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Pharmacological and non-pharmacological treatment of delirium in an oncological hospital service: an integrative review

Tratamento farmacológico e não farmacológico do delirium em serviço hospitalar de oncologia: revisão integrativa

Tratamiento farmacológico y no farmacológico del delirium en servicio hospitalario de oncología: revisión integrativa

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ABSTRACT

Objectives: to analyze the production of scientific articles about the pharmacological and non-pharmacological management of delirium in adult hospitalized cancer patients. **Methods:** integrative review whose sample was obtained from the databases Scopus, Cumulative Index to Nursing and Allied Health Literature, EMBASE, Web of Science, and from the portals *Biblioteca Virtual em Saúde*, and PubMed. **Results:** among the ten studies analyzed, 80% described exclusively the pharmacological management, especially with regard to the use of haloperidol; 20% mentioned, superficially, non-pharmacological interventions/actions (educational actions) associated to pharmacological management, and adjusting them could result in the diminution and control of psychomotor agitation, contributing for the safety and comfort of the patient. **Conclusions:** there are few studies addressing pharmacological and non-pharmacological interventions/actions to manage *delirium*. As a result, it is essential to develop studies focused on increasing and advancing scientific knowledge with regard to the theme, especially in the national context.

Descriptors: Medical Oncology; Oncology Service, Hospital; Delirium; Drug Therapy; Patient Care Team.

RESUMO

Objetivos: analisar a produção de artigos científicos sobre o manejo farmacológico e não farmacológico do *delirium* em pacientes oncológicos adultos hospitalizados. **Métodos:** revisão integrativa cuja amostra foi obtida nas bases de dados Scopus, *The Cumulative Index to Nursing and Allied Health Literature*, EMBASE, *Web of Science* e nos portais Biblioteca Virtual em Saúde e PubMed. **Resultados:** dentre os dez estudos analisados, 80% descreveram exclusivamente o manejo farmacológico, predominando o uso do fármaco haloperidol; 20% citaram, superficialmente, intervenções/ações não farmacológicas (ações educativas) associadas ao manejo farmacológico cuja adequação poderia resultar em redução e controle da agitação psicomotora, contribuindo para segurança e conforto do paciente. **Conclusões:** há escassez de estudos abordando intervenções/ações de manejo farmacológico e não farmacológico do *delirium*. Torna-se imprescindível o desenvolvimento de estudos com foco na ampliação e progressão do conhecimento científico relacionado à temática em questão, notadamente no contexto nacional.

Descritores: Oncologia; Serviço Hospitalar de Oncologia; Delírio; Tratamento Farmacológico; Equipe de Assistência ao Paciente.

RESUMEN

Objetivos: analizar la producción de artículos científicos sobre el manejo farmacológico y no farmacológico del *delirium* en pacientes oncológicos adultos hospitalizados. **Métodos:** revisión integrativa cuya muestra ha sido obtenida en las bases de datos Scopus, *The Cumulative Index to Nursing and Allied Health Literature*, EMBASE, *Web of Science* y en los portales Biblioteca Virtual en Salud y PubMed. **Resultados:** entre los diez estudios analizados, 80% describieron exclusivamente el manejo farmacológico, predominando el uso del fármaco haloperidol; 20% citaron, superficialmente, intervenciones/acciones no farmacológicas (acciones educativas) relacionadas al manejo farmacológico cuya adecuación podría resultar en reducción y control de la agitación psicomotora, contribuyendo para seguridad y comodidad del paciente. **Conclusiones:** hay escasez de estudios abordando intervenciones/acciones de manejo farmacológico y no farmacológico del *delirium*. Se vuelve imprescindible el desarrollo de estudios con enfoque en la ampliación y progresión del conocimiento científico relacionado a la temática en cuestión, especialmente en el contexto nacional.

Descriptores: Oncología; Servicio Hospitalario de Oncología; Delirio; Tratamiento Farmacológico; Equipo de Asistencia al Paciente.

