Chapter

Multimodal Pain Management in the Setting of Palliative Care

Marija V. Sholjakova and Vesna M. Durnev

Abstract

Pain as an integral part of palliative care (PC) is often present at the end of the life. Today, many different analgesics from opioids and non- opioids origin are in use. The integration of their use is the most effective method for pain relief. The aim of this chapter is to discuss different therapeutic approaches to pain management in palliative care. Palliative care is being confronted between the expectations and the possibilities to provide an efficient relief from the symptoms, the pain and the stress. The possibility to use opioids for pain management, with all side effects, and non-addictive drugs as additional treatment, improves the quality and the duration of life for the patients in palliative care. Since the origin of the pain is different, the use of analgesic therapy should be individualized and adapted to the real need of every person. Finally, only a good organization and institutionalization of palliative care in the society could allow for better prevention of suffering at the end of the life.

Keywords: pain in palliative setting, multimodal analgesia, non-opioids, opioids, non-pharmacological therapy

1. Introduction

Pain is an integral part of palliative care (PC) and it is often present at the end of the life. Nowadays the understanding of "palliative care" has changed. The new approach in palliative care services integrates the latest knowledge and developments in medicine [1], providing care by specialized team of doctors for pain treatment, surgery, interventions' radiology, oncology, intern medicines and others. This integration of the knowledge from different specialties, offers in "hospices" a very high-quality care for the patients at the end of their life, where pain is managed by specialized professional teams [2]. This care is enriched with support in daily living, with psychological and spiritual care for patients and their families [3].

The philosophy of palliative care is to provide advanced care planning and support which helps the patient live an active, pain-free life, and the pain treatment is one of the most important curative methods during their habitation in a Hospice. Difficulties with impairments, such as sense of hearing, sight, and speech, often represent barriers in communication. Since the patients in palliative care are elderly persons, they are also burdened with the presence of some neurological diseases such as Alzheimer's disease, dementia, or cognitive impairment, which is an additional problem in this context. Additionally, in patients with cardio-circulatory, respiratory or kidney disorders, symptoms of fatigue, insomnia, and shortness of breath dominate.

Pain is very often present at the end of the life, but unfortunately the presence of pain in palliative care is underestimated. The reasons for that are multi-factorial. One of the reasons is a lack of communication and difficulties between the patients and the palliative care providers; the second is unrecognized and misunderstood presence of pain; the third is the mixture of different symptoms or other reasons [4]. Due to these reasons, it is necessary to improve the knowledge about the pathogenesis of pain and the modern approaches to the management of pain relief.

2. Pain

According to the last guidelines by the International Association for the Study of Pain (IASP), pain is defined as unpleasant sensory and emotional experience associated with or resembling that of actual or potential tissue damage [5].

The presence of pain in patients at PC is associated with actual or potential tissue damage which has implications on their daily physical activities, produces debilitation and mental destabilization and has social consequences. In general, pain is a special medical condition which pathophysiology is complex and originates from different causes [6].

Many stimulations arising from injuries or destroyed tissues, commonly associated with prime pathological event in the body, produce noxious stimuli. Peripheral painful stimuli are detected by nociceptors, which are free nerve endings located in tissues and organs. Following complex mechanisms, the noxious stimuli are transformed and recognized by the brain as pain [7].

The released neurotransmitters and neuropeptides enable the pain stimuli to ascend to the thalamus and midbrain through two main tracts, the spinothalamic tract and the spinoreticular tract (involved in descending inhibition of the pain) and through the spinomesencephalic tract. They go from the spinal cord, are synapsing in the periaqueductal gray meter in the midbrain and are involved in the modulation of the pain [8]. Descending pathways descend in the dorso-lateral fasciculus and synapse in the dorsal horn inhibitory tracts; they are coming mainly from areas (periaqueductal gray matter, the raphe nuclei, and the locus ceruleus) in the brainstem tracts.

Modulation of the pain is a process of inhibition or amplification of the pain signals [9]. It happens along its ascending pathways on several levels, at segmental level (the primary afferent neuron and dorsal horn), supra-segmental level (midbrain) and cortical, or through the descending pathways. In this process the following excitatory substances are included: excitatory amino acids (EAA), acetylcholine (Ach), glycine, substance P (sP), Oxytocin, central corticotropin releasing hormone (CRH), and the inhibitory substances as serotonin, noradrenalin (NE), and gamma-amino butyric acid (GABA) including endorphins (eg, enkephalin) [10].

Many drugs are acting as modulators of pain. They are acting at segmental level (local anesthetics), supra segmental (opioids, non-opioids, and adjuvants), and central or cortical levels (opioids). The endogens opioids endorphins and enkephalins are acting via the descending system and are responsible for the analgesia induced by stress.

Modulation and perception are the component of the plasticity of the pain. Pain plasticity is a result of the possibility of the nervous system to modify its function under different conditions [9]. For the perception of the noxious stimuli and the formation of the memory of the pain, the middle and higher levels of the brain are responsible. The subconscious pain information's are ended in sub cortical level at hypothalamus, thalamus, amygdale, and hippocampus. They are transferred to the cortical centers where they are recognized as pain in somato sensory cortex, insula, and anterior cingulate cortex [10].

In general, pain can be acute (physiological) and chronic (pathological). Some authors make a distinction between physiological and pathological pain, classify it as Nociceptive (somatic, visceral), and Neurophatic (burning along the nerves, dysesthesia, allodynia, Hyperalgesia) [11]. Under certain conditions, acute pain can become maladaptive and non-protective and turn to pathological, dysfunctional pain - chronic pain.

The evidence concerning pain among patients in PC show that during the care phase, pain is present in one moment in approximately 70–90% of the patients [9]. Pain is seen in many end stage diseases. The prevalence of pain is most common in cancer; 70–90% in latter stages of the illness and 33–70% in patients receiving treatment [12]. Comparatively, the prevalence of chronic pain in the general adult population ranges from 2% to 40%. It is known that back pain alone affects "up to 84%" of adults.

