8,06)
		C3.2 Drug dose of a single active ingredient too high	14(22,58)
		C3.3 Dosage regimen not frequent enough	1(1,61)
		C3.5 Dose timing instructions wrong, unclear or missing	7(11,29)
	4 Treatment duration	C4.2 Duration of treatment too long	3(4,84)
Dispensing	5 Dispensing	C5.2 Necessary information not provided or incorrect advice provided	4(6,45)
Use	6 Drug use process	C6.2 Drug under-administered by a health professional	1(1,61)
		C6.3 Drug over-administered by a health professional	1(1,61)
		C6.4 Drug not administered at all by a health professional	1(1,61)
Other	9 Other	C9.1 No or inappropriate outcome monitoring (incl. TDM)	10(16,13)
		C9.2 Other cause; specify (administration device)	5(8,06)
		C9.3 No obvious cause	1(1,61)

Table 5. Quality assessment tool for Randomized Controlled Trials by the tool "JBI Critical Appraisal Checklist for Randomized Controlled Trials".

Criteria	Kuisma *et al*., 2006	Stub *et al*., 2015	Girardis *et al*., 2016	Jones *et al*., 2016	Nehme *et al*., 2016	Khoshnood *et al*., 2018
1. Was true randomization used for assignment of participants to treatment groups?	Y	Y	Y	Y	Y	Y
2. Was allocation to treatment groups concealed?	Y	Y	Y	Y	Y	Y
3. Were treatment groups similar at the baseline?	Y	Y	Y	Y	Y	Y
4. Were participants blind to treatment assignment?	Y	N	Y	N	N	Y
5. Were those delivering treatment blind to treatment assignment?	N	N	N	N	N	Y
6. Were outcomes assessors blind to treatment assignment?	U	Y	U	Y	N	Y
7. Were treatment groups treated identically other than the intervention of interest?	Y	Y	Y	Y	Y	Y
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y	Y	Y	Y	Y	Y
9. Were participants analyzed in the groups to which they were randomized?	Y	Y	Y	Y	Y	Y
10. Were outcomes measured in the same way for treatment groups?	Y	Y	Y	Y	Y	Y
11. Were outcomes measured in a reliable way?	N	Y	Y	Y	Y	Y
12. Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y	Y	Y	Y	Y	Y

Legend: Y: yes, N: no and U: unclear

Table 6. Quality assessment tool for cross sectional study by the tool "JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies".

Criteria	Albin *et al.*, 1992	Pancioli *et al.*, 2002	Lazić *et al.*, 2008	Susanto *et al.*, 2015	Rioseco *et al.*, 2017	Kamran *et al.*, 2018
1. Were the criteria for inclusion in the sample clearly defined?	Y	Y	N	Y	Y	Y
2. Were the study subjects and the setting described in detail?	N	Y	N	Y	Y	Y
3. Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y
5. Were confounding factors identified?	N	N	N	N	N	N
6. Were strategies to deal with confounding factors stated?	N/A	N/A	N/A	N/A	N/A	N/A
7. Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y
8. Was appropriate statistical analysis used?	N	Y	N	Y	Y	Y

Legend: Y: yes, N: no and N/A: not applicable.

Table 7. Quality assessment tool for cohort study by the tool "JBI Critical Appraisal Checklist for Cohort Studies".

Criteria	Aakerlund, 1994	Elmer *et al.*, 2015
1. Were the two groups similar and recruited from the same population?	Y	Y
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Y	Y
3. Was the exposure measured in a valid and reliable way?	Y	Y
4. Were confounding factors identified?	Y	Y
5. Were strategies to deal with confounding factors stated?	Y	Y
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Y	Y
7. Were the outcomes measured in a valid and reliable way?	Y	Y
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Y	Y
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Y	Y
10. Were strategies to address incomplete follow uputilized?	N	N
11. Was appropriate statistical analysis used?	Y	Y

Legend: Y: yes and N: no.

Table 8. Quality assessment tool for quasi-experimental study by the tool "JBI Critical Appraisal Checklist for Quasi-Experimental Studies".

