MINISTRY OF HEALTH OF UKRAINE

ODESA NATIONAL MEDICAL UNIVERSITY

International faculty

Faculty of Medicine and Pharmacy

Department of General and Clinical pharmacology with Pharmacognosy

Zerouali Chaima

Medical and pharmaceutical support for patients in palliative care: emphasis on pain relief / Медична та фармацевтична підтримка пацієнтів паліативної допомоги: акцент на знеболенні

Specialty: 226 "Pharmacy, industrial pharmacy"

Specialization: 226.01 "Pharmacy"

Field of knowledge: 22 "Healthcare"

Qualification work for obtaining the educational level "Master"

Supervisor: PhD, Associate professor

Sergey STRECHEN

Reviewer: PhD, Associate professor

Oksana BIELIAIEVA

Recommended for protection:

Department meeting protocol

№ 14 from 28.05.2026

Head of the Department

Yaroslav ROZHKOVSKY

Defended at the EC meeting № 272-0

Protocol № 3 from 12.06.2026

Estimate excellent / 185

Head of the EC

Valeria LIASHENKO-SHCHERBAKOVA

Odesa 2026

ЗАТВЕРДЖУЮ
Перший проректор
Одеського національного
медичного університету
Валерія МАРЧЕВЦА
«__» _____ 2026

ВИСНОВОК
Комісії щодо запобігання академічного плагіату
від «19» лютого 2026 р., протокол № 2

Комісія щодо запобігання академічного плагіату Одеського національного медичного університету (голова – Олена РУДІНСЬКА, секретар – Катерина ОСТАПЧУК та 5 членів комісії) розглянула науковий текст магістерської роботи на тему: «MEDICAL AND PHARMACEUTICAL SUPPORT FOR PATIENTS IN PALLIATIVE CARE: EMPHASIS ON PAIN RELIEF», CHAIMA Zeroual здобувача освіти другого (магістерського) рівня вищої освіти кафедри загальної і клінічної фармакології та фармакогнозії зі спеціальності 226 «Фармація, промислова фармація» на наявність академічного плагіату із застосуванням автоматичного сервісу «StrikePlagiarism» (https://panel.strikeplagiarism.com) та визначила наступне:
надання текст є оригінальним **– 94,17 % оригінальності (висока унікальність).**

Комісією рекомендовано роботу до публічного захисту.
Рішення прийнято одноголосно.

Голова Олена РУДІНСЬКА

Секретар Катерина ОСТАПЧУК

RESPONSE

for the master's thesis Zerouali Chaima

«Medical and pharmaceutical support for patients in palliative care: emphasis on pain relief»

for the OQR "Master" in specialty 226 "Pharmacy, Industrial Pharmacy"

Pharmacoepidemiological and clinical studies of the last few decades have shown a significant increase in oncological diseases of various localization in both women and men. The increase is so significant that today this pathology takes second place both among nosoforms and among the causes of mortality of the world and the state population. Pain is the leading symptom of primary and secondary metastatic lesions, is most often constant from tolerable to severe, requires appropriate effective and safe pharmacotherapy.The above-mentioned determined the relevance of choosing the topic of the master's thesis – identification of the main global trends in pain relief therapy in cancer patients.

The master's work was completed in accordance with the work plan and approved by the Academic Council of the International and Pharmaceutical Faculty of the University in the specialty 226 "Pharmacy, Industrial Pharmacy".

The master's thesis was completed and designed by a student who conducted a theoretical search of literature sources to study the main etiopathogenetic issues of pain, classification and type of pain, mastered the methods of pharmacological, clinical analysis, scientific and practical experiment, and interpretation of data, proved active, creative, thinking and capable of scientific work as a student.

The work consists of 2 sections, conclusions, list of references. The conducted research was embodied in the analysis of the literature sources stated by clinical and pharmacological results. The work is of great scientific and practical importance and can be implemented in the practical activities of the

palliative and oncological departments and the educational process at the Faculty of Pharmacy and Medicine.

Zerouali Chaima master's thesis "Medical and pharmaceutical support for patients in palliative care: emphasis on pain relief" was performed at a certain scientific level using modern research methods, the volume of which is adequate. The work is performed in the traditional style, is a completed scientific work, the design meets the established requirements and is recommended for defense in the EC ONMedU for OQR "Master" in specialty 226 "Pharmacy, Industrial Pharmacy".

Supervisor,

Candidate of Medical Sciences, Associate professor  Strechen S.B.

REVIEW

for the master's thesis of the 5th group student of the 5th year of the Faculty of Pharmacy full-time Zerouali Chaima

on the topic: "Medical and pharmaceutical support for patients in palliative care: emphasis on pain relief"

(Scientific adviser - PhD, Associate Professor Strechen S.B.)

Zerouali Chaima master's thesis is devoted to the topical issue of theoretical and practical palliative medicine and clinical pharmacy – choice and optimization of anesthetic methods and principles of the pharmacotherapy of different tipes of pain in oncology at the cancer patients.

The decision of the main purpose and sequence of tasks led to the content of the master's thesis, the transition from defining the etiology and pathogenesis of various types of pain, main groups of drugs for it correction, to analysis of clinic and pharmacological methods to assess the effectiveness and safety of the proposed schemes. Based on the main areas of research, the topic of the master's thesis should be considered unconditionally disclosed.

The content of the master's thesis corresponds to the set purpose, the set tasks are solved, the purpose of the work is achieved. The material is presented consistently, in accordance with internal logic. The results of the work are relevant, deepen the understanding of the problem of pathogenetic treatment, compliance with its effectiveness in terms of clinical parameters, and at the same time safety.

Evaluating the work based on completeness, validity of conclusions and proposals, it is worth paying attention to the diligence in developing theoretical and practical material on the problem under consideration. The presented master's thesis takes the form of an independent study. In general, the work of Zerouali Chaima meets the established requirements. There are some comments that do not affect the overall positive impression of the master's thesis.

In this regard, the master's thesis of Zerouali Chaima deserves a positive assessment - good/170.

Reviewer,PhD, Associate professor Oksana BIELIAIEVA

Abstract

The master's thesis presents a modern analysis of the problem associated with the physical, mental, and social status of patients who need symptomatic care, unfortunately most often at the final stage of their lives. This stage is caused by very serious chronic diseases, in which all possible radical methods are ineffective. Therefore, we are talking about the so-called palliative care, palliative therapy, which is in demand in wide circles. These include chronic diseases of the cardiovascular system, chronic obstructive pulmonary diseases, pulmonary tuberculosis, diseases of the nervous system, mental and autoimmune diseases, etc. Symptomatic palliative therapy is widely used in inoperable forms of malignant neoplasms, in stage 3-4 cancer, when it comes to pain relief, which does not solve the problem, but reduces the negative impact of pain on the quality of the last days of life. The work was devoted to determining the clinical characteristics of pain, the differentiated choice of analgesia in hospital and outpatient settings.

Using existing standards for subjective assessment of pain syndrome, its level, impact on emotional perception, physical condition, sleep, mental health and social activity were determined. Different degrees of severity were identified, which coincided with existing triggers and characteristics, which further allowed the selective appointment of analgesics from non-narcotic to strong opiates in various forms of release and with different methods of application, and with chronic appointment allowed monitoring of clinical efficacy and safety. Processed three-stage standard: the use of nonsteroidal anti-inflammatory drugs and non-narcotic analgesics for the treatment of mild pain, mild opioids for moderate pain, and strong opioids for severe pain.

Keywords: palliative care, symptomatic pain relief drugs, malignant cancer patients, non-narcotic analgetics, opioid analgetics.

CONTENT

LIST OF ABBREVIATIONS AND SYMBOLS

WHO - World Health Organization

PHC - palliative and hospice care

NSAIDs - non-steroidal antiinflammatory drugs

IASP - International Association for the Study of Pain

PS - pain syndrome

NP - neuropathic pain

CPS - chronic pain syndrome

PCA - patient-controlled analgesia

DKPT - dexketoprofen trometamol

COX-1 - cyclooxygenase type 1

COX-2 - cyclooxygenase type 2

CNS – central nervous system

TTS - transdermal therapeutic systems

INTRODUCTION

Relevance of the topic: The current state of treatment of many human diseases involves, first of all, the focus of targeted personalized pharmacotherapy, which, while being effective, should be as safe, accessible and as effective as possible, improving the patient's quality of life, prolonging his social, mental and physical abilities, the ability to be an active member of society and family. The prevalence of nosoforms is constantly changing, but diseases of the cardiovascular system and neoplasms continue to occupy leading positions in both the causes of morbidity and mortality. These patients require attention from both relevant specialists and services, and loved ones who spend some time with them. This is how we approach the modern direction of medicine - palliative medicine, which involves monitoring patients who, unfortunately, have little prospect of life, but it is necessary to improve the last days of life. One of the areas of palliative care is the provision of pain relief therapy to cancer patients, whose pain syndrome is caused by both direct effects on nerve endings in the area of the primary process and secondary bone metastasis. The different nature of pain, different localization, and different subjective sensations pose certain questions for the doctor when choosing and prescribing appropriate medications at different stages of treatment and prevention. Analysis of existing literature, retrospective analysis of relevant medical documents of patients in specialized palliative care departments, analysis of relevant diagnostic and treatment methods, comparative analysis of relevant issues in different countries (Ukraine and Morocco) determined the approach to forming the topic of the master's thesis, its relevance, and determining the main goal and objectives for solving the main issues of the work.

Main purpose: The main purpose of work was to study methods and techniques of analgesic palliative pharmacotherapy, determination of modern trends in the selection of stepwise use of analgesics depending on the characteristics of the pain, its intensity and impact on the general psycho-emotional, physical, and socially active state of the patient.

To achieve this purpose, the following **tasks** were formulated:

1. Analyze modern medical and pharmacological literature to determine further directions for the implementation of the practical part of the work, draw interim conclusions.

2. Identify and develop methodological approaches and methods for individualized selection of analgesic therapy, based on the necessary subjective and objective signs of pain syndrome, its impact on the general emotional and physical condition of the patient, the course of the disease, the presence of concomitant nosoforms, compliance of patients and their relatives.

3. Implement a stepwise selection of palliative analgesic therapy, conduct educational activities with patients and their family members, develop an appropriate algorithm for further observation, taking into account the effectiveness and safety of the prescribed medications.

Object of research: clinical pharmacology of analgesic drugs (non-narcotic, narcotic) for the palliative analgetic therapy; patients with oncopathology; medical documentation, lists of prescriptions.

Research methods: general clinical (subjective, objective), laboratory-instrumental, pharmacological.

Practical significance of the work. The study allowed us to determine the predominant types of pain, their localization and intensity, the appropriate groups of drugs with analgesic action for palliative care of cancer diseases; to recommend an in-hospital three-step protocol for the use of non-narcotic analgesics for the treatment of mild pain, mild opioids for moderate pain, and strong opioids for the treatment of severe pain.

Approbation of work results. The main provisions of the masters work were presented at the meeting of the Department of General and clinical pharmacology with the pharmacognosy ONMedU; in the materials of the

International Multidisciplinary Scientific Internet Conference “World of Scientific Research. Issue 48” (January 27-28, 2026; Ternopil-Opole, Ukraine-Poland).

CHAPTER 1. Pain syndrome as a marker and trigger of the severity of palliative patients (literature review)

A new modern type of medicine, a type of care, a type of medical practice is gaining wide clinical application - palliative care, palliative medicine, palliative pharmacology. Different terms, but united by one main principle - the provision of comprehensive medical, social, psychological care to patients who are at the final stage of life, to patients who are shown symptomatic care, to seriously ill patients.

According to the definition of the World Health Organization (WHO), palliative care is an approach that allows to improve the quality of life of patients and their families and to solve the problems associated with life-threatening diseases, preventing suffering and alleviating them through early detection, careful assessment and relief of pain and other physical symptoms, and also includes the provision of psychosocial and spiritual support (WHO, 2002). According to these data, annually in the world about 20 million people need palliative care at the end of life, during the last year. Thus, the total number of people who need palliative care annually reaches 40 million [1].

Palliative care:

- provides relief from pain and other distressing symptoms or disorders;
- affirms life and regards death as a natural process;
- does not intend to hasten or postpone death;
- integrates the psychological, social, and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help families cope during the patient's illness and in their bereavement after the loss of a loved one;
- uses a comprehensive interdisciplinary (team-based) approach focused on the needs of the patient and their family.