Many conditions in palliative settings could provoke the pain. Mainly they are caused by the primary diseases, disorders, and conditions. An accidental situation such as trauma, blunt trauma, broken bone, burning, electrical injury, eye injury, heart attacks or postoperative state (amputation, removal of a part of an organ) needs corresponding analgesia. In chronic illnesses from circulatory, infectious, or malignant origins, the pain is expressed as neural compression or malignant infiltration, bone metastasis, obstructions, and infiltration of the soft tissues. Many degenerative processes produce inflammation and are reason for pain.

Resulting from the type of the pain, the feeling pain is different. The pain is reported as dull, achy, stabbing, shooting, burning, severe, or pins-and-needles sensations.

The patients on PC fear pain because of its physical, emotional, and psychological components [3]. Unrelieved or undertreated pain with all its effects to the body systems, may transit to chronic pain. The pain experience is unique for each individual and the way everyone perceives pain, and its severity is different, leading to changes in the personality that has social implications. If the pain is with chronic persistence, it disturbs the sleep and appetite, lowers the tolerance to stress and is often the reason for depression. There are evidences that pain contributes to the development of some cognitive dysfunctions. It impairs attention, memory, concentration, and content of thought [13].

The reaction to pain and thresholds to pain are complex and individual and depend to the individual experiences to pain. The intensity of the pain is in the proportion of the extent of the tissue damage, the severity of the illness and the degree of the patients' discomfort [14]. The after-effects of persistent pain are multiple due to stress-reaction with the involvement of the adreno-cortical axis and hyperactivity in many organs and systems. Increased heart rate with low cardiac output, presence of fear, increase respiration rate, cold vasoconstricted skin, neurological dysfunctions and other impairments in homeostasis are often seen as associated symptoms to the pain [15]. Patients with chronic pain may have low levels of endorphins in their spinal fluid [16].

Modifications of the quality of the pain are product of different physiological and psychological phenomena. The protective function of the pain has function to restore the homeostasis at both levels (autonomic and psychological). The intensity of pain can be modulated by psychological factors where emotions have an important role in the perception of pain. The memory of pain episodes, the patients' reactivity to pain, families and friends supports, religion, personal defense skills, and therapeutic strategies are the most frequent reasons for these modifications [8]. The levels of education, culture and tradition have an important part in the formation of the pain experience. Severe pain produces mental and physical torture of the body [17]. The person is exhausted, fatigued and without energy. Fatigue is one

of the leading symptoms of terminal states and often concomitant symptom of the malignancy, producing a poor quality of life.

3. New approaches of pain treatment

Pain is a common symptom in many advanced illnesses [18]. Nowadays, the treatment of pain is approached from neurobiological, clinical, and behavioral perspective.

The main goals of the pain management are early recognition, early proper pain relief, monitoring and documentation. New approaches to the management of pain in palliative care integrate the standard pain relief methods with complementary health techniques [19]. The expectations of the patients at a Hospice are to have an active, pain-free life. The potential to reach these expectations is though the patients tailored analgesia and the integrations of alternatives with medical treatment in multimodal analgesic approach. A multimodal flexible approach to pain relief therapy for palliative care provides the best results. It consists of the use of more therapeutic abilities at the same time frame, at different time intervals. The main characteristic of this therapy is a continuum of analgesic management [20]. The last advancement in pain management treatment is multimodal analgesia with individual tailoring of the therapy to the real needs [21].

3.1 The multimodal approach to pain management

The multimodal approach to pain management which was introduced in 1993 by Kehlet and Dahl as an analgesic model for postoperative pain is already well established [22]. The fact that nearly 10–30% of patients with cancer pain were not satisfied with the standard pain relief treatment (use of systemic analgesics alone) [23] commanded research for new analgesic approaches for more severe pain. The complex mechanism of pain in which physical and psychological disorders are involved need corresponding therapeutic approaches; complex and focused on pain relief, improvement of mental status, psychological treatment, education, and socialization. It seems that multimodal approach in pain management can reach all those necessities providing less use of opioids for 10–20% sparing effect [24].

The multimodal analgesia (MMA) and its opioids sparing effect, provides a significant efficacy in pain treatment and takes an important place for curing acute or chronic pain in palliative medicine. It involves multiple combinations of drugs (opioids, non-opioids, and sedatives), non-pharmacological therapies and some specialized techniques to provide better analgesia.A variety of fixed combinations of analgesic drugs are available on the market. In those combinations, the paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDS) play important part of the multimodal approach to analgesia. Used in palliative setting the multimodal approach may meet the individual patient needs of altered nociception and the variety of experiencing pain [25, 26].

The main goal of this therapeutic approach is the treatment of pain by targeting different physiological causes of the pain.

Data about genetic polymorphism speaks about the necessity to tailor the pain management according to the real patients' need [27]. According to the ladder algorithm, selection of non-opioid, opioid, and adjuvant analgesic therapy should be adapted to the intensity of the pain [28]. Identification of opioid receptor gene regulation, its transcription factors and post-transcriptional events are considered as alternative variations in mRNA stability and translation efficiency.

Additionally, the development of genes that increase or decrease pain opens a new dimension in the treatment of pain [29]. Perhaps the genomic profile of every person will be key to more efficient pain control. The choice of certain pain strategy and adequate medications are key principles for effective pain management.

3.2 Assessment of the pain

The assessment of the pain is the most important part of pain treatment. It is an initial step in the evaluation of the level of pain and continues during all pain relief episodes, as constant reevaluation of the effects of pain management. An effective relief of pain depends mainly on a comprehensive assessment to identify the different physical, psychological, social, and spiritual aspects. The oral description of the presence of pain is insufficient to express the real patients' suffering. It is more visible by other objective, autonomic and behavioral sights that are expressed through mimics, sweating, tears, or with changes in vital parameters in the person [4].

The subjective feeling of pain is difficult to be measured, but its effects on vital parameters may be measured. Based on this, the evaluation of the pain is being based. Generally, there are two main principles: objective (Type I) and subjective (Type II) method for pain evaluation. The difference between those two methods is the opportunity to present the individual feelings of pain in measurable values. The objective evaluation is measurable by the detection of the changes in physiological, neuropharmacological, and neurological parameters. In the Type II evaluation approach, the subjective patients' feelings of pain, measured by self-evaluation, are presented in measurable values- scores. In practice, for PC use, more applicable are the less invasive methods, which are present in Type II evaluation [30].