Criteria	Gunathilake *et al.*, 2014	Lagan *et al.*, 2013	Managó *et al.*, 2011
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Y	Y	Y
2. Were the participants included in any comparisons similar?	Y	Y	Y
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	N	N	N
4. Was there a control group?	N	N	N
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Y	Y	Y
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y	Y	Y
7. Were the outcomes of participants included in any comparisons measured in the same way?	Y	Y	Y
8. Were outcomes measured in a reliable way?	Y	N	Y
9. Was appropriate statistical analysis used?	Y	N	Y

Legend: Y: yes and N: no.

Table 9. Quality assessment tool for Case Report study by the tool "JBI Critical Appraisal Checklist for Case Reports".

Criteria	Herren *et al.*, 2017
2. Was the patient's history clearly described and presented as a timeline?	Y
1. Were patient's demographic characteristics clearly described?	Y
3. Was the current clinical condition of the patient on presentation clearly described?	Y
4. Were diagnostic tests or assessment methods and the results clearly described?	Y
5. Was the intervention(s) or treatment procedure(s) clearly described?	Y
6. Was the post-intervention clinical condition clearly described?	Y
7. Were adverse events (harms) or unanticipated events identified and described?	Y
8. Does the case report provide takeaway lessons?	Y

Legend: Y: yes and N: no.

Discussion

The studies by Albin *et al*[28], Gunathilake *et al*[31], Lagan *et al*[36], Managó *et al*[38], Rioseco *et al*[44], Pancioli *et al*[40], and Kamran *et al*[5] evaluated compliance with clinical protocols for the use of oxygen, from the real need of patients to receive this therapy to the prescription and monitoring of use. The results were similar across all studies. Patients receiving oxygen without clinical justification, without medical prescription, with incomplete medical prescriptions, without proper monitoring, and consequent titration or dose adjustment were identified. These situations promoted both hyperoxia and hyperoxemia, as well as hypoxia and hypoxaemia, in addition to the potential increase in care costs.

These situations were observed by Masa *et al*[46] who carried out a clinical trial and highlighted the increase in care costs following the incorrect use of oxygen in hospitals. The study by Pancioli *et al*[40] also reiterates this occurrence, in which they demonstrated that oxygen therapy is commonly administered to patients with ischaemic stroke without a clear indication; thus, there are opportunities for the substantial conservation of the resources of the health system.

The aforementioned studies on the use of oxygen in hospitals exhibited flaws in the documentation of work processes associated with oxygen therapy. The literature shows that clinical documentation is an integral part of the health professionals' work and that adequate record keeping is essential for patient care, whether for consultations or effective communication within the multiprofessional team, and to ensure the quality of care-services provided.[47-49] Thus, correct documentation is considered a criterion in health service quality assessments by accreditation institutions.[47-51]

The World Health Organization (WHO) guidelines that are followed by several countries highlight the importance of complete medical prescriptions for the safety of the patient.[52,53] Similarly, the prescription of oxygen should follow the same direction and contain much information to ensure the proper use of this technology, as recommended by clinical protocols, such as the British Thoracic Society guidelines[54] and the Guideline for Acute Oxygen Therapy for Western Australian Hospitals[55]. However, the studies in this review showed that this fact is not yet a reality in the institutions evaluated. Gunathilake *et al*[31], Lagan *et al*[36], and Managó *et al*[38] showed that by following actions to standardise prescriptions and by implementing educational activities for the multidisciplinary team, it was possible to significantly improve the numbers related to compliance with current protocols.

The situations identified in these studies (such as incomplete prescriptions) can cause medication errors. These can be defined as any preventable event that can harm the patient or lead to inappropriate medication use. These events may be related to professional practices, procedures, or care in health systems.[56] Medication error detection helps to develop effective practices that ensure the proper and rational use of medications, such as medicinal gases, thus increasing patient safety.[56]