Clinical conditions in which patients may need palliative care include non-communicable chronic diseases: cancer, heart failure, chronic obstructive pulmonary disease, renal failure, chronic liver disease, multiple sclerosis, Parkinson's disease, psycho-neurological diseases, Alzheimer's disease and other types of dementia, developmental disorders, as well as infectious diseases, in particular HIV/AIDS and drug-resistant tuberculosis.

One of the most common and severe symptoms that occurs in patients requiring palliative care is pain. Opioid analgesics are the basis of analgesic therapy in cancer patients suffering from moderate to severe pain, and are also important for the relief of severe pain in patients with non-oncological progressive diseases in the late stage when radical treatment methods cannot be used. The provision of palliative care is aimed not only at relieving pain, but also at eliminating other symptoms that cause patients' suffering, in particular respiratory failure, symptoms of intoxication, nausea, vomiting, disorders of defecation and urination. Important conditions for the development of the palliative care system are measures aimed at its integration into the activities of all levels of the national health care system, relevant orders with the creation of the necessary financing mechanisms, as well as ensuring the availability of essential medicines for the treatment of various symptoms [2].

Since the second half of the twentieth century, in most developed countries of the world, the creation and development of a system or service of palliative and hospice care (PHC) for the population has become one of the priority medical, social and humanitarian problems of governments and society, gaining increasing relevance, which is due to a number of objective and subjective factors - demographic, medical, socio-economic, political, moral and ethical, etc. In the world, more than 25.5 million people die from serious incurable diseases every year, and another 35 million people live suffering from these diseases, which together makes up almost 61 million people. Unfortunately, a significant part of such patients end their lives in suffering and agony due to unrelenting pain, severe

disorders of body functions, inability to self-care, general weakness, depression, etc., which causes a significant decrease in the quality of life. According to expert estimates, up to 40 million such patients worldwide require PHCs every year [3].

1.1. Pathophysiology of pain in cancer patients – the path to effective correction

Pain is a common symptom in many types of cancer. Interdisciplinary team management, including pain assessment, explanation to the patient/family, treating the reversible, non-pharmacological treatments and reassessment are essential. This article focuses on the pharmacological management of cancer pain, and overviews and updates on the recent advances in this fi eld. Both non-opioid and opioid analgesia as well as coanalgesics (adjuvants) are reviewed. Within non-opioid analgesia the risks of non-steroidal antiinflammatory drugs (NSAIDs) are considered and recommendations for NSAIDs in patients at risk of gastrointestinal and cardiovascular toxicity are made. For opioid analgesics, side effects of opioids are discussed alongside practical guidance on opioid prescribing and converting between opioids. Newer drugs such as tapentadol are considered in this update. Amitriptyline, duloxetine, gabapentin and pregabalin, and the guidance for their use are reviewed in the coanalgesics (adjuvants) section [4].

Treatment of chronic pain in adults and children is regulated by the national standard of Ukraine, which recommends adherence to the choice of painkillers in accordance with the WHO three-step protocol. Some statistical data obtained through analysis of literature sourses. The Ministry of Health of Ukraine includes malignant stage 3–4 neoplasms, HIV/AIDS, congenital malformations, cardiovascular, respiratory, neurological, atrophic-degenerative diseases, and post-traumatic conditions that cannot be cured by modern available drugs in the list of palliative diseases [5]. The need for PHC is growing: 1.5 million Ukrainians need it immediately before the end of life, and about 600,000 in the last year of life. Unfortunately, the list of palliative diseases according to such a number of patients

is not detailed by the Ministry of Health of Ukraine. In 2023, only 130,000 people received palliative care in Ukraine (11.5–46.2% of the need). In the world, the need for PHC is 20 million at the end of life. 80% of such patients live in low- and middle-income countries. Coverage of palliative care in the world also does not exceed 50% of the need [6]. The medical component of palliative care is elimination of life-threatening symptoms (carrying the risk of premature death even with an incurable disease) by carrying out pathogenetic therapy, palliative surgical interventions, as well as symptomatic therapy, to relieve pain, first of all. Timely and sufficient analgesia significantly improves the quality of life of patients and is one of the main needs of palliative patients [7].

The nature of pain in malignant neoplasms can change with the progression of the disease. Nociceptive pain predominates in the early stages, and neuropathic pain in the later (palliative) stages. Nociceptive pain can be caused by the pressure of a growing tumor on the adjacent tissues (nerves, bones), irritation of nerves by products of inflammation accompanying the neoplastic process, tumor growth into nerves. Long-term compression of nerves disrupts their functionality; thus, the pain can be considered neuropathic. Nerve damage can be caused by surgery, radiation therapy, or the effects of certain anticancer drugs (cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, vincristine, vinblastine, and others). Pain increases the development of osteoporosis [8-10].

Pain is an important issue in oncology. The International Association for the Study of Pain (IASP) defines it as follows: "Pain is an unpleasant sensory or emotional experience that is caused by actual or potential tissue damage, or described in terms as if tissue damage". Chronic pain is defined by the IASP as pain that persists or recurred for more than three months [11]. Chronic pain differs from acute pain not only in duration, but also in qualitative differences in neurophysiological, psychophysiological, and clinical mechanisms. The key feature of chronic pain is its duration, which exceeds the normal time frame for tissue healing. Therefore, persistent pain caused by a malignant tumor is

considered chronic from the outset. Chronic pain syndrome in cancer patients most often develops with bone metastases. They are often detected in breast, prostate, kidney, and lung cancer. In breast cancer, bone metastases are diagnosed in 70-80% of patients with advanced forms of the disease, with the lumbar (59%) and thoracic (57%) spine and pelvic bones (49%) most frequently affected [12]. Pain in cancer patients is the result of a combination of several factors: 1) Direct impact of the tumor: Tumor growth can directly affect surrounding tissues, nerves and organs, causing pain. This is especially common in malignant tumors that grow in surrounding tissues; 2) During Treatment - Many treatments for cancer patients, such as surgery, chemotherapy, radiation therapy and immunotherapy, can cause side effects, including pain; 3) Psychological and emotional factors: Stress, anxiety, depression can increase the perception of pain in cancer patients.

According to the definition of the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with, or perceived to be associated with, actual or potential tissue damage [13]. Previously, there were shortcomings in the definition of pain, such as not taking into account the cognitive and social components of the experience and their importance in the treatment of pain, focusing mostly on the sensory and emotional features of pain [14]. The authors of the pain experience model review the evidence and the significant role of social and cognitive factors. They argue that without a clear recognition of these core components in shaping the pain experience, important aspects of understanding the emergence of its characteristics are lost, and therefore treatment options are limited. Recognition of cognitive and social features supports a multidimensional model of pain, expands the possibilities of interdisciplinary care, and provides advantages for cognitive behavioral therapy and patient self-management.

The formation of pain is due to the complex interaction of peripheral and central neurophysiological mechanisms of convergence, summation, correlation of nociceptive and antinociceptive afferent signals occurring at different levels of the

nervous system. Pain is always a subjective sensation, and its final assessment is determined by the location and nature of the damage, the nature of the harmful factor, the psychological state of the person, individual life experience and previous experience of pain. Today, the biopsychosocial concept of the pathogenesis of BS has acquired and is considered the most promising, in contrast to the biological model, which emphasizes the disease, focuses on the complex interaction of biological, psychological and social variables. Based on this concept, the differences are explained by the relationships between biological changes, psychological state and social influence. Under such conditions, biological factors initiate, maintain, and modulate physical disorders, psychological factors determine the assessment and perception of internal physiological signs, and social factors shape patients' behavioral reactions to experiences of physical disorders [15, 16].

There are 5 main mechanisms of pain syndrome (PS) formation in the structure of pain: nociceptive, neuropathic, nociplastic, mixed, psychogenic. In nociceptive pain, the damaging stimulus (exogenous - mechanical or thermal factor and endogenous - inflammation or muscle spasm) acts on peripheral pain receptors (nociceptors) in the skin, muscles, ligaments, joints, capsules of internal organs (pain in burns, trauma, inflammation, myocardial infarction). Neuropathic pain (NP) occurs with organic damage to various parts of the nervous system, which are responsible for the control and conduction of pain. The cause of this type of pain is damage to the afferent somatosensory system from peripheral sensory nerves to the cortex, as well as disorders in the antinociceptive system (opiate, serotonergic, noradrenergic). Examples: diabetic polyneuropathy, postherpetic neuralgia, trigeminal neuralgia, poststroke pain, pain in multiple sclerosis. Characteristics of NP: • persistent pain and abnormal sensory symptoms, such as burning, tingling, or cold sensations, even after physical recovery; • neurological disorders associated with dysfunction of the musculoskeletal system and the autonomic nervous system, of varying severity. NP does not exclude nociceptive, and therefore its mechanisms

may be observed, for example, in radiculopathy, multiple sclerosis. Nociplastic pain arises from a change in nociception, despite the lack of clear evidence of actual or potential tissue damage that could cause activation of peripheral nociceptors, as well as evidence of the presence of a disease or lesion of the somatosensory system that causes pain. This mechanism underlies many types of chronic pain, including fibromyalgia, complex regional pain syndrome, other types of musculoskeletal pain, such as chronic low back pain, as well as such types of visceral pain as irritable bowel syndrome and bladder pain. Since the nociceptive, neuropathic and nociplastic components of chronic pain are often combined, they are considered as mixed pain (radiculopathy, tunnel syndrome, cancer pain, pain in multiple sclerosis, etc.). The leading role in the mechanism of development of psychogenic pain is assigned to psychological factors that initiate pain in the absence of serious somatic disorders. Often such pain occurs as a result of muscle overstrain, is provoked by emotions, conflicts, psychosocial problems [17-19].

Thus, it has been shown that the presence of pain syndrome, its pathogenesis, and severity are one of the main markers of malaise in cancer patients, which require attention at the state level to ensure appropriate effective and safe pain pharmacotherapy.

1.2. Main state legislative guidelines for providing pain relief in palliative medicine – characteristics, regional features

As it was determined, palliative medicine and palliative care gained rapid and extensive development at the turn of the 20th and 21st centuries, when medicine was first of all squeezed by the increase in the number of cancer patients, severe complications of the course of malignant neoplasms, one of which is pain syndrome of various localization and intensity. The number of cancer patients has increased so much in the last 20-30 years that today they occupy the leading 2nd place in prevalence and, unfortunately, in the cause of death of patients. Therefore, of course, in recent years a large number of regulatory documents have appeared that define palliative medicine, the principles of providing palliative care, the

principles and indications for prescribing medications to appropriate patients. I would like to well on the characteristics of these documents.

The creation and development of a system or service of palliative and hospice care for the population is becoming one of the priority medical, social and humanitarian problems of governments and society, becoming increasingly relevant, which is due to a number of objective and subjective factors - demographic, medical, socio-economic, political, moral and ethical, etc. Every year in the world, more than 25.5 million people die from serious incurable diseases, and another 35 million people live suffering from these diseases, which together makes up almost 61 million people [3]. The global relevance of the problem of providing palliative and hospice care to the population is evidenced, in particular, by the Recommendations of the Committee of Ministers of the Council of Europe Member States (Rec 24) "On the organization of palliative care" (2003), the special Resolution of the Parliamentary Assembly of the Council of Europe No. 1649 "Palliative care: a model for innovative medical and social policies" (2008), documents of the UN (2011, 2017), WHO (2004, 2018, 2019, 2021) and other authoritative international organizations. As evidenced by the content analysis of the above documents, they all emphasize that the indications for providing palliative care are not limited to oncological diseases, but include patients of all age groups based on an assessment of the severity of the course and progression of diseases that threaten or limit the patient's life, the specific needs of the patient and his family members, and the prognosis of their life expectancy. Unlike traditional medical care, in particular etiopathogenetic treatment, which is focused on curing the patient or achieving stable remission, such an innovative type of medical care as PCD aims, first of all, to improve the quality of life by alleviating the physical suffering of patients who need palliative and hospice care - overcoming or significantly reducing pain and other severe symptoms of the disease, helping to maintain their psycho-emotional state, spiritual/religious support, as well as ensuring social needs and improving the living conditions of such a patient and his

family. The right to PCD is one of the basic human rights in the modern world. Equal access to PCD services should be guaranteed to the population in all countries, in accordance with needs and regardless of the income level, cultural and ethnic characteristics of patients. In addition, this should not create significant financial difficulties, especially for patients from low-income and vulnerable groups of the population. Practical doctors and scientists began to talk about the acute and rapidly growing need of the population for PCBs in Ukraine at the turn of the twentieth and the beginning of the twenty-first centuries in connection with the unfavorable medical-demographic and socio-economic situation in the country. Over the past five years, about 2 million people in Ukraine (about 500 thousand patients in the final period of life and about 1.5 million members of their families) need qualified high-quality PCBs every year. This determines the great medical-social, political, economic and humanitarian importance of the problem of creating and developing an optimal PCB system. The legislative basis for the development of the PCB system for the population in our country is, first of all, the Law of Ukraine "Fundamentals of the Legislation of Ukraine on Health Care" dated 19.11.1992 No. 2801-XII, where in 2011 Art. 33 "Ensuring the provision of medical care" for the first time in the history of Ukraine was supplemented by a separate type of medical care - "palliative care", and in Art. 35-4 "Palliative care" the definition and organizational principles of this type of medical care in Ukraine are provided. The Law of Ukraine "On State Financial Guarantees of Medical Care of the Population" dated 19.10.2017 No. 2168-VIII, in particular Art. 4, a number of Presidential Decrees and regulatory legal acts of the Cabinet of Ministers, the Ministry of Health and the Ministry of Social Policy of Ukraine, which regulate the provision of palliative care and social services. Today in Ukraine, regional and local authorities in many regions do not provide accessible, high-quality and effective palliative care to incurable patients both in inpatient healthcare facilities and in outpatient settings and at home, in accordance with international approaches and standards. This requires state support and development of an appropriate regulatory framework and adequate financing of PCB development programs at the

national, regional and local levels, which will allow, in the process of transforming the healthcare and social protection system of the population, to rationally redistribute available institutional, technical and human resources, ensure their effective use, achieve equal access of the population to quality PCB in all regions of Ukraine, for all types of medical care and coordination and cooperation of healthcare institutions and social care institutions, as well as institutions of non-state ownership [20-31].

