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ORIGINAL ARTICLE

Use of antidepressants and potential drug interactions in cancer patients treated at a hospital in the Southern Brazil

Uso de antidepressivos e potenciais interações medicamentosas em pacientes oncológicos atendidos em hospital do Sul do Brasil

Uso de antidepresivos y posibles interacciones farmacológicas en pacientes con cáncer tratados en un hospital en el Sur de Brasil

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ABSTRACT

Background and Objectives: Cancer is a chronic degenerative disease and its diagnosis is often associated with mental distress, doubts and insecurities that can trigger depressive symptoms, causing the need for pharmacological treatment. However, cancer patients often use multiple medications (polypharmacy), thus increasing the chances of potential drug interactions. The objective of this study was to evaluate the use of antidepressant drugs in oncological inpatients and the potential drug interactions of their prescriptions. **Methods:** Prospective, descriptive, and analytical cross-sectional study conducted with cancer patients aged ≥ 18 years, admitted to a hospital in Southern Brazil, and aware of their diagnosis. Larger and contraindicated drug interactions were analyzed using the Micromedex® and Lexicomp® databases. **Results**: The sample consisted of 50 patients, 54% were female and the mean age was 53.6 (± 15.3) years. Antidepressant drugs were used in 42% of the patients, escitalopram (selective serotonin reuptake inhibitors) being the most prescribed. 90% of the patients had some potential interaction and they occurred with any drug prescribed for treatment. Out of the patients using antidepressants, 62% had contraindicated interactions and all had at least one case of major interaction. The drugs most related to contraindicated drug interactions were dipyrone and metoclopramide. **Conclusion**: The results of this study demonstrated a high number of contraindicated interactions involving antidepressant drugs. The significance of monitoring and adjusting the pharmacotherapy of these patients is crucial.

Keywords: *Drug Interactions. Antineoplastic Agents. Antidepressive Agents. Medical Oncology.*

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RESUMO

Justificativa e Objetivos: O câncer é uma doença crônico-degenerativa cujo diagnóstico constantemente está associado a sofrimento mental, dúvidas e inseguranças, podendo desencadear sintomas depressivos, de forma que às vezes são necessárias medidas farmacológicas para tratar desses sintomas. Entretanto, pacientes oncológicos frequentemente utilizam vários medicamentos (polifarmácia), aumentando as chances de potenciais interações medicamentosas. Este estudo pretendeu avaliar o uso de antidepressivos nos pacientes em tratamento oncológico hospitalizados e as potenciais interações medicamentosas de suas prescrições. **Métodos:** Estudo transversal, prospectivo, descritivo e analítico realizado com pacientes oncológicos com idade superior a 18 anos, internados em um hospital do Sul do Brasil e cientes de seu diagnóstico. As interações medicamentosas maiores e as contraindicadas foram analisadas por meio das bases de dados *Micromedex*® e *Lexicomp*®. **Resultados**: Na amostra, composta de 50 pacientes, 54% eram do sexo feminino, e a média de idade foi de 53,6 (±15,3) anos. Além disso, dentre a amostra, 42% dos pacientes utilizavam medicamentos antidepressivos, sendo o escitalopram (inibidor seletivo da recaptação de serotonina) o mais prescrito; e 90% dos pacientes apresentaram algum tipo de potencial interação, que ocorreram com quaisquer medicamentos prescritos para o tratamento. Dos pacientes que utilizavam antidepressivos, 62% tiveram interações contraindicadas e todos apresentaram pelo menos um caso de interação maior. Os medicamentos mais relacionados a interações medicamentosas contraindicadas foram a dipirona e a metoclopramida. **Conclusão:** Os resultados deste estudo demonstraram um elevado número de interações medicamentosas contraindicadas envolvendo medicamentos antidepressivos. Nesse contexto, verifica-se a importância de monitorar e adequar a farmacoterapia desses pacientes.