The services developed at hospital pharmacies are essential for the structuring and implementation of activities related to patient safety.[57] Many adverse events resulting from medication errors can be avoided through implementation of pharmaceutical clinical services.[58,59] These services have promoted actions that improve clinical and economic outcomes[60-62], minimise medication errors, and prevent and/or solve problems related to medications, thereby improving pharmacotherapy outcomes and lowering treatment costs.[63-65] However, no study has reported the active participation of pharmacists in the care of patients using oxygen or in the management of medicinal gases, which reinforces the need to equip them, train them, and encourage the inclusion of these professionals in this area. Notably, in Brazil, and precisely in the Empresa Brasileira de Serviços Hospitalares, the participation of pharmacists is becoming a reality, which can be proven by the publication of regulations for this purpose, which mention that the involvement of this professional is mandatory.[66]

According to Holsbach[67] errors occur in approximately 30% of hospitalised patients. These errors can be due to several reasons; however, among them, errors in medication administration are the most common.[68] Studies have shown that problems in the use of oxygen can occur at any stage of the procedure (from prescription to monitoring), making the entire multidisciplinary team responsible. In view of the understanding and regulation of oxygen as a medicine, these errors reported in the literature may be important and even more representative, as they should include data from medical gas DRPs along with other medicines.[31,36,38,44,40,5]

The identification of DRPs is the first step in preventing harm to patients in relation to their treatment plan[69], enabling reduction in medication errors, adverse reactions, and hospitalisation time.[70] In addition, it is important to develop and implement a protocol for the use of oxygen in each institution, standardise an adequate and safe prescription model, and propose educational interventions that can improve the entire process associated with oxygen therapy. This will guarantee the provision of a service of higher quality, with greater safety for patients, thus optimising therapy and reducing unnecessary care costs.[6,31,36,38]

Of the six possible problems contained in the PCNE classification, only four were identified in the evaluated studies, with the most frequent problem related to the safety and effectiveness of the treatment. The study by Nascimento *et al*[71], who evaluated DRPs through the PCNE classification in neonatal ICUs has been corroborated by other studies. Although the study evaluated treatment with drugs in "traditional" dosage forms, the most frequent problems were related to effectiveness and safety. These errors are considered avoidable; however, if not prevented, they can result in harm to the patient and increase the costs of health services.[72] In the hospital setting, the incidence of DRPs is high in different patient populations, especially in the elderly[73] and children[74], as well as in patients with certain clinical conditions, such as surgical patients[75], and those with heart disease[76] and neurological problems[77].

Among the studies in this review, the most common causes of DRPs were absence of monitoring or inadequate monitoring of results, inadequate instructions at time of use, wrong, confusing or absent dosages, a very high dose of a single active ingredient drug, and medication without indication. Data similar were presented in the study by TASAKA *et al*[78], who claimed that the high occurrence of DRPs is associated with failure to implement the established therapeutic plans, care processes, and care goals, and negatively impacts the patient's quality of life and causes economic and social losses.

Medical oxygen has been in use in accelerated respiratory therapy since the end of the First World War, after the publication of "The therapeutic administration of oxygen" in 1917.[79] The regulation of medicinal gases began in France in 1992.[80] The concept of

drug-related problems has been introduced into clinical practice since 1998 under the name Therapy-Related Problems by Cipolle *et al*[81], and in 1999, the Pharmaceutical Care Network Europe[21] (PCNE) introduced the term, PRM, that is currently being used.[82] However, no study in this review cites this term or any synonym, such as pharmacotherapeutic failure, which was proposed by FernandezLlimos[83]. This fact reinforces the need to adopt oxygen as a medication in clinical practice and in specialised literature, and not only in legislation.

In addition to the studies that evaluated the work process in hospitals, this review presents studies that evaluated the use of this medication in patients with specific clinical conditions. Aakerlund *et al*.[29] identified hypoxaemia that consequently led to delirium in postoperative patients receiving low doses of oxygen, confirming the findings of the study by QU *et al*.[75], who showed that surgical patients are likely to have MRPs. Elmer *et al*.[32] studied patients who suffered cardiorespiratory arrest and demonstrated that, despite the absence of an association with a change in lung function, higher levels of inhaled oxygen were independently associated with decreased survival and worsening of neurological outcomes. Girardis *et al*. [43] performed a clinical trial comparing conventional therapy with conservative therapy and showed that the former subjected critically ill patients to spending substantial periods in a hyperoxemic state, despite suggestions of potential harm from unnecessary oxygen therapy. Both studies highlighted the risk of damage from hyperoxemia for patients, not being restricted to the lungs.