Today in Ukraine, regional and local authorities in many regions do not provide accessible, high-quality and effective PCD to incurable patients both in inpatient health care facilities and in outpatient settings and at home, in accordance with international approaches and standards. This requires state support and development of an appropriate regulatory framework and adequate funding of PCD development programs at the national, regional and local levels, which will allow, in the process of transforming the health care system and social protection of the population, to rationally redistribute available institutional, technical and human resources, ensure their effective use, achieve equal access of the population to high-quality PCD in all regions of Ukraine, for all types of medical care and coordination and cooperation of health care facilities and social care facilities, as well as non-state-owned institutions.

Order of the Ministry of Health of Ukraine No. 1308 dated 04.06.2020 “On improving the organization of palliative care in Ukraine” for the first time provided the opportunity to identify a patient in need of palliative care, and approved the procedure for its provision, criteria for determining a patient in need of palliative care, including a pediatric patient. A separate appendix to the order includes a patient observation plan that can be conducted at any level of palliative care provision. The choice of a place of palliative care and a place of death for the patient is discussed and agreed with him and/or his legal representative. The patient's wish is a priority and is recorded in the observation plan. The plan indicates the consent or refusal of the patient personally or his legal representative

to receive information about his diagnosis and prognosis of the possible development of the disease, determining the need for social, psychological, spiritual, legal support, respite, social assistance services, the need for transportation and care. The observation plan takes into account the doctor's actions when determining pain, which involves establishing the type of pain (nociceptive, neuropathic, mixed, psychogenic), the intensity of pain determined by the visual analog scale (VAS), its nature and localization.

The basic WHO principles for pain relief in oncological pathology are set out in the Order of the Ministry of Health of Ukraine No. 311 dated 25.04.2012 “On approval of the eUnified Clinical Protocol for Palliative Medical Care in Chronic Pain Syndrome”, dveloped on the basis of the adapted clinical guideline “Pain Control” [32].

Thus, in patients with chronic pain syndrome (CPS) with malignant neoplasms, it is recommended to give preference to oral medication for as long as possible. In this case, painkillers should be taken at fixed intervals, their appointment should be gradual (from non-narcotic to opioid) depending on the clinical picture at the time of examination, and the dose should be selected individually. As for the provision of care to patients at the primary level, a general practitioner - a family doctor (pediatrician) assesses the degree of pain and treatment of pain syndrome, prescribes narcotic drugs and psychotropic substances in accordance with the legislation, including the preparation of prescriptions for the treatment of pain syndrome (Order of the Ministry of Health of Ukraine No. 504 of 19.03.2018). In some cases, a paramedic may write such prescriptions, but his powers are limited by Order of the Ministry of Health of Ukraine No. 360 of 19.07.2005. Thus, paramedics of healthcare institutions have the right to write prescriptions for patients with long-term and chronic diseases in the event that the attending physician continues the course of treatment, indicating their position and certifying the prescription with their own signature and the seal of the healthcare institution.

A patient who needs to continue taking narcotic drugs, psychotropic substances and precursors, upon discharge from a healthcare institution, is issued a prescription on a special prescription form No. 3 (f-3) with a mandatory record of the prescription of the drug in the medical record of such a patient (Order of the Ministry of Health of Ukraine No. 1308 dated 04.06.2020). Therefore, in such a case, the attending physician should not initially prescribe analgesic therapy, but continue the prescribed one, if necessary, making adjustments to the dosage of drugs or replacing the drug with a stronger one.

The features of the clinical use of some other state protocols for providing palliative pain relief therapy will be described in the following sections of the work. A detailed description of analgesics is presented below.

1.3. Clinical and pharmaceutical aspects of the use of different classes of analgesics and methods of analgesia

Pain is one of the first symptoms indicating the presence and progression of a malignant process in the body. If in the early stages of cancer no more than a third of patients complain of pain, then in the later stages they are noted by almost all patients. Pain can be caused not only by the tumor itself, but also by inflammatory reactions that lead to spasms. Gradually, the pain develops into a strong, unbearable, constant pain [33].

Pain syndrome can be classified according to various signs. Thus, according to the degree of intensity, pain can be weak, moderate and strong, according to the subjective assessment - stabbing, pulsating, burning; according to the duration - acute and chronic.

According to the origin and features of pathogenesis, they are distinguished: 1. Visceral - pain in the abdominal cavity without clear localization, long-lasting, aching. For example, painful sensations in the back in kidney cancer. 2. Somatic - pain in ligaments, joints, bones, tendons: dull, poorly localized. It is characterized

by a gradual increase in intensity. Appears in the late stages of cancer, when metastases are detected in the bone tissue and cause damage to internal vessels. 3. Neuropathic - pain caused by disorders in the nervous system. For example, pressure of the tumor on nerve endings or their damage. This type of sensation is also caused by radiation therapy or surgery [33]. 4. Psychogenic - pain without physical damage, associated with fear, depression, and self-suggestion of the patient [19]. It appears as a result of strong emotional experiences and is not treatable with painkillers [34].

Pain is a protective alarm signal. It was invented by nature to indicate a problem to a person, make him think and encourage him to take action. However, chronic pain in oncology is devoid of these functions. It leads to the patient's despair, a feeling of hopelessness, depression, up to mental disorders, interferes with the normal functioning of the body, deprives the ability to feel like a full member of society. Pain takes away the strength necessary in the fight against a cancerous tumor. Modern medicine considers such pain as a pathological process that requires separate therapy. Pain relief in cancer is not a one-time procedure, but a whole treatment program designed to maintain the patient's social activity, prevent the deterioration of his condition and oppression of the psyche [35].

Choosing an effective pain therapy is a complex task that requires a step-by-step approach [36]. The recommendations of WHO experts highlight three stages of pharmacotherapy that ensure rational treatment of pain syndrome in cancer patients [37].

Drugs are also selected according to the degree: 1) for mild pain - non-opioid analgesics; 2) for increased pain - mild opioid drugs; 3) for severe pain - narcotic analgesia and adjuvant therapy [38].

First stage. Treatment of pain syndrome begins with non-narcotic analgesics and non-steroidal antiinflammatory drugs. These include paracetamol, ibuprofen, aspirin, meloxicam, etc. For pain in muscles and joints - diclofenac sodium,

etodolac, etc. All these drugs affect peripheral pain receptors. In the first days, the drugs can cause general fatigue and drowsiness, which passes on their own or is corrected by changing the dosage. If taking pills does not give the desired result, they switch to injections.

Second stage. When first stage drugs become ineffective, weak opiates are added to them. Usually these are tramadol, nefam and codeine. The analgesic effect is achieved by affecting the opiate receptors of the central nervous system and replacing endorphins - "hormones of joy", the production of which decreases with intense pain. Tramadol is prescribed in the form of tablets or injections. It is taken together with analgin, paracetamol and other first-stage medications (synergistic effect): tramadol affects the central nervous system, and NSAIDs - on the peripheral nervous system.

Third stage. The final stage of treatment, which is transferred if the patient experiences unbearable, continuous pain. Third-stage drugs are strong opiates, the key of which is morphine. However, there are more gentle substances that are less addictive. These are buprenorphine - 50% effective compared to morphine; piritramide - 60% effective; fentanyl - 75-125%. The effect occurs a few minutes after taking, but the patient must strictly follow the prescribed regimen. The drugs are started with a minimum dose, gradually increasing it.

The main thing when choosing a method of anesthesia for oncology is not only the effectiveness of the action, but also the convenience for the patient, the impact on the quality of his life. First of all, invasive methods have almost always been used - injections. Modern methods of anesthesia are diverse and as comfortable as possible for patients. Today, various forms of release exist and are used: transdermal patches, tablets [39].

Painkilling patches. This is a method of transdermal drug administration. The patch contains four layers: a protective polyester film, a reservoir with the active substance (for example, with fentanyl), a membrane that adjusts the intensity

of the release, and an adhesive layer. The patch can be stuck anywhere. Fentanyl is released gradually over 3 days. The effect occurs after 12 hours, after removal, the concentration of the drug in the blood slowly decreases. The dosage may vary, it is selected individually. The patch is prescribed, as a rule, at the very beginning of the third degree of anesthesia in oncology.

Spinal anesthesia. During spinal anesthesia, the drug is injected into the spinal canal. This leads to a temporary "switch-off" of tactile and pain sensitivity. The injection is performed through a catheter, which requires a certain experience from the doctor. Morphine, norphine, fentanyl, etc. are used as analgesics. Through the cerebrospinal fluid and the general circulatory system, they enter the brain. Side effects in the form of nausea and drowsiness are not excluded.

Epidural anesthesia. The drug is injected into the epidural space, located between the dura mater and the walls of the cranial cavity or spinal canal. Drugs similar to those used in spinal anesthesia are used. Epidural anesthesia is used to relieve pain in cancer, when secondary changes in the bones have appeared, and oral and parenteral methods of administration no longer bring results.

Neurolysis through the gastrointestinal tract using endosonography. Neurolysis (neurolysis) is the process of destroying the nociceptive (pain) nerve pathway. The introduction of the analgesic is transgastrically - through the gastrointestinal tract, accuracy is ensured by endoscopic ultrasound control. Such methods of local anesthesia are used, for example, in pancreatic cancer with an efficiency of up to 90%. The analgesic effect can last for more than a month, while narcotic analgesics in the classical way would have to be administered constantly.

Administration of drugs into myofascial trigger points. Myofascial pain syndrome is expressed in muscle spasm and the appearance of painful seals in tense muscles. They are called trigger points and are painful when pressed. Injections into the trigger zone relieve pain and improve the mobility of the body area.

Autonomic blockades. Nerve blockade involves the introduction of a drug into the projection site of the nerve that is associated with the affected organ and causes pain. For example, blockade in pancreatic cancer eliminates pain for several months. Depending on the type of anesthetic, the procedure is performed once a year, once every six months or weekly. Another plus is the minimal number of negative consequences.

Neurosurgical interventions. During the procedure, the neurosurgeon cuts the roots of the spinal or cranial nerves, along which nerve fibers pass. Thus, the brain is deprived of the ability to receive pain signals. Cutting the roots does not lead to loss of motor ability, but it can complicate it.

Patient-controlled analgesia (PCA). This type of analgesia is based on a simple rule: the patient receives analgesics when he wants them. The scheme is based on the individual perception of pain and the need for analgesics. In European countries, PCA is accepted as the standard of postoperative analgesia. The method is simple and relatively safe. However, patients need to undergo careful instruction.