INTRODUCTION

According to the International Agency for Research on Cancer (IARC), from the World Health Organization (WHO), there were, throughout the world, 17 new million new cases of cancer, with a total of 9.42 million deaths in 2018[1]. The Brazilian national cancer institute, known as the Instituto Nacional do Câncer José Alencar Gomes da Silva (INCA) estimates that, for each year from 2020 to 2022, 625 thousand new cases of cancer will take place (450 thousand, if nonmelanoma skin cancer cases are excluded). Nonmelanoma skin cancer will be the most incident (177 thousand), followed by breast and prostate cancers (66 thousand cases each), colon and rectum cancer (41 thousand), lung cancer (30 thousand), and stomach cancer (21 thousand)[2].

Most oncology patients, when in advanced stages, present with multiple symptoms, both physical and psychological, which produce a significant decline in their quality of life. These patients show an incredible diversity of symptoms related to the gravity and to the complications resulting from the progression of the disease and of antineoplastic therapies. Acute changes in cognitive functions, especially delirium, are prognostic of imminent death in oncology patients[3].

Delirium is an acute cognitive change, characterized by dysfunctions in awareness, attention, space awareness, memory, thought, perception, and behavior[4]. It is classified as hyperactive (disquiet, agitation, emotional lability), hypoactive (apathy and diminution in the capacity to respond), or mixed state (alternating between hypoactive and hyperactive), and can affect more than 50% of hospitalized adults[5].

The incidence of delirium increases with age, the presence of cognitive deficits, the severity of the disease, and comorbidities. However, despite common, this condition is underdiagnosed in health organizations; authors have stated that the incidence of this syndrome in intensive care units (ICUs) varies from 5% to 92%[6]. A study have suggested that the incidence of these cases in patients with cancer is high, and can reach 80% in more advanced stages of the disease, being related to a worst control of pain and to a diminution of survival rates[7]. In cancer patients, many studies reported associations between delirium, hospital mortality, and post-discharge mortality; in the last months of life, there is an association between its hypoactive and mixed subtypes and a lower survival rate[8].

The treatment and the outcomes of the delirium can substantially differ, depending on the trajectory of the disease (initial stage, advanced stage, or active process of death). Reverting this issue is associated to surviving longer: patients who undergo surgeries are normally considered to have better prognostics and survival rates (from months to years). This disease is transitory, reversible, and its treatment does not last long. In patients where it is advanced, whose survival rate varies from weeks to months, it is possible to reverse it through a treatment of the clinical conditions and symptom control; in patients in the final stage of their lives, whose survival rate is measured in hours or days, this condition is often irreversible[9].

The patient under delirium can feel anxious, threatened, and present themselves as aggressive, leading to significant suffering for themselves and their relatives, especially during episodes of agitation and hallucination, when communication is difficult. Caring for a patient in this stage can also bring suffering for the health team: a study carried out with nurses in Japan showed that nurses can feel preoccupied about how to evaluate and care for patients in this condition, needing to improve their knowledge about this[8].

One should be attentive to the professional impact due to the provision of care to patients with cancer, so that early interventions can be carried out to avoid fatigue due to compassion and wearing out[10]. Regarding the risks in assistance, delirium increases the length of hospitalizations and complications during them (falls, pressure lesions, infections), as well as hospital and post-discharge death rates[11].

Recognizing this abnormality and treating it early, through pharmacological and non-pharmacological actions, is essential to reach outcomes that are favorable for the patient, the family, and the multiprofessional team, provoking a diminution of hospital costs.

Non-pharmacological interventions, targeted at delirium risk factors, have been recommended to prevent and manage the condition by many directives of the clinical practice, including guidance for the care of patients who are hospitalized, who live in long-permanence institutions, in hospices, and in palliative care units. However, the efficiency and cost-effectiveness of these non-pharmacological strategies, such as simple and multicomponent interventions for the prevention and treatment of adult cancer patients, are not clear. The use of pharmacological interventions in the management of delirium in adults should be limited to patients with perception disorders, or to those who represent danger to their own safety or to others. To reach an appropriate balance between potential benefits and potential harm, the medication should be used in the lowest efficient dosage and for a short time[8].