Taking anamnesis is the first step which helps enormously, where the patient must describe the pain in detail. It is necessary to provide information about the severity of the pain, the history – when, where, how the pain appeared, examine the location of pain, and to investigate the state of the other systems (imaging, organ function). To assign the appropriate management, it is important to discover: the origin of the pain, the states in which the pain is more intensive, the quality of the pain, the route of propagation of the pain, and the degree and the intensity of the pain. In assessing the symptoms, one can use the OPQRSTUV mnemonic (O- Onset, P- Position, Q- Quality, R- Radiation, S- Severity, T- Timing, A- Associated features, A- Aggravating Factors, A- Alleviating Factors) [19].

The received information helps in understanding the pathophysiology and in classification of the pain as nociceptive or neuropathic. An objective evaluation of the pain during palliative care is difficult; it is caused by the lack of communication with the patients so the use of conventional scales for measurement of pain is almost impossible [31]. For this reason, for patients in palliative care and in children, a multidimensional approach is accepted worldwide [4]. It works by using subjective explanations or common methods for self-evaluation of the level of pain, and objective signs from behavior and other vital parameters. Subjective feelings of the pain are measured with self-evaluation using several scales that help in the evaluation of the severity of the pain or pain questionnaires useful for children and older people (**Table 1**). In multidimensional approach the subjective methods in Type II evaluation are supplemented with the objective reports of the medical staff, relatives, parents, guardian, and others involved in the palliative care [32].

Type I – PAIN EVALUATION	Type II – PAIN EVALUATION
PHYSIOLOGICAL CHANGES	**ONE DIMENSIONAL METHODS**
Increased Plasma Cortisol Increased Plasma Catecholamine's Cardio-Circulatory Changes (Pulse, BP, CVP) Respiratory Changes (RR, VC, FEV, TV) Tears, Facial grimacing	Categorical Scale Numerical Scale Visual Analog Scale
NEUROPHARMACOLOGICAL	**MULTI DIMENSIONAL METHODS**
Inverse Correlation with Plasma Beta Endorphins Changes in Dermal Temperature	Mc GILL Questionnaire Dartmaut' Questionnaire List of West Haven-Yale Pain perception profile Behavior observation Pain Diary Pain Scoring Prevocational Test Rehabilitation Test
NEUROLOGICAL	
Changes in Nervous Conductance Velocity Evoked potential (neurologic dysfunctions) Micro- neurographics	

Legend: BP-blood pressure; CVP-central venous pressure; RR-respiratory rate; VC-vital capacity. FEV-forcefully expired volume; TV-tidal volume.

Table 1.
The evaluation of pain [4].

A simple observation can discover any kind of discomfort, lack of interest, anxiety, crying, tears, abnormal position or movement, or changes in vital parameters as high blood pressure, tachycardia, sweating, impairment in dieresis and other [30].

3.3 Treatment plan

In the *preparation of the treatment plan,* it must be considered that pain is a syndrome with neuropathic, nociceptive, emotional, and psycho-social overlays and it can be used to guide an individually tailored treatment plan because of its subjective nature. To improve outcomes, it is necessary to integrate the PC with other settings [33]. Patient / family must be involved in the planning of the pain treatment. The common problems in planning appear from the conservative believes and myths about pain. The existence of the pain is inevitable at the end of the life; the patient/family has fears about the use of opioids because of addiction and side effects. For this reason, is necessary to discuss the management strategy for pain relief. All parties must be very well informed about the multimodal approach and the incorporation of the interdisciplinary team in pain management that comprises integration of the use of medicines, physical therapy, music, meditation, hypnotherapy, and others alternative methods. Additionally, the personal abilities of the patient/family regarding the terminal stage, culture, religion, and other socio-economic factor must be taken in consideration.

3.4 Pain services

The pain services as special teams working on pain treatment takes place in or out of the Hospices. They could practice pain treatment as "patronage services",

visiting the homes of persons at the end of their life or patients with cancer pain. The goal of such services is to achieve the best care and to improve the life for patients and their families.

4. Pharmacotherapy in pain management in palliative setting

In normal conditions, the primary analgesic management in palliative care starts with *oral administration of the medicines.* The WHO in 1986, for nociception pain, proposed a "step by step" approach which understands escalation of the drugs from non-opioid to opioid analgesics [34].

Primarily the ladder approach was used for cancer pain, but today it is widely used for any kind of pain. In 2010, Vargas-Schaffer G. suggested a re-adapted four steps ladder [35] (**Figure 1**), which in 2012 was revised by Leung, who advised pain treatment in a tridimensional multimodal platform [36], and at list, in 2019 Cuomo introduced the trolley model for multimodal tailored therapy [37].

The administration of drugs in palliative care is recommended to be less invasive. When possible, the most appropriate method is oral administration. Also, among less invasive methods well accepted by the patients are rectal or transdermal (patches) application. When it is necessary to apply the invasive parenteral routes, intra venous (IV), intramuscular (IM), subcutaneous (SC), can be considered. Dosing is different and varies depending on the type of the pain from around-the-clock dosing, "as-needed dosing" to "patient-controlled analgesia (PCA)".

4.1 Non-opioids

Non –opioids are a group of medications consisting of anti-inflammatory and non-steroidal anti-inflammatory drugs. They have antipyretic, anti-inflammatory, and anti-platelet effects. Their use in palliative care takes an eminent place because most of the etiological factors of the pain are related to inflammation. Traditionally they include anti-inflammatory drugs such as salicylic acid, paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs), which remain the major players for the treatment of pain in PC [38]. They have an opioid sparing effect when used in multimodal therapeutic approach (see below).