Treatment of pain syndrome with non-opioid non-narcotic analgesics. A group of drugs that includes non-steroidal anti-inflammatory and antirheumatic drugs that are effective only in the initial (local) phase of the development of a malignant neoplasm, i.e. the phase of nociceptor irritation, which corresponds mainly to mild and moderate pain. These drugs do not affect the development of the main pathological process, the central neurophysiological mechanisms of pain development, but only reduce pain and inflammation. Always when prescribing NSAIDs, it is necessary to remember their safe use. The main side effect of long-term use of NSAIDs is damage to the gastric mucosa, which is less pronounced in selective COX-2 inhibitors, however, high doses and long-term use of the newer COX-2 inhibitors have a higher level of cardiotoxicity. With long-term use of paracetamol, hepatotoxicity is possible, especially in people who abuse alcohol. Long-term use of NSAIDs also increases the risk of renal failure, especially in

patients with diabetes, which requires monitoring for signs of deterioration of renal function (serum creatinine, urea, creatinine clearance) [40].

Treatment of pain syndrome with opioid analgesics. For chronic pain that is not responsive to non-narcotic analgesics and NSAIDs, opioid analgesics are prescribed [38]. The main representative ("gold standard") of analgesics of this class is morphine [41]. The fundamental principle of quality medical practice is to treat pain using the least invasive medical interventions. Emphasizing the advantages of oral forms of morphine for palliative medicine, it should also be noted that they provide the patient, who is outside the hospital, with the opportunity to independently (or with the help of family members) relieve pain when it occurs or intensifies, in particular at night, without waiting for the arrival of a medical professional, and to avoid injections, which are especially painful in generalized pain syndrome. All the more unacceptable from an ethical point of view is the situation when restrictions on the use of opioid analgesics are applied to a patient in the terminal phase under the pretext of the possibility of developing addictive dependence. It is absolutely clear that both from a purely clinical point of view and from considerations of general humanity, the question of the danger of developing painful dependence in these conditions is no longer relevant and makes no sense. (WHO. Cancer pain relief. Geneva: WHO, 1986).

Principles for the use of opioid analgesics proposed by the National Pain Foundation (USA) (National Foundation for the Treatment of Pain; USA) [http://www.paincare.org/], the main of which are the following provisions [41]:

1. When using opioids, standard pharmacological principles should be followed, namely: a. The drug used should be used according to the WHO recommended “ladder” concept, i.e. starting with the initial available opioid and moving “up” to more potent drugs of the opioid group based solely on the clinical effectiveness of the previous drug. The dose and regimen of the drug should also be titrated “up” with a gradual rational increase in the dose, careful monitoring of the clinical effect, complications and side effects. b. Side effects and complications

should be strictly monitored and recorded and taken into account in the subsequent dosing regimen of the drug. Side effects and precautions: Common: constipation, dry mouth, nausea/vomiting, sweating, sedation. Rare: hallucinations during sleep, dysphoria, delirium, myoclonic seizures, pruritus/urticaria, bronchospasm, urinary retention, respiratory depression.

2. When choosing an opioid drug, recommendations from well-known international pharmacological resources should be taken into account. a. The maximum dose of a drug from the opioid class used in palliative medicine should be justified only by achieving the necessary clinical effect. b. Respiratory depression is the main side effect of opioids, therefore this effect should be strictly controlled. Other side effects, such as sedation, nausea, itching and constipation, should be treated symptomatically. If these reactions are not eliminated, it is necessary to switch to another opioid. The patient should be informed about the possibility of physiological dependence and its clear distinction from addictive disorders. The patient should understand that, unlike physiological dependence, when painful symptoms (pain) reappear upon complete withdrawal and reduction of the drug dose, the state of addiction consists in compulsive dependence on an opioid, which is accompanied by destructive physical, functional and social consequences for the person. d. Pseudoaddiction is a situation where a patient is forced to demand an additional dose of the drug because the prescribed dose of opioid is insufficient to completely relieve pain. e. Patients should not be misinformed that opioid use will necessarily lead to addictive dependence, as this is not supported by scientifically sound evidence. e. Patients should not be misinformed that opioids necessarily cause organotoxicity and brain damage.

3. Opioid drugs should be used to relieve pain and suffering only in the case of: a. Reliable diagnosis of the disease that causes the pain syndrome. b. Pain should be treated using all possible medical approaches: pharmacological, physiotherapeutic, psychiatric, psychological, surgical and others. The doctor

should make every effort to eliminate the patient's pain syndrome as soon as possible.

4. To eliminate unbearable pain, injections of analgesics should be used.

Adjuvant drugs. At all stages of pain relief in the treatment of chronic pain syndrome, the appointment of adjuvant (additional, auxiliary) pharmacotherapy is necessary. Most often, adjuvant drugs are used in palliative and hospice care, as agents that contribute to pain relief and are used against the background of basic analgesic therapy. This group of drugs of neuro- and psychotropic action, which can increase the effectiveness of drugs with purely analgesic effects, expand the therapeutic range of action of the latter. Adjuvant drugs potentiate the effect of analgesics and have an independent analgesic effect in nociceptive and, especially, neuropathic pain. Such drugs include drugs from the classes of antidepressants, anticonvulsants, anxiolytics, neuroleptics, hypnotics and sedatives, antihistamines, local anesthetics, central alpha-adrenoceptor agonists.

Pain in bone tissue damage is, unfortunately, the result of metastasis to the bones, accompanied by osteoclastic bone resorption, hypercalcemia and pathological fractures. In order to reduce the pathological process in bone tissue and, accordingly, relieve pain, bisphosphonates and calcitonin, which are inhibitors of osteoclastic processes, are used in palliative care. The analgesic effect of bisphosphonates is due to a decrease in osteoclastic activity and hypercalcemia and has been clinically confirmed in bone pain due to breast cancer and prostate cancer metastases [42].

In the future, I would like to focus on the clinical and pharmacological characteristics of the main analgesics used in palliative medicine, both non-narcotic and narcotic (dexketoprofen, ketorolac, nefam, paracetamol (influgan), morphine, fentanyl, tramadol, oxycodone, buprenorphine).

Chemical identification of the dextrorotatory stereoisomer of ketoprofen and elucidation of its role in the development of its pharmacological effect led to

the development of a new drug, dexketoprofen trometamol (DKPT), a water-soluble salt of the dextrorotatory stereoisomer of ketoprofen. The drug was developed by Menarini (Italy) and marketed under the trade names Dexalgin and Keiver. The therapeutic dose of DKPT is half that of regular ketoprofen. Furthermore, due to its chemical properties, DKPT is one of the few NSAIDs that can be administered intravenously. DKPT has pronounced analgesic, anti-inflammatory, and antipyretic effects [43]. DKPT is available in several dosage forms (oral and injectable), allowing its use in a variety of clinical situations. The drug has been most studied in the treatment of acute pain, but can also be used to enhance analgesic therapy for chronic pain of various origins. DKPT has been effective in outpatient practice for the treatment of moderate to moderate pain in cancer patients with bone metastases or primary malignant tumors affecting bone tissue [44]. Dexketoprofen, due to its pathogenetic action, effectively treats nociceptive pain, which is almost always associated with inflammation, making it a valuable NSAIDs in the modern arsenal of pain treatments. Its unique chemical structure determines the drug's pharmacokinetic parameters, allowing it to quickly and effectively penetrate the enteral and blood-brain barriers. Rapid accumulation of the drug in plasma and CNS structures leads to a pronounced and rapid analgesic effect in various pathologies. In cancer patients, dexketoprofen can be successfully used to potentiate the effect of opioid analgesics, providing an opioid-sparing effect and reducing the risks associated with their use. When administered intravenously, the drug can be used to relieve breakthrough pain in cancer patients and pain caused by tumor metastases to bone. While highly effective, the drug simultaneously has a good safety profile, expanding its potential for use in patients with multiple morbidities [45].

Ketorolac is a synthetic drug that is a derivative of acetic acid in its chemical structure and belongs to the group of NSAIDs. In terms of its chemical composition, it is a racemate of two enantiomers. The mechanism of action of the drug, like other representatives of the group of nonsteroidal anti-inflammatory

drugs, is to inhibit COX, which ensures the conversion of arachidonic acid into prostaglandins, which are mediators of inflammation at the site of tissue damage, and also participate in the process of pain transmission along the nerve trunks. Ketorolac is a non-selective inhibitor of cyclooxygenase type 1 (COX-1), and also acts on cyclooxygenase type 2 (COX-2). A feature of ketorolac is its higher analgesic effect compared to other drugs of the group of nonsteroidal anti-inflammatory drugs, which is equivalent to the analgesic effect of narcotic analgesics, and also has antipyretic and antiplatelet effects. Due to its pronounced analgesic effect, as well as the absence of side effects characteristic of narcotic analgesics - nausea, vomiting, respiratory depression, urinary retention, constipation, as well as the absence of an effect on opiate receptors in the CNS, which leads to the absence of the development of drug dependence, ketorolac is used mainly as an analgesic, including in preoperative preparation of patients and analgesia in the postoperative period. Ketorolac has synergy when used together with narcotic analgesics, and helps reduce the dose of narcotic drugs when used together [46].

Nefam (nefopam hydrochloride) is a central non-narcotic analgesic, structurally unlike other analgesics. In vitro experimental studies indicate a central effect consisting in the inhibition of catecholamine and serotonin reuptake at the synapse level. In vivo studies in animals have shown the antinociceptive properties of nefopam. In clinical studies, nefopam has shown a positive effect on postoperative tremor. Nefopam does not have anti-inflammatory or antipyretic effects, does not depress respiration and does not affect intestinal peristalsis. Nefopam has an anticholinergic effect. After a single dose of 20 mg intramuscularly, the time to reach maximum serum concentration (Tmax) is from 30 to 60 minutes, and the maximum concentration (Cmax) is on average 25 ng/ml. The half-life is on average 5 hours. After intravenous administration of a dose of 20 mg, the half-life is 4 hours. Plasma protein binding is 71–76%. Biotransformation is significant, three metabolites have been identified:

desmethylnefopam, nefopam N-oxide, and nefopam N-glucuronide. Desmethylnefopam and nefopam N-oxide are not conjugated and do not exhibit analgesic activity in animal studies. 87% of the administered dose is excreted by the kidneys, less than 5% of the administered dose is excreted unchanged. Metabolites found in the urine account for 6%, 3%, and 36% of the intravenous dose, respectively. The drug is indicated for postoperative analgesia as part of multimodal analgesia (nefopam also exhibits a positive property to prevent postoperative tremor); symptomatic treatment of acute pain conditions (oncology, injuries, pain after surgical operations, analgesia of renal and hepatic colic [47].

Infulgan belongs to the fundamental pharmacological group of non-narcotic analgesics and antipyretics. The drugs of this group are intended to eliminate pain and reduce elevated body temperature, without causing central nervous system depression or developing addiction, unlike narcotic analgesics. Infulgan occupies a special place in it due to its powerful analgesic effect, which allows it to be used to eliminate pain syndrome. The main and only active ingredient of the drug Infulgan is paracetamol. Its key property is the ability to effectively reduce body temperature and eliminate pain of mild and moderate intensity. Infulgan is available exclusively in the form of a solution for intravenous infusions. Due to this, the active substance enters directly into the bloodstream, which ensures its instant and complete absorption, bypassing the digestive system. Non-narcotic analgesics and antipyretics are one of the key pharmacological groups that combine drugs that affect the mechanisms of pain and thermoregulation, without causing central nervous system depression or drug dependence. Their main task is symptomatic treatment: eliminating pain of various origins and reducing elevated body temperature in febrile conditions. The mechanism of action is associated with the inhibition of the synthesis of pain and inflammation mediators (prostaglandins). The main indication for the use of Infulgan is the short-term elimination of moderate pain syndrome [47].

The experience of using intravenous paracetamol for pain relief in oncological practice is described by S.M. Nedashkivskyi et al. (2015). The authors used infulgan to treat pain syndrome. The method of its use was as follows: infulgan was started to be administered intravenously before or at the beginning of surgery to provide the effect of "preemptive analgesia" (preemptive analgesia) in a starting dose of 12-15 mg/kg (up to 1000 mg). During the first day, 1-3 more infusions were performed, guided by the presence and severity of pain in the patient. The interval between injections was 4.5-12.0 hours. No more than 4 injections of infulgan were performed per day (the maximum daily dose for paracetamol is 4 g). After the third day of intravenous administration, all patients continued to receive analgesia by taking paracetamol per os, and in case of increased pain, they switched to therapy according to the "staircase" principle, which was described above. This tactic of analgesia allowed most patients to achieve satisfactory results – a decrease in the severity of pain, an increase in the patient's activity, improved sleep, etc. The patients tolerated the prescribed treatment well, no side effects were noted [48].