According to the findings of the clinical practice of the authors of this study, who work in a public hospital specialized in teaching, research, and in the humanized treatment of adult cancer patients, delirium has been verified in patients with an advanced stage of cancer, and is associated to high death rates and to an increase in hospital costs. Therefore, this integrative review was carried out considering that this complication demands an adequate management to guarantee the best results for the patients and for the health institution.

OBJECTIVES

To analyze the production of scientific articles about the pharmacological and non-pharmacological management of delirium in adult hospitalized cancer patients.

METHODS

This is an integrative review, a method that offers a summary of the knowledge and incorporates the applicability of outcomes of significant practical studies[12]. It was conducted according to the following guiding question: "What are the interventions/actions shown in literature for the pharmacological and non-pharmacological management of delirium in adult hospitalized cancer patients?".

The strategy used was the PICO, an acronym that includes Population, Intervention, Comparison, and Outcome[13]. The terms used were those related to the letters P - cancer patients hospitalized with delirium; I - interventions/actions conducted; C - there was no intervention for comparison; and O - delirium management.

To guarantee that the review would be carried out rigorously, the research was conducted in the following stages[13]: the objective was determined; criteria of inclusion and exclusion were established (sample selection); the information to be extracted from the articles selected was determined; outcomes were analyzed; and then outcomes were presented and discussed.

To select the articles, all databases that would allow an expansion of the scope of the research were used[14]. As a result, searches were carried out from April 16 to April 22, 2019, in the databases Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, and Web of Science; also, researches were carried out in the portal of the *Biblioteca Virtual em Saúde* (BVS), which includes 14 databases of bibliographic data in health sciences, among which were consulted the *Literatura Latino-americana e do Caribe em Ciências da Saúde* (LILACS) and the *Base de Dados de Enfermagem* (BEDENF). The portal PubMed, which includes MEDLINE - Medical Literature Analysis and Retrieval System Online was also searched.

The following inclusion criteria were defined: primary articles published in Portuguese, English, and Spanish, with texts available in full, in the databases and platforms mentioned above, from 2014 to 2019, whose methodology showed interventions for the pharmacological and non-pharmacological management of delirium in adult clinical patients with solid tumors. Were excluded: articles that described interventions in pediatric and surgical cancer patients and in those with onco-hematological disease.

The descriptors and keywords used were: delirium AND Neoplasms OR Oncology OR Cancer, *Neoplasias* AND *Câncer*, *Delirio* AND *Cáncer* OR *Neoplasia* OR *Oncología*. The qualifiers "prevention" and "control", "drug therapy" and "therapy", were active. The searches were carried out independently by two researchers, and the consensus was reached through an application of the inclusion and exclusion criteria. The search strategies adopted are exemplified below:

Terms: delirium/th, Neoplasms/CO

Portal BVS=*tw:((instance:"regional") AND (mh:("Delírio/DT" OR "Delírio/PC" OR "Delírio/TH" AND "Neoplasias"))) AND (instance:"regional") AND (year cluster:("2015" OR "2014" OR "2016" OR "2017"))*=8

Portal PubMed=("delirium/drug therapy"[Mesh] OR "delirium/prevention and control"[Mesh] OR "delirium/therapy"[Mesh]) AND ("Neoplasms"[Mesh] OR "Neoplasms"[tw]) AND ("2014/04/18"[PDat]: "2019/04/16"[PDat] AND "humans"[MeSH Terms] AND (English[lang] OR Portuguese[lang] OR Spanish[lang]) AND ("adult"[MeSH Terms] OR "adult"[MeSH Terms:noexp] OR "aged"[MeSH Terms] OR ("middle aged"[MeSH Terms] OR "aged"[MeSH Terms]) OR "middle aged"[MeSH Terms]))=37

The time frame selected was of five years (2014-2019) so that the most up-to-date articles about the theme of the study would be selected.

