

The use of opioids in the treatment of oncologic pain in the elderly

O uso de opioides no tratamento da dor oncológica em idosos

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ABSTRACT

BACKGROUND AND OBJECTIVES: The use of opioids in cancer is already widespread and proven by several well-controlled clinical trials. However, the elderly with cancer pain are undertreated due to the lack of knowledge in the management of these patients, the underestimation of pain, as well as the fear of complications arising in this age group. Therefore, the scientific community contributes to giving inputs to create possible clinical and health guidelines. The present study aimed to perform a systematic literature review of opioid treatments proposed for cancer-related pain in elderly patients.

CONTENTS: The search on the literature included papers addressing cancer pain treatment with opioids among the elderly, published from 2008 to 2018, and available in Portuguese or English. Searches were conducted on Medical Literature, Analysis, and Retrieval System Online (MEDLINE) and Latin American and Caribbean Health Sciences Literature (LILACS) electronic databases using the keywords “cancer pain”, “opioids”, and “elderly” in both languages, combined with the Boolean operator “AND”. To analyze the quality of the method, the adapted Critical Appraisal Skills Programme was used. Of a total of 411 studies found, 32 were included. About 75% of the selected articles were published in the last five years.

CONCLUSION: The results showed that opioids remain the pillar to treat cancer-related pain in the elderly. They can be used for better management of pain, but with caution due to the possible adverse effects. In addition, pain management in the elderly requires a multifactorial analysis, including comorbidities, polypharmacy, and patient functionality. Therefore, an individualized approach in the elderly patient is required in order to enhance results, reduce side effects, and improve quality of life.

Keywords: Cancer pain, Elderly, Opioids.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O uso de opioides em dor oncológica já é amplamente difundido e comprovado por diversos ensaios clínicos bem controlados. Entretanto, os idosos com dor oncológica são subtratados pela falta de conhecimento no manejo, a não valorização algica nesses pacientes, bem como o receio das complicações advindas nesse grupo etário. Portanto, contribui a comunidade científica, dando substrato para a elaboração de possíveis diretrizes clínicas e de saúde. Este estudo teve como objetivo realizar uma revisão sistemática da literatura sobre o tratamento farmacológico com opioides proposto para dor oncológica em pacientes idosos.

CONTEÚDO: A busca na literatura incluiu artigos sobre o uso de opioides para o tratamento da dor oncológica em idosos, publicados entre 2008 e 2018, disponíveis em português ou inglês. Foram conduzidas buscas nas bases eletrônicas de dados Medical Literature, Analysis, and Retrieval System Online (MEDLINE) and Latin American and Caribbean Health Sciences Literature (LILACS) utilizando os descritores “dor oncológica”, “opioides” e “idoso” em ambas as línguas, combinados com o operador booleano “AND”. Para a análise da qualidade metodológica, foi utilizado o Critical Appraisal Skills Programme adaptado. Do total de 411 estudos resultantes, foram incluídos 32. Cerca de 75% dos artigos selecionados foram publicados nos últimos cinco anos.

CONCLUSÃO: Os resultados demonstraram que os opioides continuam sendo o pilar no tratamento da dor oncológica em idosos. Podem ser usados para o melhor gerenciamento da dor, mas com cautela por causa dos possíveis efeitos adversos. Além disso, o manejo da dor em idosos requer uma análise multifatorial incluindo as comorbidades, a polifarmácia e a funcionalidade do paciente. Portanto, é necessário tratar de modo individualizado o paciente idoso com o intuito de maximizar os resultados, diminuir os efeitos adversos e melhorar a qualidade de vida.

Descritores: Dor oncológica, Idosos, Opioides.

INTRODUCTION

Aging is a worldwide phenomenon. Over the next 43 years, the number of people over 60 will be three times higher than the current one¹. The elderly population in Brazil has also been growing exponentially. By 2030 there will be 41.5 million older people or 18% of the population². Due to this, population aging has been one of the major public health challenges, because as people get older, they are more likely to develop or contract chronic diseases such as cancer, as risk factors accumulate for certain types of this disease³. Currently, more than 70% of cancer cases worldwide occur in

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the elderly⁴. Therefore, there is an increase in the prevalence of chronic health problems and disabilities associated with the population of this age group, involving important specificities such as multimorbidities, polypharmacy, and their complications³.

In elderly cancer patients, pain is the most prevalent symptom, as about 80% of them report some kind of painful sensation. Inadequate pain treatment can have serious consequences, both individually and socially⁵⁻⁸.