Descritores: *Interações de Medicamentos. Antineoplásicos. Antidepressivos. Oncologia*

RESUMEN

Justificación y objetivos: El cáncer es una enfermedad crónico-degenerativa, que tiene su diagnóstico frecuentemente asociado a angustia mental, dudas e inseguridad, lo que puede resultar síntomas depresivos, que necesitarán, a menudo, medidas farmacológicas para tratarlos. Sin embargo, los pacientes con cáncer muchas veces usan varios medicamentos (polifarmacia), lo que aumenta las posibilidades de interacciones farmacológicas. Este estudio propone evaluar el uso de antidepresivos en pacientes con cáncer hospitalizados y las posibles interacciones farmacológicas que proceden de sus prescripciones. **Métodos:** Estudio transversal, prospectivo, descriptivo y analítico realizado con pacientes con cáncer de edad superior a 18 años, ingresados en un hospital en el Sur de Brasil y conscientes de su diagnóstico. Las interacciones farmacológicas más grandes y contraindicadas se analizaron utilizando las bases de datos *Micromedex* y *Lexicomp.* **Resultados:** La muestra consistió en 50 pacientes, el 54% eran mujeres y el promedio de edad fue de 53,6 (±15,3) años. El 42% de los pacientes utilizaban fármacos antidepresivos, de los cuales el escitalopram (inhibidor selectivo de la recaptación de serotonina) fue el más recetado; el 90% de los pacientes tuvieron alguna interacción que ocurrió con cualquier medicamento recetado para el tratamiento. De los pacientes que usaban antidepresivos, el 62% tuvieron interacciones contraindicadas y todos presentaron, al menos, un caso de interacción mayor. Los fármacos más relacionados con las interacciones farmacológicas contraindicadas fueron dipirona y metoclopramida. **Conclusión:** Los resultados de este estudio demostraron un alto número de interacciones farmacológicas contraindicadas que involucran fármacos antidepresivos. En este contexto, se verifica la importancia de monitorear y ajustar la farmacoterapia de estos pacientes.

Palabras clave: *Interacciones Farmacológicas. Antineoplásicos. Antidepresivos. Oncología médica*

INTRODUCTION

Depression is a common mental disorder worldwide. It is estimated that more than 300 million people suffer from this disorder. It is characterized by sadness, loss of interest or pleasure, feeling of guilt or low self-esteem, altered sleep and appetite, tiredness, and lack of concentration, and it can become a critical health condition, especially when it has long duration and moderate or severe intensity.[1]

Individuals with chronic conditions are more likely to have depressive symptoms. In fact, worldwide, depression is more prevalent among patients with cancer, heart disease, diabetes, stroke, or chronic respiratory problems than in the general population. Cancer patients are up to three times more likely to suffer from depression than people who do not have the disease. However, it may be difficult to make a definitive diagnosis due to the overlap of clinical symptoms.[2-5]

Cancer is the second leading cause of death in the world and in 2018 it accounted for 9.6 million deaths. According to the Brazilian National Cancer Institute (*Instituto Nacional de Câncer* — INCA), an estimated 420,000 new diagnoses of the disease are estimated for 2019, except for non-melanoma skin cancer. It is a chronic-degenerative disease characterized by the uncontrolled and disorderly growth of cells that prevent the normal functioning of the

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body. This type of cancer has a multifactorial origin and it is mainly triggered by genetic changes, environmental factors and lifestyle.[6-8]

The diagnosis of cancer causes intense suffering to patients and generates a greater sense of anguish than other non-neoplastic diseases with a worse prognosis. Patients tend to have high levels of mental suffering, doubts, and insecurity for prolonged periods, which can lead to the development of anxiety disorders, depression, or both.[5,9]

The prevalence of depressive symptoms among cancer patients varies according to the type of cancer, stage of the disease, and demographic profile of the population. Depression not only compromises the quality of life of patients, but also increases their mortality.[5,10]