Next, we will focus on the clinical characteristics of narcotic analgesics in palliative oncology.

Physical, psychological, emotional, and spiritual distress, as well as pain, are common among patients with cancer [49-53]. A significant proportion of patients at the end of life experience pain that is not relieved despite the availability of pain management strategies. Approximately 50% of patients dying from cancer have severe pain, but only 50% of patients with severe pain receive reliable pain relief [51]. In dying patients, oral opioid therapy is convenient and cost-effective. Sublingual administration is also convenient because patients do not need to swallow. Once the patient has reached a stable effective dose, transdermal patches can be used to provide sustained relief without the need for frequent dosing. Opioids can also be administered rectally or by injection (IM, IV, or SC).

Long-acting opioids are best suited for long-term pain. Physicians should prescribe opioids in adequate doses on a continuous basis and keep short-acting opioids available for the treatment or prevention of breakthrough pain and anticipated activities associated with pain (e.g., dressing changes, physiotherapy).

Morphine is a natural alkaloid with pronounced analgesic and sedative effects (hypnotic and anxiolytic), and has potent central effects; pronounced analgesic effect is associated with agonistic action on various subtypes of opioid receptors of the CNS in the cerebral cortex, thalamus, reticular formation, limbic-hypothalamic system, periaqueductal gray matter and gelatinous substance; causes supraspinal analgesia, euphoria and drug dependence; miosis, respiratory depression and slows down intestinal motility; spinal analgesia, miosis and sedative effect; acting on the CNS, significantly reduces acute and chronic pain, reduces psychomotor agitation, causes general relaxation and euphoria [46-47].

Tramadol is a centrally active opioid analgesic; it has a mixed mechanism of action; it is a non-selective pure agonist of opioid μ-, d- and κ-receptors with maximum affinity for μ-receptors; other mechanisms involved in providing the analgesic effect of tramadol are inhibition of norepinephrine reuptake in neurons and enhancement of the serotonergic response; it also has a sedative and antitussive effect; analgesic doses of tramadol in a wide range do not suppress breathing; motility of the digestive tract is less inhibited; the effect on the cardiovascular system is usually weak; the activity of tramadol is estimated in the range from 1/10 to 1/6 of the activity of morphine. Indications for use of the drug: treatment of moderate and severe pain [46-47].

Fentanyl is a synthetic opioid analgesic; similar to morphine; has a rapid, short-term analgesic effect; when administered parenterally, it causes pronounced analgesia, respiratory depression, bradycardia and other effects characteristic of morphine (vomiting, constipation, physical dependence, some vagal effects and sedation of varying degrees); the maximum effect lasts 30 minutes. Indications for

use of the drug: in small doses for analgesia during minor operations; in large doses, analgesia and reduction of spontaneous breathing rate during mechanical ventilation; neuroleptanalgesia in combination with neuroleptic drugs; relief of severe pain [46-47].

Buprenorphine - centrally acting opioid analgesic; by its mechanism of action, it belongs to the group of partial agonists/antagonists of opioid receptors (μ- and κ-receptors); inhibits the action of other agonists, while buprenorphine's own activity towards μ-receptors is very low, and for κ-receptors it is not detected. Activates the antinociceptive system, etc. disrupts the interneuronal transmission of pain impulses at different levels of the CNS, changes the emotional coloring of pain; the duration of the analgesic effect is longer than that of morphine; to a lesser extent than morphine, it suppresses the respiratory center; with prolonged use of buprenorphine, the risk of drug dependence is significantly lower than with the use of morphine. The partial agonist effect of buprenorphine reduces its suppressive effect on cardiac and respiratory activity, which increases the safety of its use. Indications for use of the drug: moderate and high intensity pain syndrome after surgical interventions, chronic high intensity pain syndrome in cancer patients [46-47].

Oxycodone is a semi-synthetic drug belonging to the group of opioid analgesics and is a derivative of thebaine. The mechanism of action of the drug is to stimulate the δ-, μ- and κ-subtypes of opiate receptors without the effect of inhibiting any of the subtypes of opiate receptors. The result is the blocking of interneuronal transmission of pain impulses in various parts of the CNS, including the cerebral cortex and spinal cord. When using oxycodone, a pronounced analgesic and sedative effect is observed, the emotional coloring of pain changes, however, unlike morphine, the use of oxycodone is accompanied by a less sedative effect and depression of the central nervous system, the drug is less likely to cause addiction than opiates, and tolerance to the drug develops less often when used. Oxycodone is used for severe pain syndrome, mainly malignant tumors, and pain

syndrome of other etiology, which requires the use of narcotic analgesics. The drug has also been used for neuropathic pain in patients with diabetic neuropathy, but the effectiveness of oxycodone in this pathology has not been proven. Oxycodone has relatively fewer side effects than other opiates, in particular, it has fewer infectious complications than morphine, since oxycodone has a less immunosuppressive effect than morphine.

According to the Ministry of Health guideline No. 00931 dated 27.09.2017 "Treatment of chronic pain syndrome", the intensity of pain is decisive in choosing a narcotic drug. Opioids can be classified into three groups based on their effectiveness and effect: 1. Weak opioids ▪ Codeine (only in combination) and tramadol. Both drugs are prodrugs that require a functioning CYP2D6 enzyme to act as opioids. 2. Medium-strength opioids ▪ Buprenorphine 3. Strong opioids: Fentanyl (transdermal patch) ▪ Methadone ▪ Morphine ▪ Oxycodone. If the dose of opioid that was prescribed is not effective, it should be changed to another. Morphine is a strong first-line opioid for oral use. Depot tablets are available containing either 10 mg oxycodone and 5 mg naloxone or 20 mg oxycodone and 10 mg naloxone (naloxone is an opioid antagonist that is metabolized in the liver but prevents the constipation caused by oxycodone). If the patient requires more oxycodone, it should be administered as depot tablets, which are administered simultaneously with the combination product. Opioids very rarely cause psychological dependence in cancer patients. Due to neuroadaptation (physiological dependence), abrupt withdrawal of the drug leads to the appearance of symptoms (this is not psychological dependence). Therefore, opioids should not be withdrawn abruptly. Other side effects are more likely to occur with increasing dose. The need for opioids may increase as the disease progresses and the intensity of pain increases, as a result of the action of other drugs, or in the event of tolerance. For example, drugs that induce hepatic metabolism, such as rifampicin and carbamazepine, reduce the effects of oxycodone and methadone, and drugs

that inhibit CYP2D6, such as paroxetine, render codeine and tramadol ineffective as analgesics.

Morphine and oxycodone are available in sustained-release tablets for twice-daily administration. The onset of action is 1–2 hours. Breakthrough pain requires rapid relief, which is achieved with morphine or oxycodone solutions or with oxycodone immediate-release tablets. The additional dose for breakthrough pain is one-sixth of the usual daily dose of the respective drug. The fastest pain relief can be achieved with fentanyl nasal spray. Oral administration of opioids is simpler and more humane than intramuscular administration; patients in the final stages of the disease have very little muscle tissue remaining, injections are very painful and require repeated administration every 2–4 hours. Patients in critical condition face the problem of drawing up a small amount of the drug into a syringe for self-injection. In sufficient doses, oral administration of opioid solutions is as effective as intramuscular administration. If the patient cannot take a tablet due to gastrointestinal obstruction or severe vomiting, sustained pain relief can be achieved by subcutaneous infusion. Both morphine (1/3 of the daily oral dose) and oxycodone (1/2 of the daily oral dose) can be used for subcutaneous administration. Transdermal fentanyl administered via a patch is an alternative to subcutaneous infusion.

Tramadol: Oral, intravenous, or rectal administration. The weak opioid effect of tramadol is mainly mediated by metabolites. Blockade of the CYP 2D6 isoenzyme prevents the formation of "opioid metabolites". Tramadol inhibits the reuptake of serotonin and norepinephrine. The most common side effect is nausea. It is also used in the treatment of moderate neuropathic pain. Buprenorphine: Sublingual or transdermal administration. Maximum daily dose is about 4.2 mg. Buprenorphine is a partial opioid agonist. At high doses, its analgesic effect may

be reduced, as with other opioids. Dizziness and nausea are the most common side effects.

CHAPTER 2. Practical evaluation of different analgesic regimens in the palliative care unit

2.1. Materials and research methods

The practical part of the master's work was carried out by retrospective analysis of information obtained from medical records of patients who were in the specialized palliative care department of the city hospital for the last two years. According to the resolutions of the Ministry of Health of Ukraine, orders of the National Health Service of Ukraine, the provision of palliative care is a necessary link in medical and social assistance to the population, patients who need special psychological, physical, medical, medical rehabilitation during severe, sometimes incurable, diseases, conditions and symptoms that they are characterized and manifested by. Unfortunately, such manifestations include pain syndrome of different localization, different intensity, different tolerance. We are talking about patients with oncological pathology. It is the analysis of pain, methods and ways to combat it, the use of different classes of analgesics and were discussed in the practical part of the work, and the information obtained in the conditions of treatment in Ukraine was also compared with the local features of providing similar care in Morocco. This may allow comparing national approaches and drawing a general conclusion.

The department is designed for 20 beds for patients in need of special palliative care. In the comparative aspect, female patients prevailed in the ratio of 60% to 40% of men. According to the working conditions, the condition of patients with 3-4 stages of oncopathology, who were prescribed analgesic therapy, was assessed. Among women, the localization of breast cancer, pelvic organs with

localization of pain syndrome in the thoracic or lumbar spine, ribs, pelvic bones prevailed. Men were mainly found with localization of lung cancer, prostate gland, hollow organs of the digestive system; and accordingly, the pain was either in the spine, or in the ribs, or in the pelvic bones.

The primary diagnosis was formed and proven by previously necessary laboratory and instrumental methods that are included in the diagnostic standard of a particular nosoform.

The process of diagnosing pain syndrome is carried out in stages:

- Collection of anamnesis: careful clarification of the patient's complaints (nature of pain, localization of pain, intensity, duration, factors that increase or relieve pain;

- Physical examination: general and local examination of the skin and visible mucous membranes, palpation of the area to which the patient draws attention due to the localization of pain, palpation of accessible regional lymph nodes, thyroid gland, mammary or chest glands, abdominal and pelvic organs;

- Laboratory and instrumental diagnostics: depending on the presumed cause of pain, general clinical manifestations, additional methods of radiography, computer diagnostics, magnetic resonance imaging, biopsy are prescribed;

- Assessment of the patient's psychological state: psychological factors that affect the perception of pain, general well-being using questionnaires for anxiety, stress, depression.

Treatment of pain syndrome should begin with a thorough and systematic investigation, including the determination of the possible etiology and nature of the pain. Important characteristics are the intensity of the pain, its type, the impact of the pain syndrome on the general condition and the possibility of its relief, as prescribed in the clinical special protocol [54]:

• Pain intensity. A standard numerical scale of 0 to 10 is used to describe pain, with 0 being described as no pain and 10 as the worst pain possible. It is especially important to use this scale at regular intervals in a particular patient to monitor changes in their condition and response to pain medication.

• Pain type. Nociceptive pain can be described as deep, throbbing, dull, or aching. Neuropathic pain can be described as burning, tingling, prickling, ringing in the ears, numbness, or other abnormal sensations. These characteristics can help guide the choice of pain medication, especially if neuropathic pain is suspected.

• Impact of pain. The impact of pain on the patient's functional and mental state, ability to perform normal daily activities, is assessed and the results of this assessment should be clearly documented in the medical records.

• Possibility of pain relief. Assess and describe conditions or interventions that lead to an increase or relief of pain syndrome. Severe chronic pain is most often found in patients with malignant tumors, chronic pancreatitis, joint damage and severe neuropathy.

According to the developed and implemented procedure for providing palliative care (July 2020) with amendments (November 2024), a PLAN FOR OBSERVATION OF A PATIENT IN NEED OF PALLIATIVE CARE was developed and implemented in the work of specialized departments. It was used to assess the practical part of the work. It has 6 points, which provide for the characterization of pain: nociceptive, neuropathic, psychogenic, mixed; pain level (from 0 no pain to 10 unbearable pain; localization of pain (according to the scheme of body parts); nature of pain (pulsating, burning, stabbing, cutting, dull, aching, unbearable, shooting, severe, tiring, phantom or other characteristics). Of course, to assess the effectiveness of analgesic therapy, these characteristics were the leading ones, but to assess the safety and tolerability of the drug, the overall picture of the course of the disease was taken into account.