Pain management should be performed according to the three-step analgesic ladder proposed by the World Health Organization (WHO) in the 1980s⁹, in which opioids are recommended for the treatment of moderate to severe pain^{8,10}. In addition to limited evidence for opioid use in elderly patients, there are still barriers such as fears, myths, and stigmas regarding this type of prescription^{5,10-12}.

Therefore, this study aimed to conduct a systematic literature review addressing the use of opioids in the treatment of cancer pain in the elderly. The study also aimed to explore the repercussions of opioid use in pain treatment, as well as its main barriers to adequate management in this population.

CONTENTS

This study was conducted as a systematic literature review following the guidelines established by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). In order to achieve a systematic literature review, the research question was initially established considering the proposed theme, i.e., the use of opioids in cancer pain treatment in the elderly, thus classifying individuals over 60 years. Then, between March and December 2018, searches were done in the Medical Literature, Analysis, and Retrieval System Online (MEDLINE) and Latin American and Caribbean Health Sciences Literature (LILACS) electronic databases, aiming at gathering and evaluating the main articles on the use of opioids for cancer pain treatment in the elderly, published between

2008 and 2018, available in Portuguese or English, using the descriptors “cancer pain,” “opioids,” and “elderly” and their respective Portuguese terms, all present in the Health Science Descriptors (DeCS) and Medical Subject Headings (MeSH), combined with the Boolean operator “AND”.

The criteria used for articles inclusion were: a) articles concerning the proposed theme, i.e., the use of opioids in cancer pain treatment in the elderly; b) articles published between 2008 and 2018; c) articles in Portuguese or English; d) articles available in full; e) articles on randomized studies, systematic reviews and observational studies; f) articles that met the criteria proposed by the Critical Appraisal Skills Program (CASP) checklist for qualitative research.

Exclusion criteria were a) articles addressing a non-pharmacological treatment of pain; b) articles describing animal studies; c) dissertations, theses and case reports; d) repeated articles among electronic databases.

The articles were categorized, allowing the gathering of information such as identification of the original article and its authors, journal, year of publication, database, methodological characteristics, level of evidence, measured interventions, and results found. The critical analysis of the data obtained in the studies was performed after the organization of the selected articles. The CASP instrument was applied to ensure the methodological rigor, relevance and credibility necessary for an integrative review of studies with different approaches.

Searches in the MEDLINE and LILACS electronic databases resulted in 411 articles published between 2008 and 2018. The initial evaluation was performed by reading the title, excluding 321 articles that did not present the theme “opioids in cancer pain treatment in the elderly”. Then, the remaining 90 articles with inclusion potential were previously selected for evaluation of their abstracts according to the eligibility criteria. Three independent reviewers read the abstracts, and the publications that met the inclusion criteria were then fully assessed. In total, 32 articles were selected for this study; 75% were published in the last five years (Figure 1, Table 1).