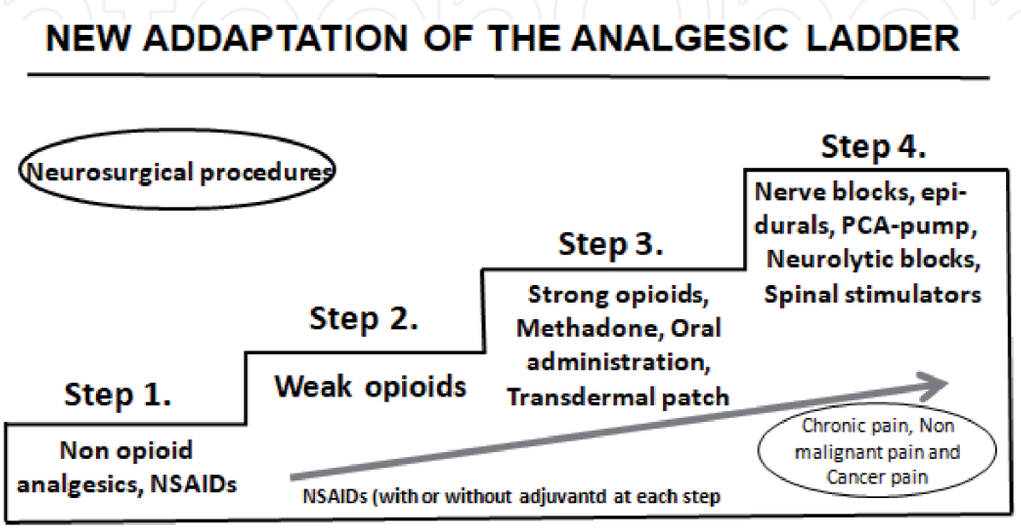

Figure 1.
Readapted WHO ladder for analgesic management [22]. (legend: NSAIDs- non-steroidal anti-inflammatory drugs; PCA- patient control analgesia).

4.1.1 Anti-inflammatory drugs

Acetaminophen (paracetamol) chemically belongs to para-aminophenol derivatives; it is an active metabolite of phenacetin with an analgesic-antipyretic property and weak anti-inflammatory activity. It is recommended as a first step analgesic for mild to moderate pain [39]. Its mechanism of action is based to inhibition of central prostaglandin synthesis in the central nervous system and possible increases of noradrenaline in CNS and peripheral beta-endorphins [40]. It describes its analgesic and antipyretic activity without any effects on inflammation. Its use in PC is crucial on its formulations in form of tablets, coated tablets, or ampoules; therefore, it can be administered orally or IV. The onset of action for oral form is slow (15 min), so the use of intravenous application is the more appropriate. The maximum recommended therapeutic dose is 4000 mg/24 h, or 80/kg BW/24 h. According to a Meta analyses made from Schüchen RH et al. (2018), it was shown that there was no conclusive evidence that Acetaminophen in treatment of cancer pain produces satisfactory pain relief [41], but often it is used in combinations with opioids and it shows a decrease of the need for opioids (spearing effect). Its metabolites contribute to the toxic effects, so doses over its maximum dosage provoke liver damage. Therefore, it must be used with precaution in patients with liver diseases.

Aspirin (acetylsalicylic acid) chemically belongs to the group of salicylates [42]. It is the most widely used drug for the treatment of mild to moderate pain. Aspirin has an analgesic-antipyretic, anti-inflammatory effect and prevents clotting. It is usually used for pain relief with low intensity. Its mode of action is through the decreased production of prostaglandins and thromboxane A2 by an irreversible inactivation of the ciclooxygenase enzymes (COX). It is an important additional medicine for patients with severe inflammatory pain (rheumatoid arthritis and similar). It is suitable for long-term use, because it is safe, with lower toxicity than paracetamol or opioids. In PC it can be safety used for pain control of acute pain, such as headache, toothache, minor back pain, for prophylaxis of myocardial infarction due to its well-established anti-platelet action. Its formulation is prepared in tablets and suppositories (100 mg, 300 mg, and 500 mg). Its use is 4–6 times per day, with maximum dose of 3000 mg/24 h. Among its side effects, the most important are appearance of peptic ulcer, allergy to salicylates and development of Reye's syndrome, if it is used in children younger than 16 years old. Overdosed, aspirin can cause cardiovascular instability, exacerbate underlying renal insufficiency, and even lead to coma with renal failure, metabolic acidosis, and respiratory arrest [42].

4.1.2 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of potent analgesics, antipyretics, and anti-inflammatory agents which are efficient in reliving of moderate to severe pain from musculoskeletal origin. They are widely in use at the institutions of palliative care as mono or combined therapy. The list of NSAID medicines is long and, in this document, only the most often used drugs will be mentioned. The NSAIDs mode of action is through peripheral and central inhibition of prostaglandin production from arachidonic acid through acetylating of two cyklooxygenase isoenzymes (COX-1 and/or COX-2). The non-selective NSAIDs inhibit the activity of both cyklooxygenase - COX-1 and COX-2. The most often used non-selective NSAIDs are ibuprofen, ketonal, diclophenac, naproxen, etc. [43].

On the other side, the selective inhibitors to isoenzyme COX-2 (celecoxib, valdecoxib and rofecoxib) have the same analgesic effects as the non-selective NSAIDs,

but with a reduced risk for gastrointestinal tract (GIT) and platelets that makes those acceptable for pain management [44]. Unfortunately, the COX-2 inhibitors in 2001–2010 failed to be adopted because of cardiovascular side effects [45]. Some authors described the development of acute myocardial infarction and sudden cardiac death, and in 2004 rofecoxib was withdrawn from the market. However, some additional studies show that inhibitors to isoenzyme COX-2 are powerful agents for control of intractable pain. They also have antitumor effects and are suitable for treatment of patients with bone metastasis what is due to inhibition of the production of cytokine and prostaglandin responsible for solid tumors and bone pain [46].