2.2. Efficacy and safety of different groups of analgesics in hospital use

When a patient is admitted to a specialized palliative care department of a multidisciplinary clinical hospital, the first thing to do is to fill out a form – CRITERIA FOR DETERMINING A PATIENT IN NEED OF PALLIATIVE CARE, which has two columns. One of them contains information about the disease and its features, the second – information about conditions, clinical indicators and functional disorders. If one criterion is determined in both columns, then such a patient needs palliative care. So, in the left column there is a section on neoplasms (malignant or benign), and in the right column – there is a condition – pain in the form of chronic pain syndrome or phantom pain. This makes it possible to classify patients with cancer with the presence of pain as those in need of palliative care – based on the purpose of the study – pain relief.

VAS (Visual Analog Scale) and NRS (Numeric Rating Scale) are the main quantitative and qualitative tools used to measure pain intensity. They allow the patient's subjective feelings to be translated into numerical indicators that are easy to evaluate, compare and analyze over time.

VAS (Visual Analogue Scale):

This scale is a 10 cm horizontal or vertical line. At one end it says “no pain” and at the other end it says “worst pain imaginable”. The patient marks the point that corresponds to their feelings.

NRS (Numerical Rating Scale):

The patient rates their pain on a scale from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable.

This approach is convenient for quick assessment, especially in clinical practice or during follow-up.

How does it work in practice? Adults can self-report their pain, assess its intensity, and provide a qualitative description that is recorded as initial information in the medical history and then used to monitor the effectiveness of pain relief therapy.

1) Ask the patient to rate their pain on the scale;

2) Record the results in the medical record;

3) Monitor the dynamics to adapt the rehabilitation program.

Returning to the design of the work – using the example of assessing the effectiveness and safety of symptomatic analgesic therapy in a palliative oncology clinic – it should be said once again that patients with neoplasms of the mammary glands, lungs, pelvic organs, and hollow abdominal organs were observed. Therefore, the pain sensations were localized mainly in the skeletal system (spine, ribs, pelvis), were of varying intensity and duration, and were accompanied by additional vegetative symptoms (nausea, vomiting, general weakness, appetite disturbance, bowel movements).

Only the patient can assess the level of pain they are experiencing. At each examination, ask about pain and listen to their complaints. Assess the intensity of the pain before prescribing analgesics. Ask the patient:

• When did the pain begin and how long has it lasted (weeks, months)?

• Where does it hurt?

• Does the pain occur during the day or at night; is it constant, intermittent, or breakthrough?

• What type of pain is it: sharp, dull, burning, stabbing, pressing, bursting, throbbing, etc.?

• Are there symptoms of neuropathic pain: shooting pain, burning sensation, areas of numbness, hyperesthesia, allodynia, dysesthesia?

• How does the patient sleep? If sleep is disturbed, how often does the patient wake up and why: discomfort, pain, habit of sleeping little, shortness of breath, awkward position? If there is difficulty falling asleep, what is the cause: discomfort, pain, shortness of breath?

• If sleep is not disturbed, does the patient experience discomfort, pain, etc., when waking up in the morning?

• What aggravates the pain (eating, defecating) and what relieves it (a particular position in bed)?

• Is the pain accompanied by other symptoms: nausea, vomiting, diarrhea, constipation, shortness of breath, loss of appetite, cough, weakness?

• Does the patient take analgesics? If so, which ones and for how long? How long does one dose of analgesic last?

• Are there any side effects from the analgesic and how severe are they?

• What concomitant diseases are there and what medications does the patient take to treat them?

This allows us to divide pain as a symptom into 3 types:

1. MILD, barely perceptible pain that barely interferes with normal activities. Sleep is not disturbed at night. Regular analgesics last at least 4 hours. Causes mild discomfort. Tolerable.

2. MODERATE PAIN interferes with normal activities and prevents self-care. Sleep is disturbed by pain. Regular analgesics last less than 4 hours. Subjectively, it is very bothersome and severe.

3. SEVERE PAIN overshadows everything and makes the person dependent on others for help. Sleep is disturbed by pain. Weak opioid analgesics (tramadol) last less than 3-4 hours. This pain is described as Terrible, Excruciating, or Unbearable.

Almost any pain can be controlled. Do not allow the patient to endure pain: pain causes suffering and shortens the patient's life. The physician must adhere to the algorithm described in the work [55]:

• Discuss the ongoing treatment and future pain management strategies with the patient and their family.

• Regularly assess the patient's pain intensity using a comprehensive pain assessment scale at rest and during movement.

• Be sure to record the values of the comprehensive pain assessment scale in the medical records.

• Remember that for palliative care patients, morphine and fentanyl have no maximum analgesic dose; however, doses should be titrated based on potential side effects, especially in elderly patients.

• Actively monitor and prevent the side effects of opioids and other analgesics.

• Remember that opioid dependence is rare in patients with pain without a history of drug abuse.

• In complex cases, conduct consultations with related specialists or palliative care specialists from other institutions.

• It is recommended to avoid intramuscular administration of drugs (if possible). • Oral medications (capsules or tablets) or transdermal therapeutic systems (TTS) with opioids are preferred (if the patient is unable to swallow and/or the pain is persistent).

• In some cases (e.g., if TTS is intolerant), bolus subcutaneous administration of opioids (morphine, omnopon) or continuous subcutaneous administration using an infusion pump, wearable pump, or syringe pump may be possible.

• For mild to moderate pain, it is recommended to prescribe medications as needed at the beginning of therapy, and later switch to continuous administration "by the clock."

• Several medications from the same group should not be used simultaneously (e.g., diclofenac and nimesulide).

• In elderly patients, therapy should be initiated with the minimum dosage and gradually increased slowly.

• When prescribing analgesics, it is important to evaluate and consider the possible risks: – NSAIDs should not be prescribed if there is a risk of gastrointestinal bleeding or a high risk of cardiovascular complications; – do not prescribe paracetamol in case of liver failure; – avoid prescribing morphine in case of kidney failure; – do not prescribe tramadol when taking antidepressants.

Here are 2 examples:

1. A woman P., 28 years old, was admitted to the department as a planned procedure for working out analgesic therapy in the lumbar spine with a verified tumor of the right adrenal gland. The pain was moderate in nature, accompanied by dyspeptic symptoms, and sleep disturbance. Analgesia included intravenous drip administration of Infulgan 100.0 ml with the addition of analgin 2.0 ml to the system for pain, as well as intramuscular administration of Nefam. At the same time, taking into account pharmacotherapy, before and during treatment, safety was monitored by laboratory monitoring of general and biochemical blood tests. The effect is the transition of moderate characteristics to a weak version of the pain syndrome. Further recommendations are to select the minimum doses and the

appropriate regimen for using a transdermal patch with fentanyl in outpatient settings.

2. Woman P., 60 years old, was admitted to the department with pain syndrome in the pelvic bones on the background of ovarian neoplasm. Again, the pain was moderate in nature, accompanied by nausea, diarrhea, and sleep disturbance. A combination of intramuscular injection of caver and nefam was used as anesthesia in the department. Efficacy was monitored by the nature of the pain, safety by laboratory blood tests.

As we can see, non-narcotic analgesics are most often used in the hospital, which are better tolerated by patients and do not cause certain additional side effects, the condition of the gastrointestinal tract was controlled by the preventive appointment of proton pump inhibitors (pantoprazole) in combination with prokinetics, which simultaneously have antiemetic and antiemetic activity (metocloramide).

It should be noted that the existing approaches to providing palliative pain relief inpatient care in Ukraine meet world standards. The next practical part of the work was carried out by comparing relevant pharmacotherapy in the countries of the Middle East and North Africa, using the example of Morocco.

Pain in Morocco - Introduction

Pain is among the most feared and burdensome symptoms experienced by patients with life-limiting illnesses. In palliative medicine, the alleviation of pain is not only a clinical priority but a moral and humanitarian obligation. Analgesic therapy—the systematic use of pharmacological agents to relieve pain—forms the cornerstone of palliative symptom control. However, its application must extend beyond technical administration to embrace individualized care, ethical responsibility, and scientific rationale. The theoretical justification for analgesic therapy lies in an understanding of the multifactorial nature of pain, especially in the context of terminal illness. Pain in palliative care is not simply a nociceptive

experience; it is profoundly influenced by psychological, social, and spiritual factors— an idea encapsulated in the framework of “total pain.” Thus, effective analgesia must be based on principles that recognize both the biological and the existential dimensions of suffering. From a practical perspective, analgesic therapy requires precise clinical assessment, evidencebased pharmacological knowledge, and a flexible, patient-centered approach. This includes mastery of the WHO analgesic ladder, appropriate selection and titration of opioids, integration of adjuvant medications, and management of common complications such as constipation, sedation, and opioid-induced hyperalgesia. Importantly, palliative clinicians must also navigate the ethical challenges surrounding opioid use, including public fears of addiction, regulatory barriers, and the delicate balance between adequate relief and over-sedation. This thesis aims to explore both the theoretical underpinnings and clinical applications of analgesic therapy in palliative care. It will analyze current literature, review pharmacological strategies, and present real-world case studies to highlight how theory translates into compassionate and effective practice. By doing so, it contributes to the advancement of evidence-informed, ethically sound, and patient-centered palliative care.

Palliative Care in Morocco: Situation, State Programs & Regulatory Orders

1) Executive summary • Morocco has formal policy and clinical guidance for palliative care anchored in the Plan National de Prévention et de Contrôle du Cancer (PNPCC) 2020–2029 and a national Guide des soins palliatifs (2018). Services are progressively integrated into oncology networks, with growing—but still uneven—coverage across regions. • Service delivery is centered on regional oncology centers (public CRO/INO network) and supported by “Maisons de vie” that reduce social and logistical barriers to care. • The legal framework for narcotics and psychotropics (key for pain control at end of life) rests on Dahir n° 1-73-282 (21 May 1974) and implementing professional rules, including strict

prescription/dispensing limits (e.g., 7-day validity for stupéfiants) and record-keeping obligations.

2) Need and context • The country's cancer burden (and other life-limiting conditions) drove the inclusion of palliative care as a pillar of the national cancer response, with explicit actions to expand symptom control, psychosocial support, and continuity of care. The current PNPCC 2020–2029 is the operative strategy. • Morocco's palliative model explicitly adopts the "total pain" perspective (physical, psychological, social, spiritual) in its national guide and organizes care pathways across hospital, ambulatory and home settings.

3) National programs, strategies and operational guidance **3.1** The policy backbone • PNPCC 2020–2029 (Ministry of Health & Social Protection) o Continuation and scale-up of the first plan (2010–2019). o Palliative care actions include: developing national reference protocols, standardizing pathways, strengthening psycho-social and spiritual support, organizing respite/hospital-at-home options, and improving continuity o • PNPCC access point (Fondation Lalla Salma) o Public posting and dissemination of the plan (FR/AR) and programmatic materials to providers and the public. **3.2** National clinical guidance • Guide des soins palliatifs pour les patients atteints de cancer – Édition 2018 o Morocco's official clinical reference for palliative care: assessment, pain management (WHO ladder adaptation), symptom protocols, psychosocial/spiritual care, family support, care coordination (hospital–ambulatory–home), and appendices with essential medicines/supplies. The guide is aligned with WHO's "Planning and implementing palliative care services" managerial guidance, contextualized for Moroccan health services. **3.3** Service infrastructure and social support • Regional oncology centers ("Les centres d'oncologie") The Fondation Lalla Salma's directory shows the geographical backbone where pain and palliative services are typically embedded (public CRO/INO and private centers). • "Maisons de vie" (lodges near oncology centers) Provide accommodation and social support for patients/families during

treatment—an enabler for continuity and adherence, particularly for those traveling from rural areas

4) Organization of care (how the system is supposed to work) Care levels and pathways (per national guide): • Hospital level: Oncology units (and selected internal medicine/surgery units) provide specialist palliative assessments, analgesic titration (including strong opioids), symptom control, and discharge planning. • Ambulatory clinics: Follow-up for analgesic adjustment, adjuvants, psychosocial and spiritual support, and linkage with primary care/community actors. • Home-based support: Encouraged when feasible; the guide details home symptom monitoring, caregiver education, community resources, and communication standards for shared care with the treating oncologist/GP. Core components: systematic pain assessment, individualized care plans, interdisciplinary teamwork, and documentation/continuity across settings.