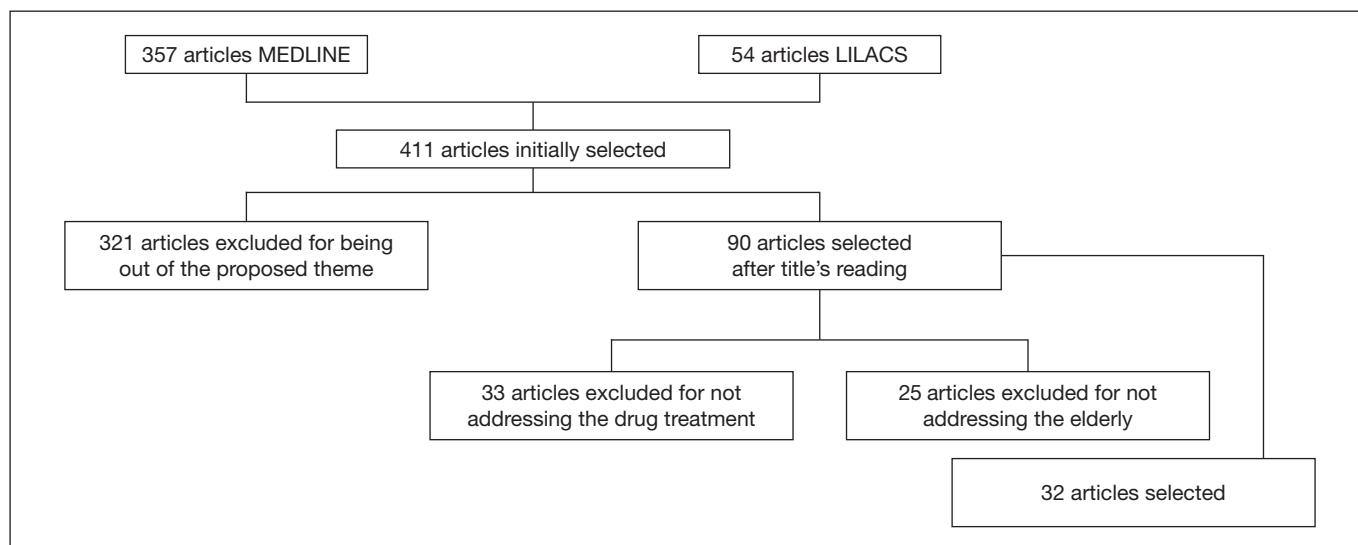


Figure 1. Data collection

Table 1. Selected articles

Authors	Purpose	Methodology	Therapy	Conclusion
Passik ¹³	Assess long-term opioid therapy, including unmet needs, risks, and solutions	Literature review	Opioids	Chronic pain and abuse of prescribed opioids are common and substantially affect patients, doctors, and the society. Aggressive treatment of chronic pain should be balanced with the need to minimize the risks of opioid abuse, misuse, and deviation.
Wilson et al. ¹¹	Examine the prevalence of pain, its perceived severity, and its correlation across a range of physical, social, psychological, and existential symptoms.	Multicenter study addressing cancer patients' pain and assessing 21 other symptoms and concerns		Continued pain is a problem for many cancer patients under palliative care, especially in younger individuals approaching death
Paice and Ferrell ⁶	Review available pain management treatments considering the individual needs of patients as well as special populations, including the elderly, cancer survivors, patients with addictive diseases, and those at the end of life.			The urgent need to address cancer pain issues emerged in oncology in the 1970s, largely influenced by the introduction of palliative care (PC). PC providers demonstrated that pain could be relieved, and failure to do so meant the decreased quality of life. Over the past 30 years, cancer pain relief has become a priority in oncology. Despite significant advances, there are still continuing barriers to quality of care and pain relief. There are many resources to assist doctors in treating cancer pain.
Rangel and Telles ⁵	Address the principles for cancer pain treatment, as well as barriers related to patients, health professionals, and the health system.	Literature review		All physicians should be familiar with the use of analgesics. Opioids should not be prescribed just because the patient has a fatal disease, but according to the intensity of his/her pain.
Hennemann-Krause ¹⁴	Present the rational use of analgesic drugs, highlighting their indications, doses, adverse effects, and proper care for the adequate prescription of common analgesics and opioids for the control of chronic cancer pain.	Literature review	Common analgesic drugs and opioids	Opioids prescription should not be done because the patient has a fatal disease, but according to the intensity of the pain.
Madadi et al. ¹⁵	Identify patterns and characteristics among opioid users	Qualitative study	Opioids	New susceptible groups of opioid users with related cause of death were identified. The first evidence to help quantify the contribution of opioid misuse to user mortality in Canada
Srisawang et al. ¹⁶	Assess the knowledge and attitudes of physicians and policymakers/regulators regarding the use of opioids for cancer pain management.	Cross-sectional study	Opioids	Continued education for physicians and conference organization is required for policymakers/regulators. Special education and training should be addressed to clarify the terms of physical addiction.
Zeppetella ¹⁷	Known non-parenteral opioid formulations, such as sublingual fentanyl, which can provide faster and more effective relief from transitory exacerbation cancer pain.	Systematic review	Non-parenteral opioids, such as sublingual fentanyl	Fentanyl formulation available at doses of 100, 200, 400, 600 and 800 µg approved for the treatment of transitory exacerbation pain in opioid therapy tolerant adult cancer patients for underlying persistent cancer pain
Kraychete, Siqueira and Garcia ¹⁸	Discuss recommendations for opioid use in newborns, children and the elderly	Systematic review	Opioids	The use of opioids at extreme ages is still a challenge. However, continued education around the subject is needed, stimulating clinical research and the creation of evidence-based recommendations. The safe use of these agents in the correct indication and proportion for pain relief decreases risks and should be the basis of sound clinical conduct.

Continue...