4.1.3 Recommended non-conventional non-steroidal anti-inflammatory drugs

They are used in palliative medicine for the treatment of moderate and severe chronic pain, alone or in combination, including cancer pain:

Metamizole or dipyrone is an old non-opioid drug patented in 1922 in Germany. It has analgesic, antipyretic, spasmolytic, and fewer anti-inflammatory effects. The possibility to provoke a life-threatening agranulocytosis after long use made metamizole for a long time to be under scrutiny. It was restricted in many countries in the world, but today after relevant clinical studies, the evidence has changed. Now, metamizole is recommended as an effective pain reliever in treatment of acute pain, particularly for renal colic and acute pancreatitis. It is found in form of tablets, suppositories, and injections for IM use [47].

Ketorolac is the most widely used non-steroidal, anti-inflammatory drug for treatment of moderate to severe pain in adults. Its mode of action is by blocking both cyklooxygenase (COX1 and COX2) and decreasing the prostaglandin production. Its' medical use dates to 1989, predominantly for postoperative pain relief. It is found in form of tablets, nose spray, injection for IM and IV use, as well as eye drops. Its use shows many benefits. It is an efficient analgesic, an opioid sparing NSAID drug, and improves the bowel motility what makes it suitable for postoperative analgesia in abdominal and obstetric surgery. Its adverse effects limit its use up to 6 days [48].

4.1.4 Toxicity of NSAIDs

In general, the use of non-steroidal and NSDAIDs in recommended therapeutic doses is well tolerated, but they contribute in various degrees to gastrointestinal (GI), renal and cardiovascular (CV) toxicity. In 2003 Schung SA and all [49] studied the efficacy and potential toxicity of opioids and non-opioids. They concluded that paracetamol used in therapeutic doses is safe, but an overdose is fatal, requiring specific treatment. The inhibition of the activity of COX-1 provokes impairment of gastric mucosa, renal parenchyma, and platelet function, manifesting several life-threatening side effects. The most important are the development of gastrointestinal bleeding, asthma, renal dysfunction, hepatotoxicity, cardiotoxicity, and others.

There are general recommendations for the choice of NSAIDs in palliative medicine based on individual risk of GI or CV toxicity [50]. With the aim to avoid any GI risks, all patients on regular NSAIDs/COX-2 inhibitors -therapy, must receive proton pump inhibitors (**Table 2**).

NSAIDs used alone may not achieve its satisfactory effects; the combination of NSAIDs and step III opioids showed beneficial effect [38]. The essential drugs for palliative care are drugs that are effective for the treatment of common symptoms in palliative medicine, easily available, and are affordable, and are ones that correspond with the use of non-opioid drugs [51].

Drugs	*Only GI problems*	*CV problems/±GI*	*CV/GI problems*	*No CV/GI problems*
NSAIDs	*Avoid if possible, if is essential:* Celecoxib 200 mg/24 h	*Avoid as possible or:* naproxen –1 g/24 h or ibuprofen 1.2 g/24 h	*Alternative therapy*	naproxen, ibuprofen, diclofenac

Legend: GI-gastrointestinal; CV-cardiovascular; CV/GI – bough (gastrointestinal and cardiovascular).

Table 2.
Recommended NSAIDs therapy in patients with risks [32].

4.2 Opioids

They are particularly important medicines in PC for treatment and control of moderate to severe, acute, or chronic pain. Opioids are a group of medical agents that have opium or morphine –like properties with analgesic and many other pharmacological effects. In the past, their use was limited by the clinicians as undesirable drugs, especially in high doses, because of its possibility for addiction and appearance of several side effects, including respiratory depression.

Nowadays, as the population ages, with an increased prevalence of chronic pain, it has been agreed that this concern was unfounded. The new multimodal approach for pain control, the development of safer opioids analgesics and the use of opioids sparing agents, promise more regular prescription [42]. Cancer's intractable pain remains the most horrific condition where opioids take an eminent place in the treatment [43]. Concerning the ladder algorithm for severe pain, patients tailored therapy to its need, provides the right choice of opioids, non-opioids and adjuvant leading to more satisfactory pain relief [52].

Today it is accepted that opioids act on an endogenous opioidergic system which controls the nociception, and participates in modulation of other functions as autonomic, GI, endocrine or cognition. Exogenous opioids administered in the body have the affinity to bind with several distinct types of receptors for opioids. These receptors are the previously known G-protein-coupled receptors: "delta", "kappa" and "mu", which were named according to the exogenous ligand or tissue where they were isolated. By a recommendation from the International Union of Pharmacology (IUPHAR), in 2000 the opioid receptors were renamed to DOP, KOP and MOP [53].

The identification of the MOP receptors and the isolation of its protein helped in more profound study of the structure and pharmacological properties of morphine. The opioid receptors are found in peripheral and central nervous system including spinal cord (PNS & CNS). They are found also within vas deferens, GIT, heart, immune system, and knee joint. The endogenous opioids peptides, active ligands to the receptors, were identified in the brain extract, having analgesic properties similar as morphine, and known as "endogenous opioids". Endogenous opioids in CNS are derived from their precursors: pro-enkephalin, pro-opiomelanocortin, pro-dynorphin, and pre-pro-N/OFQ (pp-noc), and function as neurotransmitters important in control of hormone secretion, thermoregulation, and cardiovascular system [54]. The opioids' receptors are presented at **Table 3**.

The main event is in the CNS where, by the opioids activated MOP receptors, the descending inhibitory neurons producing opioids are activated –induced analgesia.

Opioids are divided upon its pharmaco-chemical origin in naturally occurring, semi-synthetic and synthetic compounds. According to their activity at opioids receptor, they are divided to agonists, partial agonists, and antagonists.

Receptor& Precursor of endogenous ligand	Peptide-endogenous ligand	Effects	Clinical drugs		
			Agonists	**Partial agonists**	**Antagonists**
MOP (POMC Unknown)	β-Endorphin Endomorphin-1/2	Analgesia, sedation, nausea, vomiting, reduction of gastric motylity	Morphine Meperidine Diamorphine Fentanyl/ Remifentanyl	Pentazocine Buprenorphine Butorphanol	Naloxone Butorphanol Nalbuphine
DOP Pro-enkephalin	[Met]-enkephalin [Leu]-enkephalin	Spinal/supraspinal analgesia, reduced gastric motility	Low Affinity; Fent/remifen– no affinity	Weak affinity Buprenorphine	Low Affinity;
KOP Pro-dynorphin	Dynorphin A/B	Spinal analgesia, dieresis, dysphoria	Low Affinity;	Butorphanol	Buprenorphine Low Affinity;
NOP Pre-pronociceptin	N/OFQ	Spinally–analgesia, hyperalgesia&allodynia; Intracerabrovasular antianalgesic effect	**X** No Affinity;	**X** No Affinity	**X** No Affinity

Table 3.
Opioid receptors, endogenous ligands, and clinical drugs.