Herren *et al*.[34] evaluated the case of a 72-year-old man with severe chronic obstructive pulmonary disease and concluded that management is safer using low-volume nasal cannulas, otherwise, these patients may experience increased partial pressure of carbon dioxide in the arterial blood. Susanto *et al*.[42] evaluated chronic cases of obstructive pulmonary disease and demonstrated that oxygen administration is a common medical intervention for emergency treatment of COPD exacerbations and that high-flow oxygen is often administered. Also, based on current guidelines, most patients did not need the oxygen supplementation offered, as the mean oxygen saturation was ≥88%, or the condition could have been managed at a lower fraction of inspired oxygen (FiO_2). The study further showed that the diagnosis of COPD was not necessarily appreciated as a relative contraindication to high-flow supplemental oxygen, despite the risk of hypercapnia.

The study by Abdo *et al*.[84] highlighted that oxygen therapy titrated to reach saturations of 88% to 92% is recommended in patients with an acute exacerbation of COPD to avoid hypoxaemia. Furthermore, Ahmadi *et al*.[85] highlighted that both hypocapnia and hypercapnia were associated with mortality in patients with oxygen-dependent COPD. Therefore, it is clear that there are clinical situations in which oxygen is routinely administered. However, the care team should initially assess the patient's real need to receive this treatment or to receive it with the adjusted dose while being properly monitored.

Lazić *et al*.[37] studied patients with severe chronic respiratory failure (CRF) and concluded that controlled oxygen therapy in these patients greatly reduces the risk of unwanted increases in the partial pressure of carbon dioxide ($PaCO_2$), but does not completely exclude it. This increase in carbon dioxide in the blood can promote carbonarcosis, respiratory acidosis, and coma. According to the study by Abdo *et al*.[84], patients with more severe hypoxaemia are more susceptible to oxygen-induced hypercapnia. This finding reinforces the need for adjustments in work processes with an emphasis on monitoring.

In parallel, Jones. *et al*[33] demonstrated that the use of high-flow oxygen through nasal cannulas (HFNC or CAFN) has not been shown to reduce the need for mechanical ventilation in individuals with acute respiratory distress compared with standard O_2, although it is safe and may reduce the need for intensification. Of oxygen therapy within the first 24 h of admission, but in contrast, patients may experience dryness in the mouth and nose. Although patients experience this MRP (dryness) while using CAFN, the study by Masclans *et al*[86] showed that this device is less associated with oral dryness compared to a venturi mask and was found to be more comfortable than face masks. Therefore, professionals should be alert to mitigate these problems to ensure the adherence of patients to treatment.

Khoshnood *et al*[35] provided evidence and reiterated current recommendations that patients with acute coronary syndrome should only receive supplemental O_2 if they have hypoxia, dyspnea, or signs of heart failure, and are yet to find any effect of high-flow oxygen compared to room air on the size of ischemia before percutaneous coronary intervention, myocardial salvage, or the size of the resulting infarction. Nehme *et al*.[39] studied patients with myocardial injury after ST-segment elevation infarction (STEMI), and their results suggest that incremental oxygen exposure in the first 12 h after STEMI is associated with a significant increase in myocardial injury. Stub *et al*[41] pointed out that oxygen administered to patients with ST-segment elevation myocardial infarction without hypoxia may increase early myocardial injury, and is associated with a larger myocardial infarction size assessed at six months. The study also demonstrated an increase in the rate of myocardial infarction recurrence in the oxygen group compared to the no-oxygen group and an increase in the frequency of cardiac arrhythmia. The results of these studies reinforce that one of the most important criteria for deciding on the use of oxygen therapy is hypoxaemia, whether in patients with infarction or with any other clinical condition.

Kuisma *et al*[30] compared the effects of 30% and 100% inspired oxygen concentrations on blood oxygenation and the levels of serum markers of neuronal injury during the early post-resuscitation period. Marker values did not differ significantly between groups, but when analysing subgroups, the results supported the hypothesis that 100% oxygen can worsen neuronal injury during the early post-resuscitation period; however, it appears that harmful effects are only seen in normothermic individuals. Therefore, therapeutic hypothermia would be protective for these patients.