Table 1. Selected articles – continuation

Authors	Purpose	Methodology	Therapy	Conclusion
Nunes, Garcia and Sakata ¹⁹	Assess the use of morphine as the first drug for moderate cancer pain treatment in patients with advanced disease and/or metastasis, as an option to the recommendations of the WHO-recommended analgesic ladder.	Randomized controlled study	Morphine	The use of morphine as the first drug for pain treatment did not promote a better analgesic effect than the WHO-recommended ladder, and there was a higher incidence of adverse effects.
Rocha et al. ²⁰	Analyze the self-care of older people living with cancer in outpatient treatment, from the perspective of their autonomy	Qualitative and descriptive research		The autonomy for self-care of the elderly is manifested in the concern with food, knowledge of the body's limits, changes imposed by living with cancer, and family support.
Kim et al. ²¹	Assess pain response to opioid rotation or opioid combination in patients with uncontrolled cancer pain	Randomized study	Opioids	For patients with chronic uncontrolled cancer pain, both opioid rotation and combination strategies appear to provide significant pain relief and better patient satisfaction.
Reticena, Beuter and Sales ²²	Understand the experiences of the elderly with cancer pain	Qualitative research based on Heidegger's phenomenology, with recorded interviews		Cancer pain has biopsychosocial repercussions for the elderly, generating changes in their life activities and requiring holistic and authentic care.
Reyes-Gibby, Anderson and Todd ⁶	Determine the risk of opioid misuse among emergency services for cancer pain patients and assess the demographic and clinical factors associated with increased risk of opioid abuse.	A cross-sectional study with a convenience sample	Opioids	The risk of opioid misuse among cancer patients is substantial. Tracking misuse in emergency departments is feasible
Coluzzi et al. ¹⁰	Review some basic principles of opioid analgesia based on experience and knowledge of current publications on this care	Literature review	Opioids	Establish titration, individualization, and gradual reduction, along with the application of other good medical practice and clinical experience/judgment, including non-pharmacological approaches, can assist health care professionals in the effort to achieve optimal pain treatment.
Galicia-Castillo ¹²	Manage chronic pain safely in the elderly	Literature review		A complete assessment, including description and management of pain, comorbidities, physical examination, and diagnostic tests are required for patient control. It is also important to inquire about the history of substance abuse.
Cella et al. ²³	Assess the prevalence of pain and opiophobia in cancer patients.	A cross-sectional study with patients undergoing exclusive cancer clinical treatment in an outpatient cancer hospital	Opioids	A high prevalence of moderate to severe pain was found in the observed patients, as well as a high prevalence of opiophobia.
Lin et al. ²⁴	Examine Taiwan's opioid prescribing standards for cancer patients to discover their potential concerns	Review of claims in the Taiwan National Health Insurance database for cancer-diagnosed patients from 2003 to 2011	Opioids	The use of strong short-acting opioids increased during the study period. Instead of oral opioids, transdermal fentanyl was the most commonly used opioid among cancer patients in Taiwan.
Oosten et al. ²⁵	Study the pharmacokinetics of subcutaneous and transdermal fentanyl and assess relays between subcutaneous and transdermal uses	Cohort study	Subcutaneous and transdermal fentanyl	Absorption may lead to fluctuations in plasma transdermal and subcutaneous fentanyl concentrations. Relay schemes are not applicable for subcutaneous and transdermal fentanyl rotations
Reddy et al. ²⁶	Determine the relationship between the equivalent daily dose of morphine and the dose of transdermal fentanyl in opioid rotation	Retrospective study	Morphine and transdermal fentanyl	The median rotation rate of transdermal fentanyl for the equivalent daily morphine dose was 100 mg/day and 2.4 µg/h, suggesting that 100 µg/h is equivalent to the 240 mg daily morphine dose.

Continue...