Agonists are all opioid drugs which by binding to the receptors produce complete response morphine-like. Antagonists binding to the receptor have functional response and prevent binding of an agonist (naloxone). Partial agonists provide only partial functional response which is not corresponding to the amount of the drug [55].

According to the ladder algorithm, which is in use in palliative care centers, the opioids are divided upon their power in weak and strong opioids. In the following text, this classification will be taken in consideration.

4.2.1 Weak opioids

4.2.1.1 Tramadol

It is centrally acting non-opiate analgesic with low affinity for MOP receptors and is effective in the treatment of moderate to severe pain. It has modest affinity to MOR and has weak interaction with DOR and KOR receptors. Because of its non-opioid properties, it is included in bouts group as weak non opioid agent with centrally acting analgesic effect and is favorable for PC use. As it possesses MOR agonist properties, it also, through the activation of monoaminergic spinal inhibition of pain, acts in inhibition of the reuptake of serotonin and norepinephrine, which synergistically enhances its weak opioid mechanism of action [56].

Chemically tramadol is present in two isomers which separately (one or other) inhibit the reuptake of noradrenalin or serotonin. The activity of tramadol depends on its metabolic activation which differs among the patients. Its' use is convenient for treatment of acute and chronic pain, moderate and severe, from cancer and non–cancer origin, as diabetic neuropathy, and fibromyalgia as well.

Tramadol is found as tramadol hydrochloride in form of tablets or capsules (50 mg, and 100 mg) for oral use 4–6 times per day, and in injections of 2 ml (50 or 100 mg/ml) for IV, SC, IM and via spinal routes. The maximal daily dose is 400 mg which could be exceeded only in special clinical circumstances. Clinically used for moderate pain, can provoke some adverse reactions as, dizziness, nausea, sedation, dry mouth, sweating and gastrointestinal dysfunctions. It is an extremely popular drug used for pain relief in PC in musculoskeletal injuries and as postoperative analgesic drug.

4.2.1.2 Codeine

It is used as a weak opioid. It is a naturally occurring substance derived from opium (opiate) and is a pro-drug of morphine. Codeine is metabolized in the liver and is excreted through the urine. About 10% of codeine by demethylation is converted to morphine [57]. Codeine has incredibly low affinity to opioid receptors - 200 times lower than morphine; its analgesic property is due to converted morphine. Its dominant use is orally, in the form of tablets or suspensions, for control of mild to moderate pain, coughing and diarrhea. It is a drug with reliable effects, and particularly useful in PC for pain relief. It can be used alone or as a combination with some non-opioid drugs, which increases its analgesic profile. The onset of its effect is after 30 minutes, with maximum effect at two hours and its offset about four to six hours. It comes in form of tablets (15 mg, 30 mg and 60 mg), a liquid (25 mg/5 ml spoon) to swallow, and syrup (15 mg/5 ml) or as an injection-codeine phosphate - of 2 ml (60 mg/ml). The dose is repeated every 4 hours and should not exceed more than 4 times per day. The adverse effects of codeine are like all opioids: constipation, nausea, vomiting, drowsiness, lightheadedness, confusion, euphoria, vertigo, dry mouth, headaches, pruritus.

The safe treatment of codeine understands titration of the doses of codeine (starts with a small dose of the drug and gradually increases it, until a satisfied result of complete analgesia is obtained). Symptoms of overdoses of codeine are also like those of morphine and other opiate analgesics. They are miosis, sweating, cold skin, respiratory depression, bradycardia, hypotension, skeletal muscles flaccidity and other which need an emergent resuscitation.

Hydrocodone is a more potent synthetic opioid, hydrogenated ketone derivative of codeine. It is selective full agonists to MOP receptors. It is used for control of moderate to severe pain. It comes in form of tablets (5 mg and 10 mg) for oral use. Its duration of action is 4–5 h, and plasma half-life of 4 h. It is typically available in combination with acetaminophen or ibuprofen, which is very well suited for the treatment of mild to moderate pain syndromes in multimodal analgesia. In the past, hydrocodone has been used as a cough suppressant. For the treatment of severe chronic cancer pain, it has found a wide use with prolonged duration and the more potent metabolite hydromorphone [58]. As an agonist it poses all adverse reactions described above.

4.2.2 Strong opioids

4.2.2.1 Morphine

Morphine is a strong naturally occurring opiate, isolated in 1805 from the poppy straw. Morphine is a "gold standard" among the opioids, against which the other drugs are measured in equal-analgesic doses. Morphine is a full MOP agonist with appreciable affinity to DOP and KOP. Its major effects are apperceived on parts of the CNS (posterior amygdala, hypothalamus, thalamus, nuscleus caudatus, putamen, and some cortical areas), producing drowsiness, analgesia, changes in the mood. MOP agonists further inhibit gastrointestinal tract (GIT) secretions and peristalsis; often causing constipation, also present is decreased bowel motility, vomit, nausea, and other sensations. MOP opioids also have effects on the cardiovascular system, thermoregulation, hormone secretion and immune function [59].