Pharmacological options are often required to treat symptoms related to depressive disorders. Furthermore, antidepressant medications can be used for other purposes, such as pain treatment. However, many antineoplastic medicines share the same metabolic pathways, potentiating their undesirable effects. Concomitant administration of antineoplastic drugs and antidepressants can lead to drug interactions, both pharmacokinetic and pharmacodynamic, reducing the drugs effectiveness or increasing its toxicity. Generally, the patients most exposed to DI are those who use five or more medications (polypharmacy). Cancer patients are most often prone to polypharmacy because they use – in addition to cancer treatment-medicine – drugs to treat side effects of chemotherapy, neoplasia-related syndromes, and other associated diseases.[10-13]

Drug interactions can be considered responsible not only for the clinical deterioration of the patient, but mainly for the increase in hospital measures and the time of hospitalization, affecting the quality of care and making the treatment more expensive for the health care system. It is noteworthy the significance of the entire health team to monitor these DI, in addition to the fundamental role of the pharmacist in this scenario.[14]

The prescription of antidepressant medications for patients undergoing cancer treatment can be made by several professionals, which may generate negligence in the observation of potential drug interactions resulting from this use.[10]

This study analyzes the use of antidepressants in patients undergoing cancer treatment admitted to a hospital in the Southern Brazil and the potential drug interactions of the prescriptions given to these patients.

METHODS

This is a cross-sectional, descriptive, and analytical study carried out in a teaching hospital, a reference in the treatment of childhood and adult cancer, in addition to be a High Complexity Care Unit in Oncology (Unidade de Assistência de Alta Complexidade – UNACON).

The sampling was non-probabilistic and non-random, performed with patients hospitalized in the proposed period. The collection was carried out in two periods, to continue the existing database, covering the period from August to September 2018, and from April to June 2019. Patients aged ≥ 18 years, who were hospitalized for cancer treatment and who had cognitive conditions to answer the questionnaire were included in the study. The volunteers who agreed to participate in the study signed an informed consent form.

Data were collected by information from the patient's electronic medical records and by a structured bedside interview, whose variables were: name, age, schooling level, occupation, marital status, number of children, breastfeeding, family history of cancer, and continuous use medications. The questionnaires were applied by a pharmacist of the Multiprofessional Residency Program in Cancer Care. The research was approved by the Research Ethics Committee of the University of Passo Fundo, under opinion no. 3,220,803 and CAAE 93508318.1.0000.5342.

The Micromedex® and Lexicomp® databases were used to evaluate the drug interactions between antidepressant, oncological therapy, and supportive medications. Since some medications were not included in the arsenal of some bases, both were used to analyze the interactions. Considering the clinical relevance, this study was based on the description and detailing of the contraindicated drug interactions, so that the higher-severity drug interactions were only mentioned in terms of their frequency, because they occurred in large numbers, which hindered their detailing.

The severity of the interactions was described according to the Micromedex® database classification: "contraindicated," when the drugs cannot be used concomitantly because they cause risk to the patient's life; and "higher," when drug interactions can threaten the patient's life, requiring or not medical intervention to minimize or prevent adverse effects.

The collected data were stored as a database in Excel 2016 software. Continuous variables were expressed as mean and standard deviation, and the categoric ones with relative frequencies and absolute number.

RESULTS

The sample was composed of 50 cancer patients hospitalized and undergoing chemotherapy. The patients' mean age in the study was 53.6 (±15.3) years, with a minimum age of 22 years and a maximum of 78 years, among which 66% were aged ≤ to 60 years. Most patients were women, 54% (n=27), among whom 92.6% (n=25) reported having children, 64.0% (n=16) breastfed, on average, for 16 (±14.7) months. The sociodemographic characteristics of the study participants are described in table 1.

Among the patients, 54% (n=27) reported having a family history of cancer, whose diagnosis had occurred on average 13.8 (±2.9) months; 24% (n=12) had distant metastasis and 24% (n=12) had recurrences, in addition to 10% (n=5) who were undergoing palliative treatment.