5) Workforce, training and quality • The national guide identifies the required multidisciplinary team (physicians, nurses, pharmacists, psychologists, social workers, spiritual care and volunteers) and sets competency expectations for pain assessment, opioid stewardship, and communication at end of life. • The PNPCC emphasizes capacity-building and standardized protocols; oncology networks and affiliated training initiatives (including those supported by the Fondation Lalla Salma and partners like WHO/IARC for screening programs) are used as channels for palliative training and quality improvement.

6) Regulatory framework (“orders”) that enable and constrain palliative care **6.1** Core narcotics law • Dahir portant loi n° 1-73-282 du 28 Rebiâ II 1394 (21 mai 1974) Foundational statute governing production, import, storage, prescription, dispensing and use of narcotic drugs and related offenses. It sets penalties for violations and mandates compliance mechanisms—this framework underpins all opioid availability for palliative pain control. Internationally catalogued summaries (UNODC SHERLOC) confirm scope and key penal provisions. **6.2** Implementing professional rules for prescribing/dispensing •

Moroccan professional and ministerial guidance on stupéfiants & psychotropes specifies: Special prescription requirements and registers (ordonnancier, registre spécial) for controlled medicines. Validity/quantity limits—notably, it is forbidden to prescribe or dispense stupéfiants for a period exceeding seven (7) days; registers must be kept for 10 years and produced on inspection. (Cited text excerpts used in pharmacy education and ministerial materials.) Why it matters: these rules are central to palliative practice—they shape how hospitals and community pharmacies stock, prescribe, and dispense morphine, fentanyl, buprenorphine, etc., and how clinicians manage continuity at home near end of life.

7) Current achievements and gaps Progress • National policy continuity (2010–2019 → 2020–2029) and official clinical guidance exist; oncology centers and Maisons de vie support access and adherence. • Palliative care is explicitly integrated into cancer pathways, including pain assessment and opioidbased analgesia protocols. Gaps (commonly highlighted) • Geographical inequities: services are more available in major cities; rural/remote regions face travel/logistics barriers despite the lodge network. • Home- and community-based capacity still maturing; sustained training and standardized pathways are ongoing needs under the PNPCC. • Controlled-medicine logistics: ensuring continuous availability of essential opioids within the 7- day prescribing framework requires strong forecasting, pharmacy practices, and hospital– community coordination (emphasized in guide and professional circulars).

8) Practical implications for services 1. Embed structured palliative assessment (including validated pain scales) at every oncology contact; follow the national guide algorithms for symptom control and transitions to home care. 2. Plan opioid continuity proactively: align hospital discharge quantities with the 7-day rule, schedule timely follow-up, and coordinate with the community pharmacist (register entries, stock levels). 3. Strengthen regional pathways: use the oncology-center map and Maisons de vie as anchors; build referral links with primary care and social services for remote patients. 4. Invest in team training: the

PNPCC and national guide call for ongoing multidisciplinary capacitybuilding and protocol adoption; align internal SOPs to those references. Opioid Analgesia for Severe Cancer Pain: Routes, Forms, and Morocco-Approved Drugs 1) Clinical frame (why so many forms?) In advanced cancer, pain control usually combines: • Baseline (around-the-clock) analgesia to keep a steady opioid level (e.g., sustained-release oral morphine or transdermal fentanyl). • Breakthrough pain (BTP) rescue for sudden spikes despite baseline control (e.g., immediaterelease morphine or rapid-onset fentanyl SL). • Route switching as disease evolves (dysphagia, bowel obstruction, delirium), favoring sublingual, transdermal, or parenteral routes. The WHO ladder still guides escalation (non-opioids → weak opioids → strong opioids), but in severe cancer pain, clinicians often start at Step III with strong opioids, titrating to effect and adding adjuvants (e.g., dexamethasone for edema, gabapentinoids for neuropathic components).

ORAL route (preferred when feasible)

2.1 Morphine – cornerstone drug • Immediate-release (IR) tablets: for titration and BTP; typical q4h dosing with individualized conversion. Brands (Morocco): Sevredol 10 mg, 20 mg (tablets). • Sustained-/modified-release (SR/MR) tablets: baseline control, usually q12h; combine with IR for BTP. Brand (Morocco): Moscontin 10 mg (also higher strengths in practice). Indicated for "douleurs intenses… en particulier cancéreuses." When oral morphine is ideal • Reliable gut absorption, patient can swallow, predictable titration, cost-effective, broad clinical familiarity. When to switch away from oral • Dysphagia, refractory nausea/vomiting, malabsorption, intractable mucositis, or need for very rapid effect.

2.2 Tramadol – Step II/adjunct (not sufficient alone for severe pain) • Capsules/tablets for moderate pain or as an adjunct when neuropathic features are present and strong opioid dose is being optimized. Brands (Morocco): Tramadol Normon 50 mg (caps), Nomadol 50 mg (tabs). Note: For severe cancer pain,

tramadol is usually not the mainstay; morphine/fentanyl/buprenorphine are preferred for Step III.

TRANSMUCOSAL routes (rapid rescue or when swallowing is difficult)

Fentanyl sublingual (rapid-onset) – for breakthrough cancer pain in opioid-tolerant patients • Sublingual tablets provide fast relief (onset ~10–15 min). Brand (Morocco): Abstral 100 µg, 200 µg. Labeled specifically for "accès douloureux paroxystiques" in adults already on opioids. Clinical pearl: Dose is titrated per product-specific protocol (not a fixed fraction of morphine daily dose). Reserve strictly for opioid-tolerant patients.

Buprenorphine sublingual – strong opioid option • Sublingual tablets: useful when oral morphine is poorly tolerated or when clinician favors partialagonist profile. Brand (Morocco): Temgesic 0.2 mg SL, indicated for "douleurs néoplasiques."

TRANSDERMAL route (continuous baseline without swallowing) Fentanyl patches • Transdermal systems (25–100 µg/h) deliver steady opioid levels for 72 h; helpful in dysphagia, poor adherence to frequent dosing, or stable high opioid needs. Brand (Morocco): Durogesic 25 µg/h (other strengths also marketed). Indicated for chronic severe pain requiring continuous opioids. Use cases & cautions • Good for stable requirements; not for rapid titration or opioid-naïve patients with mild pain. Avoid in fever/cachexia without dose review (absorption can change). Provide IR rescue for BTP.

PARENTERAL routes (when enteral is impossible or for rapid control)

Morphine injectable (IV/SC/IM) • Injectable solution 10 mg/mL (morphine sulfate or hydrochloride) used for: acute titration, refractory vomiting, bowel obstruction, end-of-life continuous subcutaneous infusions (CSCI). Brand (Morocco): Morphine SOTHEMA 10 mg/mL (ampoules). Practice points • SC

route is preferred for palliative infusions (less invasive than IV). Use syringe drivers for continuous delivery; maintain IR rescue.

Buprenorphine injectable • 0.3 mg/mL ampoules, reserved for rapid control when SL/PO aren't feasible or as a bridge to transdermal/oral regimens. Brand (Morocco): Temgesic inj. 0.3 mg/mL. Other parenteral opioids (e.g., hydromorphone) are standard in some countries, but Morocco's marketed options center on morphine, fentanyl, and buprenorphine; local formularies should be checked if considering alternatives.

Oral and Other Forms of Narcotic Analgesics Approved for Severe Cancer Pain Relief 1. Morphine Sulfate – Oral tablets (immediate-release and sustained-release), oral solution, injectable formulation for subcutaneous or intravenous use. 2. Fentanyl – Transdermal patches (various dosages, usually replaced every 72 hours), injectable formulation, buccal tablets, and oral transmucosal lozenges ("lollipop" form) for breakthrough pain. 3. Oxycodone Hydrochloride – Oral immediate-release tablets, extended-release tablets, oral solution; sometimes available in combination with non-opioid analgesics (e.g., oxycodone + acetaminophen). 4. Hydromorphone – Oral tablets, oral liquid, injectable formulation; often used when morphine is poorly tolerated. 5. Methadone – Oral tablets, oral solution; also available in injectable form, typically for specialized cases with opioid rotation or neuropathic pain components. 6. Buprenorphine – Sublingual tablets, transdermal patches (changed every 7 days), injectable form; sometimes preferred in patients with renal impairment. 7. Tramadol Hydrochloride – Oral tablets (immediate- and extended-release), oral drops, injectable form; considered a weak opioid, often used in step 2 of the WHO pain ladder. 7) Stewardship & safety essentials (exam-level points) 1. Start-low, go-fast (but safe): Titrate IR morphine in small steps to reach comfort, then convert to SR or patch for convenience; always co-prescribe an IR rescue (typically 10–15% of the 24-h dose).

Equianalgesic conversions: Use conservative reductions (≈25–50%) when switching opioid or route to account for incomplete cross-tolerance—especially when moving to fentanyl patches or SL fentanyl. 3. Breakthrough dosing: One rescue dose ≈ 1/10 to 1/6 of the total daily oral morphine equivalent (OME), taken q1–2 h PRN (IR morphine) or per product protocol (SL fentanyl). 4. Bowel regimen is mandatory: Stimulant laxative ± stool softener from day one; review antiemetics early. 5. Opioid rotation: Consider if uncontrolled pain despite dose escalation or intolerable adverse effects (sedation, neurotoxicity). 6. Regulatory compliance (Morocco): Strong opioids are stupéfiants/analgésiques opioïdes requiring special prescriptions and dispensing records; brands listed above are documented as commercialisés locally. Coordinate hospital–community supply to avoid gaps.

Morocco-approved opioids for severe cancer pain (quick list) Strong opioids (Step III) • Morphine oral IR — Sevredol 10 mg, 20 mg (tabs). • Morphine oral SR — Moscontin 10 mg (LP tab; higher strengths also marketed). • Morphine injectable — Morphine SOTHEMA 10 mg/mL (ampoules). • Fentanyl transdermal — Durogesic 25 µg/h (patch). • Fentanyl sublingual (BTP) — Abstral 100 µg, 200 µg (SL tabs). • Buprenorphine sublingual — Temgesic 0.2 mg (SL tab). • Buprenorphine injectable — Temgesic 0.3 mg/mL (ampoules). Step II / adjunct • Tramadol oral — Tramadol Normon 50 mg (caps), Nomadol 50 mg (tabs). Oxycodone and hydromorphone are common internationally but not reliably available on Moroccan retail lists; methadone is primarily used for addiction programs rather than routine cancer pain. Always verify current local formularies if considering these. Problems in Palliative Care in Morocco 1. Severe Under-Coverage and Access Inequality • Over 60,000 Moroccans (including ~6,000 children) require palliative care annually, yet only two dedicated public units exist (in Rabat and Casablanca) serving cancer patients exclusively . • No palliative care at secondary-care level. Interviews with medical staff across eight non-tertiary hospitals (including towns 150 km from tertiary centers) showed none offered

palliative services or even stocked oral morphine . • Patients outside urban centers face major hurdles. Most regions—especially the south and northeast—have zero local palliative care providers, forcing long, financially burdensome travel . 2. Chronic Shortage of Essential Medicines (Opioids) • Morphine availability is critically low. Consumption levels in 2013 could cover only about 20% of terminal cancer/AIDS patients in need—even before including other chronic diseases . • Though usage has increased since its introduction in 1995, morphine consumption remains classified as "very inadequate" by international standards . 3. Regulatory Barriers and Prescribing Restrictions • Morphine and its derivatives are labeled as "poisons," requiring special prescription pads and restricted to a fraction of physicians—mostly within hospital environments . • Access for insured patients outside hospitals is practically nonexistent, further limiting their coverage . • Broader regional evidence underscores widespread regulatory hurdles: need for special licenses, mandatory prescription forms, pharmacist limitations, storage burdens, and restrictions on nurse involvement or proxies in opioid collection .

Fragmented Policy, Weak Governance, and Lack of Oversight • Despite policy recognition in the 2010 and 2012 national cancer plans, goals like "100% coverage of cancer patients by 2019" went unmet, largely due to lack of clear implementation authority or monitoring systema • A 2023 review finds no comprehensive legislation, strategy, or oversight for palliative care in Morocco—resulting in fragmented services and unclear accountability .

5. Scarcity of Trained Providers & Educational Deficits • While palliative care became a mandatory undergraduate medical module in 2015, specialists remain few, and most facilities lack trained personnel . • Significant nursing shortages compound these challenges: Morocco has just ~8 nurses per 10,000 population, with projections calling for 40,000–80,000 new nurse graduates by 2025 .

6. Concentration on Oncology; Neglect of Non-Cancer Conditions • Available services are almost entirely cancer-focused. Patients with terminal non-

oncological diseases—such as heart failure, COPD, advanced kidney disease, neurological illnesses—have minimal or no pathway to palliative care . The WHO estimated that 40,000 adults annually need palliative care for non-cancer conditions alone .