The search found a sample of ten articles, as Figure 1 shows:

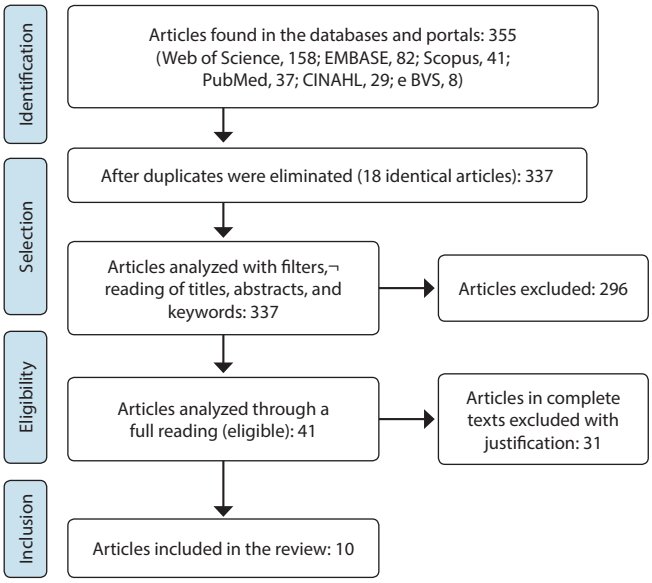

Figure 1 - Flowchart of the identification, selection, eligibility, and inclusion of the studies, according to the PRISMA recommendations[15], São Paulo, S**ão** Paulo, Brazil, 2019

In summary, the search strategies found 355 articles. During the selection process, 18 duplicate articles (identical ones) were excluded, as well as 296 that were not in accordance to the inclusion criteria after abstract, title, and keywords were read (first stage). The reading of the complete text of the 41 eligible articles (second stage) led to the exclusion of 31 (due to the fact that they were studies about: patients with chronic non-oncological diseases; pain management and evaluation; surgical patients of non-oncological diseases; management of dyspnea, anorexia, fatigue, and constipation; pediatric patients), and 10 articles were left.

The data collection of the articles[16-25] included in the integrative review was made possible by an instrument that contained: identification, characteristics of the study and evaluation of the methodological rigor[12].

To analyze the summary of these articles, synoptic frameworks were used[13]: one of them containing title, author, year, name of the journal; and another with the type of research, management/sample, summary of the outcomes and of conclusions/limitations.

RESULTS

This integrative review found a sample of ten articles[16-25], which were in accordance to the inclusion criteria. All of them took place in hospitals, four of which were in the United States, three in Japan, one in Saudi Arabia, one in England, and one in Switzerland.

Summary Chart 1 shows that they were published in several journals: the American Journal of Hospice & Palliative Medicine (one), Cancer Research And Treatment (one), the German Journal of Psychiatry (one), the Journal Pain Symptom Management (one), JAMA (one), the Journal of Pain & Palliative Care Pharmacotherapy (one), the Journal of Palliative Medicine (one), Palliative and Supportive Care (one) and The Oncologist (two); regarding their publication date, it stands out that four articles were published in 2015.

Chart 1 - Characterization of the ten primary articles included in the integrative review according to their coding/title, journal/year, authors, and place of research, São Paulo, São Paulo, Brazil, 2019