Acute myeloid leukemia (AML) and large B-cell non-Hodgkin lymphoma (LBCNHL) were the most frequent types of cancer presented by patients in 14% (n=7) and 10% (n=5) of cases, respectively. The

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Table 1. Sociodemographic characteristics of the patients in the study, treated in a hospital in the Southern Brazil. Passo Fundo, 2019. (n=50)

Characteristic	n	%
Skin color		
White	49	98
Brown/Mixed race	1	2
Schooling level		
Elementary School	20	40
High School	22	44
Higher Education	16	16
Occupation		
Farmer	12	24
Retired	6	12
Professor	5	10
Others	23	54
Marital status		
Married	32	64
Single	11	22
Widow/widower	4	8
Divorced	3	6
Health insurance plan*		
SUS	31	62
Others	19	38
Associated diseases*		
Yes	34	68

**Dichotomous variables*

most used protocols to treat these two forms of disease were "7+3" induction (which includes cytarabine and idarubicin) and R-ICE (rituximab, ifosfamide, carboplatin, etoposide, and mesna), in 28.6% (n=2) and 40% (n=2) of the cases, respectively.

Out of the 50 patients, in only 10 cases there was information on staging, among which 70% (n=4) had stage IV tumors. For cases in which there was no information on staging and grading, 70% (n=35) cases were hematological cancer, to which this classification does not apply, and for 10% (n=5) of the patients the medical records were not filled with this information.

Among the patients, 42% (n=21) used antidepressants, with an average of 1.2 (±0.5) medications (minimum 1 and maximum 3). The most prescribed medication was escitalopram, 33% (n=7), which belongs to the class of selective serotonin reuptake inhibitors (SSRIs). Table 2 describes the classes of antidepressants prescribed for the patients.

In the drug interactions analysis, 90% (n=45) of the patients presented some kind of potential interaction – which occurred between antidepressants, chemotherapy, or any other prescribed medications. Among the patients who used these medications (n=21), 62% (n=13) had contraindicated interactions and 100% (n=21) had larger interactions. Table 3 shows the drug interactions contraindicated between antidepressants that were presented by the patients.

Table 2. Description of the classes of antidepressants used by the patients in the study treated in a hospital in Southern Brazil. Passo Fundo, 2019. (n=21)

Class of antidepressant	n	%
Selective Serotonin Reuptake Inhibitors (SSRI)	16	76.0
E.g.: Escitalopram, sertraline, and fluoxetine		
Serotonin and norepinephrine reuptake inhibitor (SNRI)	6	28.5
E.g.: Duloxetine		
Tricyclic Antidepressants (TCA)	2	9.5
E.g.: Amitriptyline		
Selective Dopamine Reuptake Inhibitors (SDRI)	1	4.8
E.g.: Bupropion		
Melatonin agonists	1	4.8
E.g.: Agomelatine		

**Some patients used more than one antidepressant.*

Table 3. Sociodemographic characteristics of the patients in the study, treated in a hospital in the Southern Brazil. Passo Fundo, 2019. (n=50)

Drugs involved in interactions*	n	Interaction mechanism**	Possible conduct
Sertraline × Dipyrone	4	Increased risk of antiplatelet effect. Decrease in the therapeutic effect of selective serotonin reuptake inhibitor.	Replacement of dipyrone with paracetamol
Escitalopram × Metoclopramide	3	Increased risk of extrapyramidal reactions and malignant neuroleptic syndrome	Replacement of metoclopramide with ondansetron or dimenidrinate
Escitalopram × Dipyrone	3	Increased risk of antiplatelet effect and decreased therapeutic effect of selective serotonin reuptake inhibitor.	Replacement of dipyrone with paracetamol
Sertraline × Metoclopramide	2	Increased risk of extrapyramidal reactions and malignant neuroleptic syndrome	Replacement of metoclopramide with ondansetron or dimenidrinate
Fluoxetine × Dipyrone	1	Increased risk of antiplatelet effect. Decrease in the therapeutic effect of selective serotonin reuptake inhibitor.	Replacement of dipyrone with paracetamol
Bupropion × Linezolid	1	Increased risk of hypertensive reactions	Monitoring the patient's blood pressure or replacing with another antibiotic