Table 1. Selected articles – continuation

Authors	Purpose	Methodology	Therapy	Conclusion
Barbera et al. ²⁷	Verify whether opioid prescriptions changed among older adults after 2007, in the context of changing opioid regulations, and whether effects were different among patients with a history of cancer	Elderly patients stratified annually into three groups: no history of cancer, diagnosed with cancer for more than 5 years and diagnosed with cancer for 5 years or less. Trends over time have been assessed per year for 1) opioid prescription rate, comparing trends before and after 2007; 2) average daily dose of opioid	Opioids	Decreasing prescription rates have been observed in some drug subclasses. The potential impact of these changes on the quality of symptom control for cancer patients requires further investigation.
Bennett, Paice and Wallace ²⁸	Understand the comprehensive management of cancer pain, including a thorough assessment, along with the use of pharmacological, non-pharmacological, integrative, and interventional therapies.	Literature review	Pharmacological, non-pharmacological, integrative, and interventional therapies	Although cancer pain remains prevalent, it remains undertreated, partly due to the concerns about opioid use. Opioids' efficacy in advanced disease is already clearly established; however, there are still issues about opioids' safety and efficacy in long-term cancer survivors.
Haider et al. ²⁹	Assess changes in the opioid type and prescription dose among patients who are referred by oncologists to an outpatient palliative care clinic	Review of electronic patient health records at new CP Outpatient Consultations between January 1 and April 30 of each year from 2010 to 2015. Demographic data, cancer type, and stage, symptom assessment, performance status, opioid data were collected. Opioid type and dose defined as the equivalent daily dose of morphine	Opioids	Over the past few years, the equivalent daily dose of morphine prescribed by reference oncologists has decreased. Following hydrocodone reclassification, the use of tramadol with less stringent prescription limit increased
Kuip et al. ³⁰	Summarize the multiple factors studied that potentially influence fentanyl pharmacokinetics focusing on implications for cancer patients	Systematic review	Fentanyl	Although aging may influence the fentanyl pharmacokinetics, sound conclusions are difficult to draw. There is at least a risk of lower clearance and, therefore, greater accumulation in elderly patients. Therefore, fentanyl should be titrated with caution in elderly patients.
Lee et al. ³¹	Assess the non-inferiority of oxycodone/naloxone compared to controlled-release oxycodone for cancer pain control	Randomized, open, phase IV, parallel-group clinical trial	Oxycodone/naloxone and oxycodone	The group receiving oxycodone/naloxone was no lower than the one receiving oxycodone in terms of pain reduction after 4 weeks of treatment and had a similar safety profile.
Nosek et al. ³²	Compare analgesia and adverse effects during oral administration of morphine and oxycodone, transdermal fentanyl and buprenorphine in cancer and pain patients	Randomized clinical trial	Morphine, oxycodone, transdermal fentanyl, and buprenorphine	All opioids were effective and well-tolerated. Morphine was the most effective for pain improvement compared to some of the questionnaire items regarding the negative impact of pain on patients' daily activities.
Schmidt-Hansen et al. ³³	Assess the efficacy and tolerability of oxycodone in any pain administration route in adults with cancer.	Systematic literature review	Oxycodone	For clinical purposes, oxycodone or morphine may be used as first-line oral opioids for pain relief in cancer adults.
Yen et al. ⁷	Assess the efficacy and safety of proportional doses of fentanyl oral soluble film in patients with transitory exacerbation cancer pain.	An open, non-comparative multicenter study	Fentanyl oral soluble film	The dose of fentanyl oral soluble film proportional to the opioid regimen for basal pain treatment is effective and well-tolerated for the treatment of patients with transitory exacerbation cancer pain.

Continue...

Table 1. Selected articles – continuation

Authors	Purpose	Methodology	Therapy	Conclusion
Guitart et al. ³⁴	Assess the effect of sublingual fentanyl tablets for pain relief, quality of life and adverse effects in cancer pain patients according to cancer stage and basal opioid regimen	Qualitative study	Sublingual fentanyl tablets	Subgroup exploratory analyses demonstrate the efficacy and safety of sublingual fentanyl tablets for treating transitory exacerbation cancer pain, regardless of cancer stage and basal opioid regimen.
Masel et al. ³⁵	Document the feasibility of fentanyl oral tablets for the treatment of patients with transitory exacerbation cancer pain.	Prospective study	Fentanyl oral tablets	Treatment with fentanyl oral tablets led to quick pain relief and reductions in the number of episodes of transitory exacerbation cancer pain. Patient satisfaction was rated as excellent or good.
Peng et al. ³⁶	Compare the efficacy and adverse effects of patient-controlled intravenous analgesia with hydromorphone, sufentanil, and oxycodone in the treatment of patients with advanced cancer and pain.	Retrospective serial study	Patient-controlled intravenous hydromorphone, sufentanil, and oxycodone	There was no significant difference in analgesic effect and adverse effect between hydromorphone, sufentanil, and oxycodone.
Yamada et al. ³⁷	Assess the effect of continuous pain management interventions and opioid-induced adverse effects on outpatients with cancer	Systematic review	Opioids	Pharmacist interventions can help to adequately achieve the management of pain and adverse effects through interviews and ongoing assessments of cancer patients prior to consultations with physicians, which underlines the importance of pharmacist interventions.

DISCUSSION

The aging process is one of the factors that leads to the increased incidence of cancer, as there are inherent physiological changes that jointly cause molecular changes. These changes are combined with mitogenic factors that, associated with the insufficiency and dysregulation of the immune system that is characteristic of this age group, favor cell proliferation and, consequently, the onset of cancer³⁸.

The physiological changes caused by aging also significantly affect the metabolism of administered drugs, especially opioids. Thus, healthcare professionals should be aware of

the following factors: patient susceptibility to adverse drug effects, iatrogenic cascade, adverse drug reactions, hospitalization, and institutionalization, as well as polypharmacy commonly found in the practical reality of the elderly.