Coding/Title	Journal/Year	Authors	Place of research
A1 - Delirium management in patients with cancer: dosing of antipsychotics in the delirium subtypes and response to psychopharmacological management[16]	German Journal of Psychiatry / 2014	Boettger S, Jenewein J, Breitbart W.	EMBASE
A2 - Delirium in palliative care: detection, documentation and management in three settings[17]	Palliative and Supportive Care / 2015	Hey J, Hosker C, Ward J, et al.	CINAHL
A 3 - The frequency, characteristics, and outcomes among cancer patients with delirium admitted to an acute palliative care unit[18]	The Oncologist / 2015	Cruz M, Ransing V, Yennu S, et al.	PubMed
A 4 - Frequency and outcome of neuroleptic rotation in the management of delirium in patients with advanced cancer[19]	Cancer Research and Treatment / 2015	Shin SH, Hui D, Chisholm G, et al.	EMBASE
A 5 - Using neuroleptics to treat delirium in dying cancer patients at a cancer center in Saudi Arabia[20]	Journal of Pain & Palliative Care Pharmacotherapy / 2015	Al-Shahri MZ, Sroor MY, Ghareeb WA, et al.	PubMed
A 6 - Novel therapeutic strategies for delirium in patients with cancer: a preliminary study[21]	American Journal of Hospice & Palliative Medicine / 2016	Tanimukai H, Tsujimoto H, Matsuda Y, et al.	PubMed
A 7 - *Effect of lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: a randomized clinical trial*[22]	JAMA / 2017	Hui D, Frisbee-Hume S, Wilson A, et al.	Web of Science
A8 - Factors associated with the effectiveness of intravenous administration of chlorpromazine for delirium in patients with terminal cancer[23]	Journal of Palliative Medicine / 2018	Okuyama T, Yoshiuchi K, Ogawa A, et al.	EMBASE
A 9 - Off-label medication use in the inpatient palliative care unit[24]	Journal Pain Symptom Management / 2018	Kwon JH, Kim MJ, Bruera S, et al.	EMBASE
A 10 - Current pharmacotherapy does not improve severity of hypoactive delirium in patients with advanced cancer: pharmacological audit study of safety and efficacy in real world (Phase-R)[25]	The Oncologist / 2019	Okuyama T, Yoshiuchi K, Ogawa A, et al.	EMBASE

Chart 2 - Presentation of the ten studies coded according to type/level of evidence, management/sample, summary of the outcomes, conclusions, and limitations, related to the period from 2014 to 2019, São Paulo, São Paulo, Brazil, 2019

Type of study/ Level of evidence	Management/Sample	Outcomes	Conclusions	Limitations
A1 - Retrospective and observational study[16] / Level of evidence 4	Pharmacological management of hypoactive and hyperactive delirium/111 patients in a Cancer Hospital attended in the Psychiatric Unit (49 patients with hypoactive delirium and 62 with hyperactive delirium).	Doses from four different antipsychotic drugs were used to treat delirium; considering hyperactive delirium as compared to hypoactive delirium, haloperidol was prescribed four times more, olanzapine and risperidone twice as much; while the dose of aripiprazole was the same for both.	Patients with hyperactive delirium needed bigger doses for the control of their condition.	The antipsychotic pharmacological management was not selected randomly but based on the preferences of the physicians responsible for the treatment. The criteria for the choice of the medications were not made clear.
A2 - Observational and retrospective study[17] / Level of evidence 3	Pharmacological management of delirium, compared between one hospital and two hospices/319 records: 166 patients in a hospital and 153 in the hospices.	In the hospices, the records of management had a median of 69.4%. Midazolam was the most used medication (up to 66.7% of prescriptions), followed by a combination of midazolam and haloperidol (up to 26.6% of prescriptions), and haloperidol (up to 20% of prescriptions).	The diagnosis of delirium was registered in 8.4% of records; in the others, there were descriptions of signs and symptoms of delirium. In 56.3% of the hospital records, there was a description of the pharmacological management, but the medications used were not listed.	Patients were not classified according to the type of delirium. The drugs used in the hospital unit were not described.
A3 - Retrospective and observational study[18] / Level of evidence 3	Pharmacological and non-pharmacological management of mixed, hypoactive, and hyperactive delirium/552 patients in a Hospital Unit for Acute Palliative Care, classified as having mixed state (45%), hypoactive (30%), and hyperactive (25%) delirium.	Haloperidol was used in 66% of cases, followed by chlorpromazine in 3% of cases, and for an association of olanzapine and lorazepam in 31% of patients. Actions were carried out to educate the family about delirium, about the presence of a caregiver with the patient, minimal stimulations and interventions from the nursing team, and techniques and guidance for non-pharmacological management.	Haloperidol was the most used drug for the management of all types of delirium; the non-pharmacological management included educational actions.	The doses of the drugs used were not described. The authors mentioned non-pharmacological management actions but did not make clear what was the techniques used for advice.