Morphine in PC is primarily used to treat acute and chronic severe pain and is a drug of first choice in PC for treatment of moderate to severe cancer pain. The oral formulation is easy for administration and especially useful for long treatment. It comes in form of tablets (30 mg, 60 mg, 100 mg), sub-lingual pastilles (60 mg), or as solution/suspensions (10 mg/5 ml). It is also valuable as injections (for IV, IM, SC, or PCA), rectal and spinal applications. In some countries extended-release capsules are present and extended-release tablets which are prescribed 1–2 times in 24 h. They are suitable for patients who are long time on morphine treatment. The onset of analgesic activity appears in 30 minutes, reaching the peak effect at 60–90 minutes. The average plasma half-life is 3 hours with offset of 6 h. The rest of morphine in plasma is present up to 15 hours [49]. The best way of the application of morphine is titrating of the doses. As it has no roof of its effect, the cure starts with small dose which may be increased by 30–50% every 12–24 hours until the optimal control of the pain. The titration continues to maximum tolerability, before moving on to another opiate [60].

Proper dosing of morphine is especially important for elderly patients in PC institutions. They may be overly sensitive to the effects of morphine and a continuous monitoring of the respiration, blood pressure (BP) and the level of consciousness is necessary to be performed.

The clinical use must be corresponding to the current recommendations at national or institutional levels. In most of the recommendations it has been shown that starting with a low-dose oral morphine (eg ≤30 mg/day) gives better pain

relief than using weak opioids. National Institute for Heath and Care Excellence, UK, (NICE) [61] in its Guidelines recommends that morphine should be used as first-line oral opioid for relief of cancer pain. It is also recommended for children with cancer pain; in the guidelines of the Royal Children's Hospital Melbourne, it is advised the use of oral morphine for children over six months with start dose of 0.2–0.5 mg/kg/dose, every 4-6 h orally [32].

The adverse effects of morphine include sedation, cognitive impairment, nausea and vomiting which are frequently seen. Also seen are respiratory depression, etching, circulatory disturbances, hormonal imbalance with hypogonadism, immunodeficiency, changes in the mood with hallucinations and depression. Constipation is seen with chronic therapy; patients do not develop tolerance to it and typically require preemptive treatment with laxatives. Also seen are tolerance or intolerance to morphine and addiction. The genetic approach confirms that those effects of morphine are result of the action at the MOP receptor and N/OFQ–NOP system [62, 53].

Many opioids are made by the modification of the morphine molecule, as Apomorphine, Oxycodone, Hydromorphone. They have similar properties as morphine and only the specificity of their use in PC will be mentioned.

Oxycodone–is a synthetic opioid, with high selective affinity to MOP and low affinity to DOP and KOP receptors, working as typical agonist. It is used for treatment of moderate to severe pain, is metabolized hepatically to the active oxymorphone [63]. It comes in form of tablets with immediate and controlled release of action or in injection. The onset of the analgesic effect starts within 15 minutes and it is used widely as analgesics especially for postoperative pain. One study compared the controlled-release oxycodone and morphine tablets in 45 cancer patients and was found that both were transformed in liver to the active oxymorphone. Oxycodone was the most often used drug in USA in the last two decades and was responsible for the "opioid crisis" due to – "too much free use" of this drug [64]. It is a particularly good pain killer and because of its oral application it is recommended for patients at PC. It develops the same side effects as other morphine like drugs.

Hydromorphone- is a water-soluble opioid that is several times more potent than morphine allowing for smaller dosage. It is found in parenteral, rectal, subcutaneous, and oral formulations. It is also used for epidural and intrathecal administration for postoperative pain relief or when other ways are not appropriate [65]. It was shown more effective pain relief properties for continuous dull pain and provides superior analgesia when is mixed with epinephrine.

Meperidine- is a synthetic analgesic drug indicated for the treatment of moderate to severe pain. It is delivered as hydrochloride salt found in form of tablets (50 and 100 mg), emulsion, or injections. It is predominantly a MOP agonist with main action on CNS and the bowel. Its analgesic effects exceed after 15 minutes and the peak effect after 45 minutes. The effectiveness of parenteral application is the same as that of morphine. The adverse reactions are like those of other agonists [63].

Methadone- is synthetic opioid, MOP agonist, which is used for pain relief in PC. Its pharmacological profile is like that of morphine, but it has a very long half-life with considerably longer duration of action. It is also an antagonist of the N-methyl-D-aspartic acid (NMDA) receptor [64]. Methadone is without any active metabolites but is found as racemic mixture of 2 enantiomers; the R- methadone is responsible for analgesic effects, while S-methadone is a NMDA antagonist. It has little tendency to induce tolerance in patients, which makes it suitable drug for treatment of opioid dependence. It has unique properties that make it useful in treating pain which is poorly controlled by other opioids. Its dosing is flexible, although it can be used in neuropathic and somatic pain relief. It is safe for patients

with renal impairment and is only long-acting liquid opioid. As a result of the lack of knowledge of its metabolic changes, it has possible interactions with other drugs, and its' long half-life made, methadone is seen to be an incriminated drug [59].

Fentanyl-is a synthetic powerful opioid, related to phenyl piperidine family that includes sufentanil, alfentanyl and remifentanil, with similar properties to the other opioids, selective MOP agonists. It is a powerful analgesic, lipophylic opioid, quick acting drug which is 70 to 100 times more potent than IV morphine.

Fentanyl is used for treatment of severe acute and chronic pain, as a medicine for anesthesia, for postoperative pain relief and in the treatment of intractable cancer pain in PC. It is available in parenteral, transmucosal, and transdermal formulations. Intravenous fentanyl has very rapid onset of action 5 minutes to peak analgesia, with offset of two hours. Fentanyl and its forms administered in intrathecal and epidural space provide prolonged postoperative analgesia up to 8 hours [50].

Because of the variety of forms, fentanyl has become the most widely used drug in palliative medicine. It is found in form of fentanyl buccal soluble film (FBSF), fentanyl buccal tablets (FBT), fentanyl pectin nasal spray (FPNS), oral transmucosal fentanyl citrate (OTFC), intranasal fentanyl spray (INFS), sublingual fentanyl and transdermal patches (FTP) [66]. Most of those forms are extremely valuable for analgesia of patients whose oral access is compromised, or with existence of profuse nausea and vomiting, limiting the swallowing of the required dose of opioid. The lowest transdermal dose of patch currently available is 2.5 mg which delivers 25 mcg/h of transdermal fentanyl. Due to its quick effect, Fentanyl is the drug of choice in control of breakthrough cancer pain (BTcP) [67].

