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The impact of pharmaceutical services on pain management in oncology patients: literature review

O impacto dos serviços farmacêuticos no manejo da dor em pacientes oncológicos: revisão integrativa

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ABSTRACT
Examining the impact of pharmaceutical services on the clinical management of oncological pain in hospital settings. An integrative review was conducted using the MEDLINE (PubMed) database and grey literature. Thirty-seven studies were retrieved, and after applying eligibility criteria, seven studies were selected. There is a clear trend of benefits from pharmaceutical clinical services in enhancing clinical management of oncological pain in hospitalized patients, as well as revealing financial benefits to hospital institutions. Effective implementation faces challenges, including resistance to opioid use and conservative patterns of medical prescription, affecting the acceptance and efficacy of pharmaceutical interventions.

Keywords: Analgesics, Opioid. Cancer Pain. Pain Management. Patients. Pharmaceutical Services.

RESUMO
Analisar o impacto dos serviços farmacêuticos no manejo clínico da dor oncológica em instituições hospitalares. Realizou-se uma revisão integrativa na base de dados MEDLINE (PubMed) e na literatura cinzenta. 37 estudos foram resgatados e após a aplicação dos critérios de elegibilidade foram selecionados sete estudos. Há uma clara tendência de benefícios dos serviços clínicos farmacêuticos no aprimoramento do manejo clínico da dor oncológica em pacientes hospitalizados, além de revelar benefícios financeiros às instituições hospitalares. A implementação eficaz enfrenta desafios, incluindo resistência ao uso de opioides e padrões conservadores de prescrição médica, afetando a aceitação e eficácia das intervenções farmacêuticas.

Palavras-chave: Analgésicos opioides. Assistência Farmacêutica. Dor do Câncer. Manejo da Dor. Pacientes.

INTRODUCTION

GLOBAL PANORAMA AND CLASSIFICATION OF CANCER PAIN

The management of pain in oncology patients is a global health concern, and pharmaceutical services play a crucial role. Various countries have adopted similar approaches to improve the treatment of cancer pain, including the implementation of pain assessment protocols, the use of opioid and non-opioid analgesics, and the integration of multidisciplinary teams to ensure a holistic approach. In the United States, Canada, and the European Union, guidelines exist for managing pain in cancer patients, emphasizing the importance of regular pain assessment, individualization of treatment, and adequate access to opioid analgesics. Additionally, continuing education programs for healthcare professionals and safety monitoring strategies are being implemented to mitigate the risks associated with opioid use.[1]

However, despite these efforts, significant gaps remain in the management of pain in oncology patients. One of the main gaps is the disparity in access to pharmaceutical services and opioid analgesics between developed and developing countries. While patients in more developed nations have less difficulty accessing a variety of treatment options and well-structured multidisciplinary teams, in developing countries, access to these medications is often limited due to economic, political, and infrastructural barriers.[2,3]

In this context, cancer pain is highly relevant, affecting approximately 17 million people worldwide, with prevalence reaching up to 90% in patients in advanced stages of cancer. This pain significantly impacts quality of life, highlighting the need for adequate therapies. In Brazil, between 62% and 90% of oncology patients suffer from pain, and a considerable portion does not receive adequate treatment, with over 55% of these patients reporting moderate to severe pain. Furthermore, epidemiological data show that only a minority of patients with intense pain have access to opioids, with the majority receiving low-potency opioids, despite high-potency opioids being recommended for intense pain. This situation underscores the importance of improving the management of cancer pain.[4]

The classification of pain includes chronic and acute pain, differentiated by their temporal pattern. Acute pain, short in duration, is generally triggered by specific stimuli, such as surgeries or medical treatments, and tends to disappear when the underlying cause is treated. In contrast, chronic pain is persistent, often related to the progression of cancer, involving direct invasion of tumor tissues or compression of nerve structures, among other causes. This classification is essential for guiding pain management strategies in oncology patients.[5]

Beyond the temporal pattern, pain can also be classified based on its pathophysiological mechanisms. In the oncological context, three main types of pain are identified: nociceptive, neuropathic, and mixed. Nociceptive pain results from noxious stimuli in tissues, while neuropathic pain is associated with nerve damage, common in cancer patients due to direct injuries caused by the tumor or treatments like radiotherapy. On the other hand, mixed pain involves both neuropathic and nociceptive components, stemming from tumor growth that directly affects nerves and tissues, as well as from the activation of nociceptors due to tissue injuries associated.[6]