7. Weak Data, Planning, and Decentralization • The absence of reliable data and national-level coordination hinders planning, evaluation, and resource allocation. • There are no decentralized models or health system integration, meaning services remain siloed within tertiary institutions, without primary care or community-based linkage Solutions to Strengthen Palliative Care in Morocco 1. National Policy, Legislation, and Strategic Integration • Draft and enact a National Palliative Care Law o Establish palliative care as a legal right for all patients with life-limiting illness. o Define clear responsibilities for the Ministry of Health, regions, and hospitals. • Integrate palliative care into universal health coverage (UHC) o Include services and essential medicines in the national reimbursement list (CNOPS, RAMED/AMO). • Update and expand the National Cancer Plan to include non-oncological conditions (heart failure, COPD, neurological diseases, end-stage renal failure). • Create a National Palliative Care Committee to coordinate policy, oversee quality, and manage data. 2. Improve Access and Decentralization • Develop regional palliative care hubs o At least one specialized palliative care unit per regional hospital. o Provide outpatient clinics and day services in secondary hospitals. • Community- and home-based palliative care o Train local health workers and NGOs to deliver home visits, especially in rural areas. o Use mobile units (as trialed during COVID-19) for remote populations. • Primary care integration o Equip family doctors and nurses to handle basic pain and symptom management, with clear referral pathways. 3. Opioid Accessibility and Rational Regulation • Revise narcotics regulations to align with WHO guidelines: o Allow all trained physicians (not just hospital specialists) to prescribe morphine. o Introduce electronic prescription monitoring to prevent misuse while easing access. o Permit nurse practitioners (in rural zones) to dispense oral

morphine under physician oversight. • Ensure consistent supply chains for morphine and other essential analgesics: o Oral morphine tablets and liquid formulations available in all regional pharmacies. o Buffer stocks to prevent shortages. • Education on opioid stewardship to reduce prescriber fears and stigma.

Human Resources and Capacity Building • Expand medical and nursing training: o Make palliative care a compulsory, examined module for all healthcare students (medical, nursing, pharmacy). o Create a postgraduate diploma in palliative care at Moroccan universities. • Specialized palliative care teams: o Interdisciplinary teams (physician, nurse, psychologist, social worker, spiritual care provider) in every regional hub. • Continuous Professional Development (CPD): o Annual training for existing healthcare workers, with incentives for rural service. 5. Financing and Resource Mobilization • Allocate a dedicated budget line for palliative care in the Ministry of Health plan. • Engage with international donors (WHO, African Union, Union for International Cancer Control) for startup funding. • Encourage public–private partnerships with NGOs and pharmaceutical companies for outreach programs. 6. Research, Data, and Quality Monitoring • National Palliative Care Registry: o Collect data on patients served, opioid use, outcomes, and satisfaction. • Support operational research on culturally adapted pain management models. • Implement quality indicators (e.g., pain control within 48 hours of admission, patient-reported outcomes). 7. Public Awareness and Cultural Engagement • Launch national campaigns to reduce stigma around opioids and palliative care. • Partner with religious leaders to frame palliative care as aligned with compassion and dignity at end-of-life. • Use community media to educate families on early referral and available services.

CONCLUSIONS

1. By analyzing modern literary sources, the main types and types of pain syndrome in oncology are shown, the leading mechanisms of pain formation are considered, which are subsequently the object of medical intervention at the stage of providing hospital and outpatient care. It is shown that pain pharmacotherapy is individualized, the choice of which should be made by a multidisciplinary medical team taking into account the clinical condition of the patient, the presence of comorbid conditions to oncology, psychophysiological and social characteristics of the body.

2. The choice of a specific method and means of pain relief in carcinogenesis depends on many exogenous and endogenous factors, therefore an individual approach and a thorough examination of the patient are so important, allowing the doctor to assess the effectiveness, feasibility and possible risks. Palliative care in medicine proves that pain syndrome must be treated regardless of the prognosis for the underlying disease in order to prevent the destructive effect of pain on the physical, moral and mental state of the patient and to maximize the preservation of his social significance.

3. Pharmacotherapy of chronic pain in oncopathology in Ukraine and Morocco is regulated by an appropriate standard, which provides for compliance with a consistent three-stage standard: the use of nonsteroidal anti-inflammatory drugs and non-narcotic analgesics for the treatment of mild pain, mild opioids for moderate pain, and strong opioids for severe pain. A significant number of oncological diseases accompanied by chronic pain should be treated as palliative, in specialized departments.

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Appendices

EC-003595

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is hereby granted to

Zerouali Chaima

for participation in the International Multidisciplinary Scientific Internet Conference
«World of scientific research. Issue 48»
with a publication on the topic: «THEORETICAL BASIS OF PERSONALIZED SYMPTOMATIC PAIN RELIEF THERAPY IN ONCOLOGICAL PATIENTS»
Form of participation: remotely, duration of conference is 18 hours 0,6 ECTS credits.

The conference was held with the assistance and participation of Public Organization "Scientific Community" and Wyższa Szkoła Zarządzania i Administracji w Opolu

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Випуск 48

27-28 січня 2026 р.

ISSN 2786-6823 (print)

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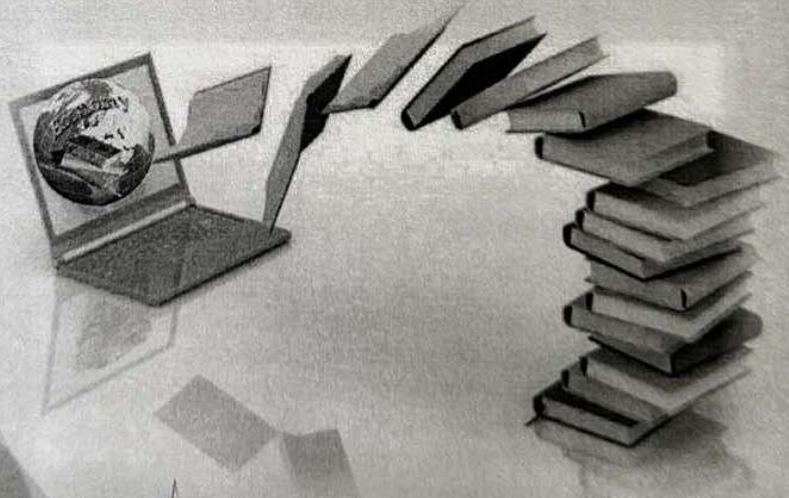

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Тернопіль, Україна – Ополе, Польща
2026

УДК 001 (063)

Світ наукових досліджень. Випуск 48: матеріали Міжнародної мультидисциплінарної наукової інтернет-конференції (м. Тернопіль, Україна, м. Ополе, Польща, 27-28 січня 2026 р.) / за ред. : О. Патряк та ін. ГО "Наукова спільнота", WSZIA w Opolu. Тернопіль: ФО- П Шпак В.Б. 2026. 175 с.

Збірник наукових публікацій укладено за матеріалами доповідей наукової мультидисциплінарної інтернет-конференції «Світ наукових досліджень. Випуск 48», які оприлюднені на інтернет-сторінці www.economy-confer.com.ua

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ISSN 2786-6823 (print)

THEORETICAL BASIS OF PERSONALIZED SYMPTOMATIC PAIN RELIEF THERAPY IN ONCOLOGICAL PATIENTS

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The incidence of oncological diseases and mortality due to them remain a leading clinical and social problem at the national and global levels and show a tendency to increase. According to the World Health Organization (WHO), cancer can claim more than 13 million lives [1, P. 169]. Pain syndrome is the most common and non-specific manifestation of diseases caused by malignant neoplasms and accounts for almost two-thirds of all cases of a generalized process; 30-40% of patients suffer from moderate or severe pain, which is chronic in nature; 40-55% experience pain at the stage of generalization, during and after antitumor therapy, and in the terminal stage of the tumor process [2, P. 1].

A new type of medical care is actively developing and being introduced into practical medicine – palliative medicine, or palliative care – which involves the use of various methods of pain relief in patients with oncological diseases [3, P. 318]. The need for pain relief arises at different stages of the disease and stages of its treatment, from the initial consultation with a family doctor to specialized examination and treatment by an oncologist, chemotherapist, or radiotherapist. The primary task is to determine the nature of pain (nociceptive, neuropathic, psychogenic, or mixed), its intensity, and to identify the cause and pathogenesis of the pain syndrome [5, P. 18]. For this purpose, the "Plan of observation of a patient in need of palliative care" was used and analyzed. It contains a large amount of subjective and physical information obtained directly from the patient and recorded by completing the relevant sections. Section 6 of this plan includes various characteristics of pain (nature, localization, extent, intensity, and previous use of analgesics).

Most often, chronic pain syndrome develops due to secondary metastases to bone tissue located in close proximity to the primary tumor site. Breast cancer

metastasizes to the thoracic spine and ribs in 70-80% of cases, with corresponding pain localization; in lung cancer, pain and metastases are diagnosed in the thoracic or lumbar spine in 55-60% of cases; in kidney cancer, cancers of the pelvic organs in women, and prostate cancer, pain and metastases to the pelvic bones and lumbar spine are observed in 50-55% of cases [4, P. 3].

There are general approaches that ensure similar principles of palliative care in accordance with international standards, as well as specific features of state regulation in different countries. These features are demonstrated by comparing pain relief practices in Ukraine and Morocco.

States have formal policies and clinical guidelines for palliative care, enshrined in the National Cancer Prevention and Control Plan and the National Palliative Care Guide (2018-2022). Services are gradually being integrated into cancer care networks, with increasing but still uneven coverage across regions. Service provision is concentrated in regional cancer centers, which reduces social and logistical barriers to care. The legal framework for narcotic and psychotropic drugs, which are essential for end-of-life pain management, is based on the implementation of professional regulations, including strict restrictions on prescribing, dispensing, and record-keeping obligations. The burden of cancer and other life-limiting conditions has led to the inclusion of palliative care as a key component of the national response to cancer, with defined actions to expand symptom control, psychosocial support, and continuity of care in hospital, outpatient, and home settings. The national guideline identifies the required interdisciplinary team (physicians, nurses, pharmacists, psychologists, social workers, spiritual workers, and volunteers) and establishes expected competencies for pain assessment, opioid therapy management, and end-of-life communication.

The legal framework regulates the production, importation, storage, prescription, dispensing, and use of narcotic drugs, as well as related offenses. It establishes penalties for violations and provides compliance mechanisms, forming the basis for the availability of opioids for palliative pain control. Moroccan professional and ministerial guidelines on narcotic and psychotropic substances define specific prescription requirements and registries for controlled drugs, as well as limits on prescription duration and quantity. In particular, it is prohibited to prescribe or dispense narcotic drugs for a period exceeding seven days. Prescription records must be kept for ten years and presented upon inspection. These regulations are crucial for palliative practice, as they determine how hospitals and community pharmacies store, prescribe, and dispense morphine, fentanyl, buprenorphine, and other opioid analgesics, and how continuity of care at home is ensured at the end of life.

Ensuring and implementing these principles is impossible without a personalized approach to the selection and continuation of palliative pain management. This requires structured palliative assessment, including the use of validated pain scales at each patient encounter, adherence to national clinical algorithms for symptom control and transition to home care, and active planning for the continuity of opioid therapy, including coordination between hospitals and community pharmacies. Pain

...ement usually includes continuous 24-hour analgesia to maintain a stable op...
...entration, means for the relief of breakthrough pain, and changes in the route... administration as the disease progresses, with preference given to sublingu... transdermal, or parenteral routes. International standards recommend a stepw... analgesic approach, progressing from non-opioid analgesics to weak opioids and th... to strong opioids; however, in cases of severe cancer pain, clinicians often initia... therapy with strong opioids, titrating the dose according to clinical effect and addin... adjuvant medications (e.g., dexamethasone for edema, gabapentinoids for neuropathi... components).

A general conclusion can be drawn: the treatment of acute and chronic pain in cancer patients in Ukraine and Morocco is regulated by relevant standards that ensure adherence to a consistent three-step approach. This includes the use of non-steroidal anti-inflammatory drugs and non-narcotic analgesics for mild pain, weak opioids for moderate pain, and strong opioids for severe pain. Escalation or de-escalation regimens are applied individually, depending on pain severity and drug-related risks. A significant number of oncological diseases accompanied by chronic pain require palliative treatment in specialized departments.

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