Usually, as a result of aging, organs and systems have less functional reserve. Therefore, they present particularities involving the pharmacokinetics and pharmacodynamics of drugs regarding absorption, distribution, metabolism and excretion variables (Table 2).

Pain is an unpleasant experience associated with tissue or potential injury, with sensory, emotional, cognitive, and social components. In turn, persistent pain is more complicated in

Table 2. Pharmacological changes due to aging

Absorption	Distribution
Reduction of: <ul style="list-style-type: none"> • Splanchnic blood flow • Gastric secretion • Absorption surface • Gastrointestinal motility 	Reduction of: <ul style="list-style-type: none"> • Plasma volume (8%) • Cardiac output • Body water (25%) • Plasma albumin (20%) • Replacement of muscle mass with fat (30 to 40%)
Increased gastrointestinal pH	Increased gastrointestinal pH
Metabolism	Excretion
Reduction of: <ul style="list-style-type: none"> • Liver mass • Hepatic blood flow (40%) Change in enzymatic activity (cytochrome P450) Change in phase I of metabolism (hydroxylation, oxidation, hydrolysis, and n-demethylation)	Reduction of: <ul style="list-style-type: none"> • Kidney mass • Number of functional nephrons • Renal blood flow (1-2% per year, reaching 50% in old age) • Glomerular filtration (30 to 50%) Increased incidence of spontaneous glomerular sclerosis

Source: Adapted from the Brazilian Society of Geriatrics and Gerontology³⁸.

the elderly than in younger patients. Up to 40% of elderly outpatients report pain, and this symptom affects 70-80% of patients with advanced cancer⁵.

For cancer pain treatment, it is necessary to know its classification. Didactically, pain can be divided into two main types: 1) nociceptive, which represents tissue damage; 2) neuropathic due to nervous system's injury or dysfunction as a result of abnormal activation of the nociceptive route. Also included in this analysis are the local effects of tumor growth and local invasion, as well as the effects of auxiliary therapies such as chemotherapy and radiotherapy, as well as other complications. Therefore, in cancer patients, mixed pain prevails^{5,38}. Pain complaints can be both precursors for cancer diagnosis as a consequence of the treatment adopted. Most of the time, pain is identified by the patient him/herself and not by health care professionals.

It is noteworthy that not only cancer involvement, but also the aging process lead to limitations in the body's physiological functions. Thus, the elderly are more predisposed to dependence on other individuals for self-care, loss of autonomy, and deterioration of quality of life. In this environment, as the evaluation of painful conditions in the elderly is a multidimensional experience, it encompasses several domains, including sensory, cognitive, affective, behavioral and sociocultural ones. Given this, the importance of pain management using validated protocols and scales is evidenced in order to provide the most appropriate treatment according to the patients' individual particularities^{5,39}.

However, there is not yet a single and exclusive standard instrument for the elderly that allows for global pain assessment and is free of bias and measurement errors, as there are different variables involved, such as patient interpretations of pain, expectations regarding the problem and its treatment. Notably, good anamnesis, detailed physical examination, and analysis of external factors are fundamental for the adoption of appropriate conduct.

From a general perspective, the WHO⁹ analgesic ladder is the most widely used. In specialized services, one-dimensional scales such as face and verbal numeric scales are employed, as well as multidimensional scales such as Geriatric Pain Measure

(GPM), McGill Pain Questionnaire (MPQ), Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC), and Pain Assessment in Advanced Dementia (PAINAID)³⁸.

Cancer pain can be controlled with simple treatments in more than 80% of cases. In the other 20%, however, it is necessary to adopt a multidisciplinary approach, with a careful reassessment of pain and the use of auxiliary drugs and/or non-pharmacological interventions for its control^{5,38}. Regarding pharmacological treatment, opioids are among the most powerful and widely available drugs, constituting the pillar for the treatment of moderate to severe cancer pain^{7,12,19}.

Recent clinical guidelines and recommendations on the management of patients with advanced cancer emphasize the importance of adequate pain relief with the use of opioid analgesics to improve their quality of life. It is essential that patients are continuously informed about the goals of pharmacological therapy and regularly reevaluated during treatment⁷.

The American Geriatrics Society has come to consider the use of opioids as an effective and sometimes indispensable option for treating pain in elderly patients. This is due, among other factors, to the potentially serious adverse events associated with the use of anti-inflammatory drugs, such as diclofenac and ibuprofen and COX-2 inhibitors (COXIB), such as celecoxib¹².