EVALUATION AND TREATMENT OF CANCER PAIN

The evaluation of pain is an individualized and subjective practice, considering the variable perception and intensity among patients. It is essential to use appropriate assessment tools, such as interviews and pain scales, that adapt to the patient's cognitive ability. A quantitative approach, like the Numerical Rating Scale,

classifies pain as mild, moderate, and severe based on specific scores, while a qualitative approach highlights the descriptive aspects of pain and its impact on daily activities. These strategies ensure a comprehensive and effective pain assessment, facilitating the development of personalized treatment plans.[7-8]

The treatment of cancer pain requires a multidisciplinary approach, with opioids being the most effective class of medication for managing pain associated with cancer. According to the WHO Analgesic Ladder, weak opioids like tramadol and codeine are recommended for moderate pain, while strong opioids like morphine and oxycodone are preferred for severe pain. Contrary to this ladder, the NCCN (National Comprehensive Cancer Network) suggests the use of low doses of strong opioids for moderate pain in cancer patients, such as immediate-release oral morphine, with a gradual increase in dose if necessary. Tolerance to opioids, marked by the need for specific daily doses, is an important consideration in the treatment of chronic pain, and opioid rotation is a strategy to improve efficacy and reduce adverse reactions associated with continuous use, ensuring a personalized and effective approach for each patient.[9-10]

PHARMACEUTICAL CLINICAL SERVICES

Pharmaceutical services play a key role in promoting the health of the population concerning the management of pain in cancer patients and in cancer prevention. Regarding pain management, pharmacists ensure timely access to appropriate opioid analgesic medications, educate patients on the safe and effective use of these medications, and collaborate with multidisciplinary teams to develop individualized treatment plans. In cancer prevention, pharmaceutical services act through the promotion of health practices, such as vaccination against Human Papillomavirus (HPV) to prevent cervical cancer, education about risk factors for cancer development, and counseling on healthy lifestyle habits, such as smoking cessation and adopting a balanced diet. Such pharmaceutical interventions not only contribute to the effective management of pain and cancer prevention but also have the potential to significantly improve the quality of life and overall well-being of the population.[11-12]

These services aim to promote the appropriate use of medications and optimize health outcomes, involving activities such as pharmacotherapy review, medication reconciliation, pharmacotherapeutic follow-up, and health education. The initial approach involves collecting patient data and history, while medication reconciliation aims to identify discrepancies in prescription and home use. Pharmacotherapy review and pharmacotherapeutic follow-up allow for personalized therapy adjustments, while health education empowers patients to understand their treatments, promoting adherence and better pain management.[13]

These services ensure a holistic and multidisciplinary approach to addressing cancer pain, ensuring the appropriate selection of analgesic agents, harmonization between different prescribed treatments, and personalized therapeutic adjustments to meet the specific needs of each patient. This integration of pharmaceutical services not only improves the quality of life of patients but also significantly contributes to effective cancer pain management in hospital settings.[14]

Therefore, the goal of this study is to analyze the impact of pharmaceutical services on the clinical management of pain in cancer patients, from a public health perspective.

METHODOLOGY

An integrative literature review was conducted, analyzing relevant scientific articles on the topic, aiming to understand and evaluate

the impact of pharmaceutical clinical services on pain management in cancer patients. The research question was structured using the adapted strategy for non-clinical research, defined by the acronym PICo: what are the impacts of pharmaceutical clinical services on pain management in cancer patients in a specialized hospital environment?

P (population): cancer patients;

I (intervention): pharmaceutical services in clinical pain management.

Co (context): specialized hospital environment.

Information source: the MEDLINE (PubMed) database was used for the search. Searches were also conducted in the grey literature, represented by websites of medical societies related to pain and cancer, and reading the references of the included studies. The searches were conducted on 11/15/2023.

Search strategy: consisted of searching for descriptors, interterms, and free terms, as presented: "Pharmaceutical Services AND Cancer Pain AND Pharmacy Service, Hospital."

The eligibility criteria adopted for this research included qualitative and quantitative studies that describe and evaluate pain relief in cancer patients where pharmaceutical clinical services are offered, along with a multidisciplinary team, for pain management. The selected studies were evaluated based on their ability to provide relevant and reliable information on the clinical management of pain in cancer patients.

Exclusion criteria adopted were systematic reviews and studies that do not evaluate interventions originating from pharmaceutical services.