To be continued

Chart 2 (concluded)

Type of study/ Level of evidence	Management/Sample	Outcomes	Conclusions	Limitations
A4 - Retrospective and observational study[19] / Level of evidence 3	Pharmacological management delirium/167 patients in a Hospital Unit for Acute Palliative Care, classified as having mixed state and hyperactive (53%), and hypoactive (47%) delirium.	77% of the patients used, exclusively, haloperidol in starting doses of 5 mg; in 23% of cases, it was necessary to introduce a second neuroleptic drug, suspending the haloperidol, due to either failure in the treatment or adverse effects. A second neuroleptic drug was used in association with the previous haloperidol regime adopted in only 15% of patients.	Haloperidol was the most used drug to deal with delirium; in 77% of cases, there was no need to change for another neuroleptic drug.	This study did not evaluate separately the efficiency of the treatment for patients with mixed state and hyperactive delirium
A5 - Retrospective and observational study[20] / Level of evidence 3	Pharmacological management of delirium/271 records of patients in a Palliative Care Hospital Unit.	Patients were treated with drugs that were prescribed periodically with standardized inte4rvals: 89.3% haloperidol; 2.4% Levomepromazine; and 8.3% used a combination of them. In association to the periodical prescriptions, 93.8% of patients needed additional haloperidol doses, while 1.4% required additional levomepromazine doses.	Haloperidol was the most used neuroleptic for the treatment of delirium, followed by levomepromazine.	Patients were not classified according to the type of delirium.
A6 - Cross sectional, observational, and multi-centric study[21] / Level of evidence 3	Pharmacological management of delirium/27 patients in 11 general hospitals, including three Palliative Care units.	Patients were treated with an association of drugs divided in two groups: 48.1% were treated with an association of haloperidol and risperidone (long-acting psychotic drugs) and 51.9% were treated with olanzapine and quetiapine (antipsychotic drugs with a short duration).	It was found that comparing the two antipsychotic associations, the prolonged action ones and the short-term ones, resulted in a similar efficiency to treat delirium.	The study was not randomized or controlled. The size of the sample was small, and the types of delirium were not separated (hyperactive, hypoactive, mixed state).
A7 - Randomized, controlled, double-blind clinical trial[22] / Evidence level 2	Pharmacological management of hyperactive or mixed state delirium/52 patients in a Unite for Acute Palliative Care	Patients of the intervention group (lorazepam and haloperidol), when compared to the control group (placebo and haloperidol) presented a significant diminution in their agitation and needed lower doses of neuroleptic drugs for recovery in their first 8 hours of treatment.	After the neuroleptic drugs were used, a significant reduction was found in the agitation of the patient from the intervention group, who felt more comfortable.	Nothing to report.
A8 - Retrospective and observational study[23] / Level of evidence 3	Pharmacological management of mixed state, hyperactive, and hypoactive delirium/97 patients, in a terminal stage of cancer, hospitalized in the Palliative Care Department of a University Hospital.	Most patients (67%) presented with hyperactive delirium. All were medicated with chlorpromazine, and the dosage was increased in the night shift. There was a significant improvement after the third day of treatment among patients with a mean survival rate of 21 days.	A high incidence of hyperactive delirium was found in the studied group. The administration of chlorpromazine was considered to be more effective for patients whose survival rate was longer than two weeks.	There was no control group.
A9 - Retrospective and observational study[24] / Level of evidence 3	Pharmacological management of delirium/744 prescriptions associated to 201 patients in a Unit for Acute Palliative Care in a Cancer Hospital.	To treat the delirium, 62% of prescriptions corresponded to the administration of haloperidol, 31% to that of chlorpromazine, 4.5% of lorazepam, and 2.5% of midazolam.	Haloperidol was the most prescribed drug to manage delirium. It was also indicated to control anxiety, insomnia, nausea, and vomit.	Patients were not classified according to the type of delirium.
A10 - Observational and multi-centric study[25] / Level of evidence 3	Pharmacological management of hypoactive delirium/223 records of patients attended in Units Palliative Care Units in 38 hospitals.	To manage hypoactive delirium, cancer patients in advance stages were prescribed the following drugs: haloperidol (37%), quetiapine (23%), chlorpromazine (12%), olanzapine (10%), risperidone (9%), trazodone 5%), aripiprazole (3%), and perospirone (1%). No significant changes were found regarding the efficiency of the drug therapy. The most common adverse effect was the sedation.	The current systematic data on pharmacovigilance suggests that the current drug therapy for hypoactive delirium in patients with advanced cancer did not result in any improvements in the severity of their situation, especially among those whose death is expected to happen in a few days. It became clear that it is important to establish appropriate goals for the treatment, considering the prognosis of the patient.	Nothing to report.