Opioids mimic the action of endogenous opioid peptides. They may suppress the activation of presynaptic and postsynaptic tension-dependent calcium channels or activate postsynaptic potassium channels. This suppression results in decreased excitability and suppression of neuron activity-dependent transmitter release or adenylyl cyclase action, reducing the impulses to the brain and spinal cord^{12,14}.

The four major opioid receptor subtypes are mu-opioid receptor (MOP), delta-opioid receptor (DOP), kappa opioid receptor (KOP), and nociceptin peptide factor (NOP). Clinically used opioids are mostly MOP selective, although they may also interact with other receptors if administered at high doses¹⁴. Indeed, elderly cancer patients suffering from severe pain may benefit from the use of strong opioids such as fentanyl, morphine, oxycodone, hydromorphone, methadone, buprenorphine, among others (Table 3).

Table 3. Opioid analgesics

Drugs	Presentation, doses	Therapeutic doses/interval	Effects (start/peak/end)
Fentanyl	Patches 5, 10 and 20 mg	5-20 mg/7 days	24 hours/72 hours
Morphine	Capsules, 10 and 30 mg Oral solution, 10 mg/mL Ampoules, 1 mL-10 mg/mL	5-200 mg/4 hours (oral dose)	15 min/2 hours/4 hours
Morphine LC	Capsules, 30, 60 and 100 mg	30-100 mg/8 to 12 hours	1 hour/6 hours/14 hours
Oxycodone	Capsules, 10, 20 and 40 mg	10-40 mg/12 hours	1 hour/8 hours/25 hours
Hydromorphone	Extended release tablet, 8, 16 and 32 mg	8-32 mg/24 hours	6 to 8 hours/24 hours
Methadone	Capsules, 5 and 10 mg Ampoules, 10 mg/mL	10-50 mg/6 to 12 hours	1 hour/12 hours/25 hours
Buprenorphine	Patches, 5, 10 and 20 µg	5-20 µg/7 days	18 to 24 hours/72 hours/7 days

Source: Adapted from the Brazilian Society of Geriatrics and Gerontology³⁸.

Fentanyl

Transdermal fentanyl is a potent, long half-life agonist opioid with lipophilicity. It is very suitable for patients unable to use the oral route due to odynophagia and/or dysphagia, with persistent nausea and vomiting, in situations that may lead to bronchoaspiration, intolerance to morphine and other opioids, and due to its ease of use. Its use is recommended in patients with constant pain but little episodic pain. After the patch placement, effective analgesia starts and lasts 12 to 24 hours. The action time of each patch is 72 hours, remaining for 12 to 18 hours after its removal. The transmucosal formulation has short action duration, non-invasive administration route, and tolerable safety profile^{14,17,25,26,34,35}.

Morphine

Morphine is indicated for pain classified as moderate to severe, with good results in pain of nociceptive or somatic origin, as 85% of them respond to this drug. It has a potent analgesic effect, short half-life, with therapeutic analgesia interval of 4 to 6 hours, without ceiling and linear effect, i.e., the higher the dose, the greater the analgesia. It is well-absorbed by the gastrointestinal tract, with action onset within 20 to 40 min. It undergoes hepatic metabolism and renal elimination, and only a small part is eliminated by the gallbladder. It does not generally accumulate in tissues and the free fraction in plasma is dialyzable. However, in patients with impaired renal function, it has a stronger effect and longer action duration, because there is an accumulation of active metabolites, especially morphine-6-glucuronide^{6,14,19,29,32,39}.

Oxycodone

Oxycodone is a MOP agonist in the brain and spinal cord and has some activity in KOP. It goes through the first-pass metabolism²⁶. It is the preferred drug for change when morphine fails to provide effective pain relief but may also be recommended as a first-line drug for severe cancer pain control^{14,31}.

Hydromorphone

Hydromorphone hydrochloride is intended for single-dose administration. It is a potent MOP agonist, showing a poor affinity for KOP. It is the only opioid that has controlled single-phase release and promotes continuous dose-dependent analgesia during the 24 hours interval between two doses. It is moderately water-soluble, has hepatic metabolism and urinary excretion. Its primary metabolite is hydromorphone-3-glucuronide (H3G), in which concentrations are approximately 27-times higher than those of the original drug, indicating that H3G has a smaller volume of distribution and/or lower clearance^{7,14}.