Study selection: screening followed the previously established inclusion and exclusion criteria, conducted independently by two reviewers. The process comprised three phases, considering the reading of: 1) study titles, 2) abstracts, 3) full text.

Data extraction and synthesis: were carried out independently by two reviewers using a previously prepared Excel® form. The extracted data included: author; publication date; country; study objective; quantity, sex, and age of patients; type of cancer; pharmaceutical activities and interventions.

RESULTS

A total of 37 studies were identified from the literature search. Subsequently, 30 were excluded. This resulted in 7 studies for full reading, after which no study was excluded, leading to 7 studies being included. Figure 1 describes the steps involved in the search and selection process.

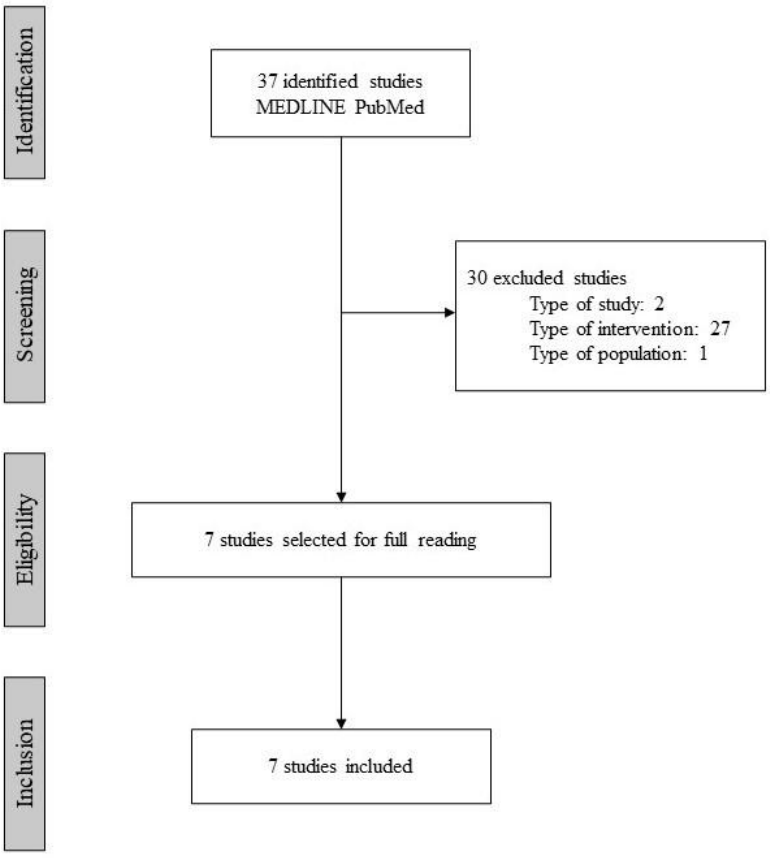

Figure 1. Steps of the study selection process
Source: research data, 2023

Table 1 presents the profile of the seven studies analyzed, highlighting demographic variables such as age and sex of the patients, as well as clinical variables such as the type of cancer of the selected patients. Additionally, Table 1 presents the prevalent types of cancer in each study, revealing the specificity of the investigations. These pieces of information provide a basis for subsequent analysis, allowing for the identification of patterns and differences that may influence conclusions related to pain management in cancer patients.

Table 1. Profile of included studies

(Continued)

Study	Patient Count	Sex	Age	Frequency of Cancer Types
Gagnon *et al.*, 2011[15]	114	68.4% Men 31.6% Women	Average: 68.3 years	Prostate (36.8%), Lung (21.9%), Breast (18.4%)
Liu *et al.*, 2019[16]	195	Not specified	≥18 years	Not specified
Lothian *et al.*, 1999[17]	1029	Not specified	≥18 years	Not specified
Patel *et al.*, 2020[18]	142	43.0% Men 57.0% Women	≥18 years	Gastrointestinal (20.0%), Lung (16.0%), Breast (16.0%)

(Conclusion)

Study	Patient Count	Sex	Age	Frequency of Cancer Types
Ryan *et al.*, 2012[19]	31	42.0% Men 58.0% Women	Average: 61 years Range: 42 to 82 years	Hematológico (7.0%), Breast (7.0%), Lung (5.0%)
Yamada *et al.*, 2018[20]	27	70.0% Men 30.0% Women	≥18 years	Gastrointestinal (44.4%), Lung (18.5%), Pancreas (18%)
Zhang *et al.*, 2021[21]	86	53.5% Men 46.5% Women	<60 years: 39.5%, 60-80 years old: 48.8% >80 years: 11.6%	Gastrointestinal (19.0%), Liver/ Gallbladder/Pancreas/Spleen (24.4%), Lung (14.0%)

Source: research data, 2023

Out of the seven studies submitted for analysis, all (100.0%) were conducted in hospital institutions. Among these, two were conducted in Canada[15,19], two in China[16,21], and two in the United States[17,18], each contributing 28.6% to the overall landscape of the analyzed studies. Additionally, one study was conducted in Japan[20], covering 14.3% of the total sample.