According to the Summary Table 2, six studies were observational retrospective ones. Two of them were carried out in Europe (Switzerland and England), two in North America (the US) and two in Asia (Saudi Arabia and Japan); one study was observational, cross-sectional, and multi-centric, and carried out in Asia (Japan); one controlled and double-blind randomized clinical trial was carried out in North America (the US); one was prospective and observational, carried out in North America (the US); and another was multi-centric and observational, carried out in Asia (Japan).

There was a prevalence of studies with a level of evidence of 3[17-21,23-25]; focused exclusively on the pharmacological management of delirium[16-17,19-25]; 50% of the articles analyzed did not classify the type of delirium[18,20-22,25]; 30% classified it as mixed, hyperactive, or hypoactive[18,22-23], 10% as hyperactive or hypoactive[17]; and 10% as hypoactive[25].

DISCUSSION

From the ten studies analyzed, two therapeutic classes were the most prevalent in the pharmacological management of delirium: antipsychotic and benzodiazepine drugs[16-25]. Most studies had a pharmacological management using only one therapeutic class. The antipsychotic drugs used among them were haloperidol, olanzapine, risperidone, aripiprazole, chlorpromazine, levomepromazine, and quetiapine[16,18,20-21,23,25].

A study that evaluated the use of the antipsychotic drugs haloperidol, olanzapine, risperidone, and aripiprazole, found that patients with hyperactive delirium required a higher dosage than those with hypoactive delirium; the drugs were not compared, and the most used one could not be determined[16].

In another study, the use of haloperidol stood out, with a very significant percentage, 89.3% of the 271 patients, in controlling the delirium, though the study was limited since it did not classify the type of delirium[20].

Considering the failure in treating delirium, a strategy suggested is the neuroleptic rotation. A study that evaluated the management of this condition in 167 patients, adopting this strategy, showed that 77% of patients were treated using only haloperidol, while 23% required a second neuroleptic drug, needing this therapeutic association for their situation to be controlled[19].

A common practice in palliative care is the off-label prescription for the control of symptoms, using medications according to indication, dosage, or in ways that are not approved by the Food and Drug Administration. A study that evaluated 744 prescriptions found that 36% of them were off-label, and that haloperidol was present in 463 prescriptions to treat delirium[24].

A study that described the treatment of hypoactive delirium in 218 patients also had, as the first-choice drug, haloperidol, followed by quetiapine. The authors reiterated that the drug therapy can affect the course of the delirium, and concluded that they do not recommend the pharmacological management of patients with advanced cancer in the final stages of life[25].

Two studies stood out in the management of delirium with the antipsychotic drugs quetiapine[21] and chlorpromazine[23], individually. In one of them, the quetiapine was recommended as the first therapeutic option for 41% of patients, while haloperidol was the second most used, representing 26%. However, this study did not classify the patients per type of delirium[21]. Another study, aiming to manage the three types of delirium (mixed state, hypoactive, and hyperactive), the chlorpromazine was used in 193 patients, and the therapeutic plan was made up of dosages that were different in the day and in the night (increased dosage during the night), resulting in high effectiveness for agitated patients and in longer life expectancy[23].

Studies that used more than one therapeutic class combined haloperidol and midazolam[17], haloperidol and chlorpromazine[18], and haloperidol and lorazepam[18,22]. In a study that had, as a second option to treat delirium, the combination of haloperidol and midazolam[17],the patients were not classified according to the type of delirium; the use of midazolam stood out as the first option, while the use of haloperidol in isolation was the third most common. The sample included 319 records. In the management of the three types (mixed state, hypoactive, and hyperactive) in 522 patients, a study indicated that haloperidol was the drug administered to most patients (66%), while chlorpromazine was used in 3% of them[18].