Methadone

The methadone is a synthetic opioid, agonist of MOP, KOP, DOP, and N-methyl D-Aspartate (NMDA) receptor. It appears to block serotonin and norepinephrine reuptake. It is a lipophilic drug, which analgesic effect usually lasts from 6 to 8 hours and may reach up to 24 hours. Its analgesic power can be up to five to 10 times higher than morphine. Its oral absorption is

quick and almost complete, and its metabolism occurs mainly in the liver. Methadone and its metabolites can be eliminated by feces and urine. Renal excretion of methadone decreases with time of use and can, therefore, be used in patients with chronic kidney disease. It causes less nausea, constipation and sedation than morphine. However, the interaction between methadone and other drugs is more frequent than with morphine^{14,40}.

Buprenorphine

The buprenorphine is a thebaine derivative, 25 to 40 times more potent than morphine. Its action mechanism is suggested to occur by partial agonist effects on MOP and KOP, as well as antagonistic action on DOP. It is found in intravenous, sublingual and transdermal presentations, the latter being the only one available in Brazil. The patches come in the 5, 10 and 20 µg/h presentations, which are released within seven days. It has no systemic accumulation and its elimination occurs mainly through the intestinal tract and is therefore considered safe in patients with renal failure⁶.

FINAL CONSIDERATIONS

Considering the main strong opioids described, it is noteworthy that pain intensity is not adequately assessed in approximately 50% of cancer patients. Besides, adverse effects of opioids, such as nausea, vomiting and constipation, may be limiting factors for the use of these drugs, leading to their early discontinuation and consequent inadequate analgesic efficacy. Therefore, in order to achieve proper pain management in cancer patients, it is necessary to simultaneously minimize both the pain and the adverse effects of opioids employed for its control^{12,36,39,40}.

It is essential that health professionals assess the barriers that prevent or hinder the use of opioids in the elderly when treating cancer pain. In several situations, these patients are undertreated due to the lack of knowledge about cancer pain management, due to their pain complaints not being adequately taken into account, due to the fear of the complications arising from the use of opioids and due to bureaucratic and cultural difficulties in the implementation of this type of pharmacological therapy.

Some points are important to elucidate the difficulties in prescribing opioids when treating cancer pain, such as inadequate pain assessment, as only a small number of physicians reported applying pain management guidelines in their practice; 23 to 31% of physicians tend to delay the adoption of strong opioids until patients reach the terminal stage of their disease, or until their pain becomes intractable due to the difficulty in managing adverse effects; 25 to 40% of physicians are concerned about opioid addiction, and there is even greater fear in patients with a family history of addiction. Moreover, although oncologists have shown excellent basic knowledge about the use of opioids to treat cancer pain than physicians in other specialties, there is still a significant information deficit within their specialty^{15,24,27,37,39,41}.

From the patient's perspective, other potential barriers to the use of opioids may include lack of communication with

physicians, resulting in insufficient notification of symptoms; misconceptions about the pain drug due to the fear of adverse effects, dependence, tolerance, and reduced immunity; and fatalistic beliefs, i.e., if the pain is increasing, the idea of inevitable and uncontrollable progression of the disease is created. Patients with drug concerns and misconceptions have worse adherence to treatment. In addition, pain intensity is associated with a higher level of psychological distress, including depression, anxiety, hostility, and mood disorders. Therefore, there is a need for psychiatric and psychological follow-up to complement and increase the efficiency of pharmacological treatment^{10,13,22,23}.

Also, bureaucratic difficulties imposed on the prescription by government agencies, as well as on the access to these drugs and their price, were reported. Regulatory restrictions on opioid prescribing differ widely across countries. Thus, in developed countries, physicians have access to a wide range of opioids, while those in developing countries have limited treatment options²⁰⁻²².

In order to solve or alleviate these problems mentioned above, there are several strategies, including the use of validated pain scales for patient pain selection and monitoring; multicomorbidities assessment; multidimensional assessment; choice of opioids according to the particularities and pathophysiology of pain; anticipation and treatment of adverse effects; referral to other specialties when necessary; education of patients, families and, especially, caregivers; provision of psychosocial support; information to patients that most cancer pain can be alleviated; establish realistic and objective expectations regarding pain. In addition to this, it is necessary to promote educational lectures to disseminate strategies to be adopted for better pain management by health professionals and to increase the availability of opioids.

CONCLUSION

The results showed that opioids remain the pillar in cancer pain treatment in the elderly. They can be used for better pain management, but with caution due to the possible adverse effects. In addition, pain management in the elderly requires a multifactorial analysis, including comorbidities, polypharmacy, and patient functionality. Therefore, it is necessary to treat the elderly patient individually in order to maximize results, reduce adverse effects and improve quality of life.

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