Regarding the age range of the patients, a sample exclusively composed of adults was characterized; with no study involving children. This disparity in cancer incidence between adults and children is a central observation in contemporary oncology. Adults are more susceptible to environmental and behavioral factors such as smoking, exposure to carcinogens, and unhealthy lifestyles. Therefore, the complex interplay between genetic, environmental, and biological factors contributes to the higher incidence of cancer in adults.[22]

In Table 2, the pharmaceutical activities and interventions carried out in the seven analyzed studies were explored, detailing the presence or absence of specific interventions, aiming to understand the scope and variability of pharmaceutical practices in the management of pain in cancer patients in the hospital setting. Based on these data, a deeper understanding of the practices that permeate this field of healthcare was sought.

Table 2. Pharmaceutical activities and interventions

(Continued)

Study	Round	Clinical case discussion	Medication information for healthcare staff	Medication Information for Patients	Pain assessment	Adjustment of analgesic pharmacotherapy	Adverse Reaction Management
Gagnon *et al.*, 201115	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu *et al.*, 2019[16]	No	No	Yes	Yes	No	Yes	Yes
Lothian *et al.*, 1999[17]	No	No	Yes	Yes	Yes	Yes	Yes
Patel *et al.*, 2020[18]	No	No	No	No	No	Yes	Yes

(Conclusion)

Study	Round	Clinical case discussion	Medication information for healthcare staff	Medication Information for Patients	Pain assessment	Adjustment of analgesic pharmacotherapy	Adverse Reaction Management
Ryan *et al*., 2012[19]	Yes	Yes	No	Yes	Yes	Yes	Yes
Yamada *et al*., 2018[20]	No	No	Yes	Yes	No	Yes	Yes
Zhang *et al.*, 2021[21]	Yes	Yes	Yes	Yes	No	Yes	Yes
Total (%) Yes	43.0%	43.0%	71.0%	85.0%	43.0%	100.0%	100.0%
No	57.0%	57.0%	29.0%	15.0%	57.0%	0.0%	0.0%

Source: research data, 2023

In all the studies analyzed, an improvement in pain was observed in all cases, totaling 100% favorable outcomes among the participating patients. It is noteworthy the study[21] where a statistically significant difference in the pain relief rate was observed between the two groups on the third day of treatment with pharmaceutical clinical service ($p = 0.039$); however, by the end of hospitalization, this difference did not remain statistically significant ($p = 0.126$). This result may have been found because there is a possibility of other members of the multidisciplinary team treating patients in the control group, which could influence their pain management practices due to collaboration with pharmacists in the intervention group.

In this context, it was demonstrated that prescribers gained greater confidence in prescribing fentanyl after the implementation of the pharmaceutical clinical service focused on adjusting analgesic doses. This finding is supported by the significant increase in the use of transdermal fentanyl, from 0 μg/day to 120 μg/day after the introduction of said service. This indicates that opioid-tolerant patients with severe chronic pain are receiving appropriate treatment.[17]

In another study,[16] it was found that the three prevalent problems were non-adherence or missed doses (27.7%), inappropriate opioid selection (22.5%), and inadequate dosage (16.4%). After the intervention by pharmacists, the prevalence of these problems decreased to 9.2%, 4.6%, and 3.1%, respectively. These results highlight the trend of the most common types of medication-related problems in hospitalized oncology patients with pain symptoms, emphasizing the significant contribution of clinical pharmacists in pain management in this context.

In this regard, in a group of 28 healthcare professionals who were invited to participate in a survey,[19] 13 responded, and all agreed during the interview that interaction with the pharmacist is advantageous for the management of pain in oncology patients. They highlighted that such interaction contributes to improving patient outcomes and experiences.