According to a systematic review performed by Villablanca *et al*[88], the main benefit of using therapeutic hypothermia was the reduction of infarct size in patients with anterior wall myocardial infarction. Therefore, this intervention, in addition to reducing the size of the infarction, reduced the risk of neuronal damage in these patients. However, despite this protection, everything can be avoided if the amount of oxygen administered is what the patient needs.

Regarding the quality assessment of the included studies, only two articles fully met the criteria proposed by the JBI (Khoshnood *et al*[35], Herren *et al*[34]), and only three met less than 70% of the criteria (Lazić *et al*[37], Albin *et al*[28], Lagan *et al*[36]). This indicates that most studies showed good robustness in their methodology, as adherence to the items of these methodological quality assessment instruments can determine the extent to which a study addressed the possibility of bias in its design, conduct, and analysis.[24]

Only two studies carried out in South America were included in this review, and none was from Brazil (MANAGÓ *et al*[38], RIOSECO *et al*[44]). Brazil approved medicinal gases as medicines in 2008, being one of the South American countries that proceeded with this regulation at a later stage, which may explain the absence of Brazilian studies in this systematic review.

This study has several strengths and limitations. To the best of our knowledge, this is the first systematic review on problems related to oxygen use in hospitalised adult patients. This review has the potential to contribute to changes in clinical practice and to provide greater safety to these patients. The selection of the year of publication, study design, and methodological quality was not limited. Furthermore, the OpenTheses database included a search for grey literature. The exclusive use of English terms may have resulted in the omission of important publications in different languages; however, this is a common limitation of review articles. Furthermore, the restriction of databases and the search strategy may have excluded important studies that were not published in the sources used.

Conclusion

The study shows that DRPs are very frequent in hospitalised patients using oxygen, with problems related to the effectiveness and safety of the treatment predominating, mainly as a result of the inappropriate process of use. In view of the fact that none of the studies in this review cited the pharmacist as an integral part of the team responsible for this care process for the maintenance of life, the various DRPs related to oxygen therapy that this review presented, the global movement for the promotion of patient safety, the evidence of the clinical, economic and humanistic benefits that the clinical performance of the pharmacist has presented for years, the regulation of oxygen and other medicinal gases as medicine on all continents, and by the evidence presented by the most diverse studies, old or current, that the process of using oxygen has a large number of flaws, it is imperative that this therapy receives greater attention, leading to the inclusion of the pharmacist in the process. There is still a need for the establishment of protocols for a multiprofessional team, the standardization of medical gas prescription system, validation of medical prescription, and pharmacotherapeutic follow-up of patients using oxygen. It is also important that institutions standardize their work processes and carry out the appropriate educational activities with the multiprofessional team in order to guarantee services of better quality, making the drug therapy optimized, safer, and economically viable. Therefore, those involved should ensure that the prescriptions include the initial flow, the device to be used, and the target saturation. Additionally, the pharmaceutical professional should actively participate in the process of monitoring the use, thereby contributing to the prevention or mitigation of DRPs.

There is need for further research to measure the impact of clinical interventions by pharmacists in oxygen therapy. That future studies should evaluate DRPs in the use of oxygen in other age groups. That evaluations be Carry out before and after of medical records and oxygen prescriptions in institutions that need interventions with subsequently evaluate the change in the scenario.

Declaration of conflict of interests

The authors declare that there are no conflicts of interest regarding this article.

Collaborators

FJRA; VAC; ROSS; IMCB; LMA; DPL; TSA: project design and data analysis and interpretation. VAC; ROSS: Search for studies in databases. FJRA; VAC; TSA: data extraction. FJRA; KSSR; IMCB: quality assessment. GASJ: mediation of the expert panel. GASJ; KSSR; FVNS; SMS; ATC; JBN; LMA: analysis and interpretation of data and revision of the final text. FJRA; VAC; ROSS; DPL; TSA: article writing and final revision.

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