**Information taken from the Micromedex® database.*
***One patient had two contraindicated interactions.*

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DISCUSSION

Although the epidemiological profile of cancer in Brazil indicates that most patients are male, in this study most cases involved women, as also shown by another study conducted in the Southern Brazil. Note that, although the disease is more prevalent in men, women seek health services more frequently, which increases the chances of early diagnosis and timely treatment. Men usually resort to care services when the disease is in a more advanced state and often do not follow the treatment.[7,15]

According to the INCA, the most prevalent neoplasms in the population are breast, prostate, intestine, lung, and stomach. However, this study showed a higher frequency of AML and LBCNHL. Patients with hematological diseases (leukemias and lymphomas) require more complex chemotherapy regimens, which have greater myelosuppressive effects and, consequently, prolonged and more frequent periods of hospitalizations. On the other hand, patients with solid neoplasms usually do not require hospitalization to perform the treatment, which may justify the higher frequency of leukemias and lymphomas in the patients in this study.[7]

Cancer patients are particularly prone to polypharmacy, which may be related to the use of medications to handle the adverse effects of cancer therapy or the comorbidities presented by them. In addition to the higher risk of DI, more than one interaction can occur in the same patient, increasing the possibility of unwanted effects that worsen its prognosis. The frequency of drug interactions found in this study is high (90%) and similar to that found in a study carried out in a reference hospital in Murcia, Spain (95%), corroborating the significance of this theme for clinical practice in oncology.[16,17]

The stigma of the death associated with the diagnosis of cancer, in addition to changes in the routine and quality of life of patients, resulting from cancer treatments, can trigger depressive symptoms. These symptoms may differ according to the type of cancer, stage of the disease, and demographic profile of the population. Depression not only compromises the patients' quality of life, but also increases their mortality.[5,10]

Physicians often resort to the use of antidepressant medications to address this clinical situation, as observed in this study, which happened in 42% of cases. In other articles with the same approach, the use of antidepressants in cancer patients was relatively lower (23.2% and 16%) than found in this study.[10,18]

However, choosing the appropriate antidepressant requires observing its use to avoid an interaction. The most prescribed class of antidepressants was selective serotonin reuptake inhibitors (SSRI), the first choice for cancer patients due to their tolerability. Among the representatives of SSRI, the most prescribed antidepressant was escitalopram. The Canadian international guideline for the treatment of depression in cancer patients recommends SSRI and, among them, citalopram and escitalopram as first-choice medications because of the lower potential for DI. The preference for these two antidepressants is due to the fact that both have low CYP450 inhibition potential, configuring a better safety profile in cancer patients.[18,20]

However, prescribing drugs with drug interaction potential does not necessarily imply damage to the patient. The drug interaction risk increases when the medications are classified as contraindicated, so replacing the prescribed medicine is recommended, unlike higher severity interactions, which do not necessarily require such change. These potential interactions become even more relevant in cancer patients due to their unfavorable clinical conditions and the physiological changes resulting from the disease.[17]

The drugs prescribed in this study that presented significant contraindicated drug interaction potentials were metoclopramide and dipyrone. Metoclopramide showed contraindicated interactions when used simultaneously with SSRI-class antidepressants (escitalopram and sertraline). The antiemetic action of metoclopramide is due to dopamine antagonism in D2 receptors. The association with antidepressants (class of TCAs, SNRI, and SSRI) can trigger or facilitate extrapyramidal effects, which generate a blockage of dopaminergic neurons, causing stiffness and tremors at rest. In extreme cases, it can cause malignant neuroleptic syndrome characterized by hyperthermia, autonomic dysfunction, altered consciousness, severe stiffness, and elevated serum creatine levels.[21,22]

Metoclopramide is widely used in oncology to minimize the effects of nausea and vomiting presented by patients. However, as observed in this study, this drug has a high potential for DI contraindicated with antidepressants. To treat these symptoms, therapeutic options that do not generate contraindicated drug interaction are dimenhydrinate and ondansetron, belonging to the class of antihistamines and antagonists of 5-hydroxytryptamines receptors (5-HT3), respectively.