Among the 31 patients who agreed to participate in a follow-up survey, 19 were available and eligible to complete the questionnaire. The results[19] indicated that 89% of the patients considered the pharmaceutical service convenient, 89% believed it was reliable in meeting their needs, 100% stated that it enabled them to obtain necessary assistance, 95% considered the quality of the pharmaceutical service exceeded expectations, no patients

reported that the pharmaceutical service did not meet standards, and 84% rated their experience with the pharmaceutical service as better than expected.

These results[19] suggest a favorable trend for both patients and healthcare professionals involved in pharmaceutical clinical services focused on pain management in oncology patients. Collaborative interaction contributes to the distribution of responsibilities in patient care, reducing the workload of healthcare professionals. Additionally, patients benefit from an improvement in pain management, with the pharmacist providing a differentiated perspective for optimizing pharmacotherapy comprehensively.

A majority of the studies[15-20] analyzed revealed an observational approach, lacking the distinction between intervention and control groups, as well as not incorporating randomization. This methodological setup presents significant challenges, compromising causal evaluation due to the inability to isolate the effects of pharmaceutical interventions from external variables. The absence of control groups hinders generalization and compromises the internal validity of the studies, as randomization and the presence of control groups minimize biases and control for confounding variables. Given these methodological limitations, the need for more robust approaches, such as randomized clinical trials, to strengthen the evidence base in the field under study is emphasized.[23]

The scarcity of studies with the profile of randomized clinical trials can largely be attributed to ethical considerations. The inclusion of control groups in such trials could imply depriving oncological patients in distress of qualified pharmaceutical care, raising ethical and humanitarian questions. Therefore, conducting randomized clinical trials in this specific context faces significant ethical challenges.[20]

Despite the inherent limitations of the analyzed studies, it is pertinent to note that the sample in question demonstrates significant statistical robustness, comprising a substantial number of patients, totaling 1.596 individuals. Data collection carried out in all studies exhibited a notable correlation, lending coherence to the results obtained. The consistent convergence of information among the studies suggests a robust observational pattern, even in the face of possible methodological constraints.[20,23]

Bedside rounds with a multidisciplinary team involve professionals from different areas to holistically assess the patient and adapt pain control strategies according to their specific needs. The discussion of clinical cases with the team provides a forum for knowledge exchange, refining therapeutic approaches, and ensuring integrated management. Detailed information about medications, for both the team and patients, is fundamental, providing understanding of analgesic agents and strengthening treatment adherence. Pain assessment is central, allowing for precise identification of patient needs, while identifying medication-related problems enables proactive interventions. Adjustment of analgesic pharmacotherapy, based on regular assessments, is essential for optimizing treatment effectiveness. Finally, the management of adverse reactions plays a preventive role, ensuring that side effects do not compromise the patient's quality of life. Together, these activities form an interconnected network of care, offering a comprehensive and personalized response in the management of oncological pain.[15-18]

In 100.0% of the studies, the implementation of specific activities and interventions was observed, notably the identification of medication-related issues, adjustment of analgesic pharmacotherapy, and management of adverse reactions. These results suggest a predominance of these actions among the activities and interventions adopted by clinical pharmacists in the hospital setting, particularly when involved in managing pain in oncological patients. This trend underscores the relevance

attributed to such practices as fundamental pillars of the pharmaceutical approach in this specific context of healthcare.[15-21]

In 42.8% of the studies,[15,19,21] the performance of bedside rounds and clinical case discussions with the multidisciplinary team was noted. This observation suggests an emerging trend of association between these specific activities. The likelihood of clinical case discussions occurring is considerable when bedside rounds are conducted by the pharmacist alongside the healthcare team, and vice versa. This pattern of association between such practices highlights the potential interconnectedness and complementarity of these activities in the role of the clinical pharmacist in the hospital setting.

In the context of health education, an analysis of the studies reveals that the majority emphasize the role of the clinical pharmacist in providing medication information to the healthcare team, offering detailed guidance on the pharmacokinetics and pharmacodynamics of opioids, highlighting specific characteristics of each medication for appropriate selection, dosage data, dose adjustments according to patient response, strategies to prevent and manage potential side effects, and identification of drug interactions, observed in 71.4%[15-17,20,21] of the studies, while for providing information to patients, presence was noted in 85.7%.[15-17,19-21] This scenario demonstrates an active involvement of the clinical pharmacist in disseminating relevant information and suggests patient engagement as an educational role.