A study that compared the use of haloperidol and lorazepam versus haloperidol and a placebo treated a single episode of hyperactive or mixed state delirium in 52 patients, showing that those who received an association of an antipsychotic and benzodiazepine drugs became significantly less agitated[22].

Regarding the non-pharmacological management, only two studies offered family education about delirium, reinforcing the need for the presence of a caregiver at the bedside, when appropriate, and the importance of offering minimal care and interventions such as stimulation and guidance techniques[18,22].

According to what is described in the methodological trajectory, descriptors were used associated to keywords, but, still, this integrative review showed a scarcity of studies addressing the non-pharmacological management of delirium, whose use could lead to a diminution in the reduction and control of psychomotor agitation, contributing for the safety and comfort of the patient.

These results drew the attention of the authors, who, as previously mentioned, work in a public hospital specializing in teaching, research, and in the humanized treatment of cancer patients, which is a Center for High-Complexity Assistance in Oncology (CACON). In this institution, there are directives aimed at standardizing the assistance through policies, protocols, and operational procedures, involving the collaborative work of health team professionals, such as nutritionists, psychologists, pharmacists, physicians, nurses, nursing technicians, and physical therapists, inserted in the prevention and in the treatment of delirium through pharmacological and non-pharmacological management actions.

The policy of the institution, called "Chemical, Physical, and Mechanical Contention", aims to guide the management of psychomotor agitation and/or aggressiveness that may be triggered by hyperactive or mixed state delirium. These actions include non-pharmacological measures such as addressing the patient verbally and limiting space; if the behavioral manifestations continue to be abnormal, and the patient presents a risk for themselves or others, the adoption of mechanical and/or chemical contention is justified.

The pharmacological management described in the institutional policy above aims to calm the patient fast, diminishing the

symptoms of aggression and agitation without the use of sedatives. The pharmacological classes prescribed are the antipsychotic drugs. The drug of choice is the haloperidol, followed by quetiapine and by the bensodiazepine drugs lorazepam and diazepam.

Considering how essential it is to identify early the cause of delirium to indicate the adequate treatment, the institutional protocol for delirium recommends diagnostic criteria (according to the International Classification of Diseases - ICD 10), describes predisposing and triggering factors, and standardizes the application of the Confusion Assessment Method scale (CAM) and of the Richmond Agitation Sedation Scale (RASS) to monitor delirium. According to this protocol, the actions recommended for the management of the disease include: actions in the prevention, identification of predisposing and triggering factors, provision of care, prevention of complications, management of the symptoms of the patients with delirium, and especially, of those with severe agitation[8, 26-27].

To apply the mechanical contention, the institution counts on the procedure "Actions of the Nursing Team in Mechanical Contention", based on the Resolution of COFEN (the national nursing council) No. 427/2012[28], which describes its installation, standardize the rigorous monitoring (level of awareness, respiratory frequency, and conditions of the member contained), guides the nursing care and the removal of contention, which must be gradual, for the safety of the patient and with the main objective of diminishing their time in contention and preventing against the risks related to the use of contention devices.

Study limitations

The decision to conduct searches in the electronic databases and platforms in the languages Portuguese, English, and Spanish, could be a limitation, since it means that publications about the theme in other languages were not included.

Contributions to the fields of Nursing, Health or Public Policy

A summary was made of the main outcomes and limitations of studies about the management of delirium in adult cancer patients with solid tumors. The institutional directives of a CACON were shared, suggesting possibilities to strengthen the collaborative interprofessional practice in the assistance of cancer patients and attempting to prevent and treat delirium, pharmacologically or not.

CONCLUSIONS

This integrative review analyzed ten primary studies, 80% of which described, exclusively, the pharmacological management of delirium. The drug haloperidol stood out in patients with advanced cancer. Only 20% of the studies mentioned interventions/actions for the non-pharmacological management of delirium, though with no details, in association to pharmacological ones.

It can be concluded that there are few studies that address pharmacological and non-pharmacological interventions/actions to manage delirium. This work reiterates how essential it is to develop further studies focused on the expansion and advancement of scientific knowledge about the theme.

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