The concomitant use of dipyrone with sertraline, escitalopram, or fluoxetine was frequently observed in the study. These SSRI, when used in conjunction with dipyrone, can increase the antiplatelet effect, potentiating the occurrence of hemorrhage, mainly gastrointestinal and intracranial hemorrhage. Cancer patients are spontaneously more likely to the risk of hemorrhage because of changes related to the disease and therapy to which they are submitted to treat cancer. Hemorrhage is more frequent in leukemias, but it may also occur in solid tumors, mainly due to tumor infiltration. Changes can happen in almost all stages of coagulation, such as quantitative (thrombocytopenia) and qualitative changes of platelets. Thus, it is noticed that drug interactions involving the use of dipyrone and SSRI antidepressants can cause damage to cancer patients. Concomitant use of these drugs should be evaluated, and the clinical status observed. If a possible effect of this interaction is evidenced, its use should be avoided.[23]

Dipyrone is widely used in cancer patients, mainly for mild to moderate pain analgesia. A therapeutic alternative to replace it is paracetamol, a non-opioid analgesic with antipyretic property, effective in relieving pain with such intensity. In addition to being effective in relieving

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pain, paracetamol does not have contraindicated drug interactions with the antidepressants sertraline, escitalopram, and fluoxetine. However, dipyrone is often chosen because its injectable option is available in Brazil, which does not occur with paracetamol.[24]

The use of linezolid in concomitance with bupropion – antidepressant of the SDRI class – is classified as a contraindicated interaction, observed in one patient in this study. The combination of these two drugs is not indicated, as it may increase the risk of hypertension. As linezolid is an effective antibiotic to treat infections with Gram-positive, microorganisms,and because its use is not continuous, it is suggested to monitor the blood pressure of patients during concomitant use of the two medications and, if necessary, adjust the dose or include an antihypertensive. If the hypertensive condition remains or progresses, an alternative is the replacement of linezolid with daptomycin, or suspension of the use of bupropion – during treatment with linezolid – which can be reintroduced 24 hours after the last dose of linezolid.

The high frequency of drug interaction potentials in cancer patients demonstrated in this study – with emphasis on contraindicated ones – reinforces the significance of evaluation in the process of medication use. Recognizing potential interactions and the main combinations of medications allows avoiding situations of therapeutic failure or minimizing the onset of drug toxicity. Studies like ours can help to establish computerized alert systems to guide the multidisciplinary team in oncology, reducing the exposure of patients to drug interactions, especially contraindicated ones. The data of this study also points to the need for the pharmacist to monitor the patient in order to adequately evaluate the occurrence of potential drug interactions in the prescription, allowing to prevent and to reduce damage.[22,25]

This study has some limitations: in it, the potential drug interactions found were not monitored and the use of antidepressants by the patients before hospitalization was not assessed, a question that was not included in the interview. It is noteworthy that the interactions described are potential, that is, they were classified based on the medical prescription and did not necessarily imply the occurrence of negative clinical outcomes. The detection of drug interaction, even those classified as contraindicated, should be contextualized with the patient's clinic and the risk-benefit of the conduct should always be considered. Further investigations should be carried out to evaluate clinical outcomes related to interactions involving antidepressants, especially correlating them to clinical parameters, hospitalization time, and mortality.

The results of this study demonstrate that many patients on cancer use antidepressants, and that most individuals were exposed to potential contraindicated drug interactions. Thus, the significance of the multidisciplinary team in the care and monitoring of the patient is emphasized, in addition to the extreme relevance of the pharmacist to monitor the pharmacotherapy of patients and evaluate potential drug interactions. The results show that drug interactions in cancer patients should be identified and monitored in order to avoid undesirable events related to pharmacotherapy. The pharmacist may suggest to the health team safer therapeutic options for the prevention of drug-related damage.

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