Among all the studies subjected to analysis, 42.9%[15,17,19] showed the inclusion of the pharmacist as the professional responsible for pain assessment in hospitalized patients. In interviews conducted by pharmacists, inquiries related to pain patterns and intensities, efficacy and use of rescue doses, as well as types and degrees of adverse reactions were assessed. For pain assessment by clinical pharmacists, pain intensity was measured through the application of the Numeric Rating Scale. This methodological approach reflects a comprehensive and structured approach to pain assessment, aligned with the use of standardized instruments and well-defined criteria for quantifying pain intensity.[15-20]

In this context, an important aspect was considered: economic issues and the financial impact of implemented pharmaceutical services. Despite its limitations, such as not including the length of hospital stay, which could imply a greater positive financial impact for the institution, the study revealed 41 interventions related to calculable costs. Of these, the discontinuation of unnecessary medications resulted in a saving of $710.3, while the prevention of Adverse Drug Reactions (ADRs), which leads to increased use of medications to control symptoms, resulted in a cost increase of $141.3. Dose adjustment increased costs by $75.89. The total cost savings were $489.90, with an average savings of $11.94 per intervention.[21]

Thus, over the three years following the implementation of pharmaceutical services, there was an 8.0% reduction in the length of hospital stay in the oncology unit for patients diagnosed with cancer upon admission, leading to decreased hospital costs and improvement in the quality of life of patients.[17]

Regarding the main barriers faced by pharmacists when performing interventions related to adjusting or changing analgesics with prescribers, it is pointed out that the conservative prescribing patterns adopted by physicians represent the main barrier to achieving adequate pain relief in oncological patients. Additionally, 28.0% of pharmacists expressed considerable concern about the possibility of patients developing dependence, which constitutes a significant barrier to prescribing opioids in pharmacotherapeutic approaches to pain treatment. These results point to the need to incorporate health education as an integral component of the treatment for patients with cancer-related pain.[24]

In another study, complementing the information about barriers, it is highlighted that, for the pharmacists who participated in the research, the fear of dependence emerges as the most prominent and difficult barrier to overcome, both for the patient and the physician. This finding underscores that opiophobia constitutes a frequent barrier to improving pain management in oncological patients. Such a scenario is particularly relevant, considering that opioids represent the primary class of analgesics for treating pain in these patients, with high-potency opioids such as morphine, fentanyl, and methadone playing a fundamental role in controlling severe pain.[16,17,19]

PRACTICAL IMPLICATIONS

The evidence found in this research presents significant practical implications, such as encouraging the integration of clinical pharmacists into multidisciplinary care teams, which allows for a more comprehensive and specialized approach to oncological pain treatment, ensuring precise evaluation of the efficacy and safety of prescribed medications. Additionally, pharmacists can play a role in educating healthcare professionals about evidence-based practices in oncological pain management, promoting rational medication use and reducing the risk of therapy-related adverse reactions.[25,26]

In terms of financial implications for hospital institutions resulting from pharmaceutical services in oncological pain management, they are also relevant. Optimizing medication use through pharmacist intervention can result in cost reduction associated with complications arising from their improper use, such as adverse reactions, prolonged hospitalizations, and readmissions. Furthermore, the implementation of effective protocols for oncological pain management can lead to a reduction in hospitalization time and improvement in patient satisfaction, which, in turn, contributes to reducing hospital operational costs and maximizing available resources. These practical and financial implications underscore the importance of investing in clinical pharmaceutical services as an integral part of the oncological pain management strategy in hospital settings.[27,28]

LIMITATIONS

It is emphasized that the factors identified in this study may not be transferable or generalizable to all institutions, as each one presents its own reality regarding the conditions for providing clinical pharmaceutical services in the management of pain in oncological patients.

CONCLUSION

In light of the results presented, even considering the inherent limitations of the studies, it is possible to analyze the impact in favor of the benefits of clinical pharmaceutical services in enhancing the management of pain in hospitalized oncological patients. This trend is evident not only in the improvement of patients' pain condition but also in the positive financial impact on hospital institutions that incorporate these services. The analysis reveals that the main activities and interventions performed by pharmacists in hospital settings include the identification of medication-related problems, adjustment of analgesic pharmacotherapy, and management of adverse reactions.

However, it is important to note that the effective implementation of these interventions faces significant challenges, notably the resistance and fear of opioid use, both by healthcare professionals and patients, and the conservative prescribing patterns adopted by physicians. These barriers directly influence the acceptance and effectiveness of pharmaceutical interventions.

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