Buprenorphine - is a semi-synthetic highly lipophilic opioid. It has partial MOP agonist properties and has been in clinical use for over 25 years for treatment of acute and chronic pain [63]. Recent studies have confirmed that buprenorphine binds with high affinity to MOP and KOP opioid receptors, and with relatively lower affinity to DOP receptors. It is found in several formulations for parenteral, sublingual, and transdermal use. It is also used as supplement to anesthesia and for psychiatric disorders (treatment of opioid addiction). Now Buprenorphine is widely used for cancer pain management. There is still debate about the potential damage of the transdermal patch and most of the authors think that because of this reason it is not suitable for PC [68]. As an opioid, a respiratory depression could occur, but it does not response to naloxone. The lowest patch strength of buprenorphine (5 mcg/h) is suitable for opioid naive patients.

Tapentadol is a new, centrally acting analgesic agent approved in Europe in 2010, used for treatment of acute and chronic, moderate to severe pain. Its molecular structure is chemically like tramadol. It has a dual mode of action, as a MOP agonist and a norepinephrine reuptake inhibitor. This metabolic change makes it a more potent opioid.

Its potency is somewhere between tramadol and morphine, like hydrocodone, oxycodone, and meperidine with more tolerable side effects profile [58–60]. Its formulation is in a form of tablets and solutions; tablets for immediate release (IR) of 50 mg, 75 mg, and 100 mg, are indicated for treatment of acute to moderate pain, with maximum toxic dose of 700 mg/day. For treatment of chronic pain, it is advised to use tablets with extended release (50 mg, 100 mg, 150 mg, 200 mg, and 250 mg). This formulation for long-release, with once-daily dosing of Tapentadol is especially acceptable for treatment in PC of chronic severe pain because of its simple use and more powerful effect [69]. The daily dose must not exceed 500 mg/24 h.

Clinical studies show that tapentadol is efficient pain reliever in various pain settings including PC setting. In a Clinical trial (NCT01500317) where the adverse effects of tapentadol with the equivalent doses of oxycodon were compared,

tapentadol reported significantly lower incidence of GI side effects [70]. Its characteristics offer an improvement in pain therapy, and easier coping with severe pain for PC patients.

The described side effects are like those of other opioids- such as development of allergy, nausea, vomiting, and loss of appetite; dizziness, worsening tiredness or weakness may be seen in some consumers. Overdose, addicting, and abstention syndrome are also present with an inappropriate use of the drug.

"*Breakthrough cancer pain*" (BTcP) - is a state of chronic pain with adequate analgesia where a temporal intensive peak pain occurs, interrupting the state of controlled pain. Traditionally the patients with cancer pain were treated with oral opioids, but for the treatment of BTcP it is recommended the fast-realizing forms of fentanyl (FPNS or INFS). Some authors reported good response to short-acting immediate-release (IR) oral opioid in advanced cancer, supporting the use of these opioids in clinical practice [67]. In this context, the National Institute for Health and Care Excellence guidelines do not recommend transdermal opioids as a first-line treatment, when oral opioids are appropriate, specifically fentanyl formulations, are now the gold standard for BTcP due to rapid action and high efficacy.

4.2.2.2 Side effects of the use of morphine and morphine like opioids

The development of constipation, nausea and vomiting; delirium, hallucinations, sedation, myoclonus, hyperalgesia, seizures, headaches, euphoria, or dysphoria are often seen as adverse reaction to morphine like opioids. Respiratory depression or non-cardiogenic pulmonary edema can appear. Pruritus, urinary retention and altered renal function may be seen also, and signs from CV system as bradycardia and hypotension as well, hypogonadism, sexual dysfunction, osteoporosis and impairment in the immune system, physical dependence, and the tolerance to the drugs [71].

In most of the Guidelines for PC is emphasized that during the pain management at the end of life, addiction should not be an issue [61, 72, 73]. It is also reported that development of life-threatening overdoses of morphine and morphine like opioids in palliative setting is exceedingly rare. In 2005, the American Assembly of Nurses referred that overdoses may be avoided with rational prescribing of opioids, proper conversion to other drugs, titration and use of adjuvant analgesics [74, 75]. The proper titration of opioids and multimodal approach with the use of other techniques such as radiotherapy, bisphosphonates, and other medicines in [76] Ca pain management, or increased dose of current analgesics, and adding adjuvants analgesic for neuropathic pain, may help patients in PC to easier cope with severe pain without a danger for overdoses.

At the commencement of therapy with opioids, sedation and drowsiness appeared, which are common side effects of opioids. The use of light stimulants such as caffeine, or methylphemidate [32] may be helpful. Other mental dysfunctions such as euphoria, dysphoria or nightmares need some additional treatment.

The main sign of overdose with morphine and morphine like opioids, besides drowsiness, is the appearance of respiratory depression (respiratory rate - RR < 8/min, SpO2 < 90% and cyanosis). Because of the progression of the main disease, the respiration at the end of the life could be slow, shallow, and noisy, what may be misunderstood as a respiratory depression. The recommendations proposed by the North East London Cancer Network (NHS)-2018, did not advise immediate use of antagonist naloxone for treatment of respiratory depression. The reason for that is the ability of naloxone to break the optimal analgesia and produce a "pain crisis" which is distressing for the patient and the family [77].

It is advised to use a conservative protocol for such events, which is as follows:

If the patient with slow RR (8/min) is not dying, has no cyanosis and is rousable, the measure "wait and observe" must be performed. If the RR decreases (<8/min), the patient is unconscious, cyanotic with SpO2 < 90% and tachycardia, opioids should be stopped and an oxygenation via mask should be administered. The treatment compromises of emergent resuscitation and application of MOP antagonist, naloxone. Naloxone (0.4 mg/ml) is given as a diluted solution of 0.04 mg/ml. The start of the application is with 0.5 ml of diluted solution (0.02 mg), and this dose is repeated until higher responsiveness is obtained [65]. If the patient is not treated, the respiratory depression can cross to respiratory arrest, with hypoxia, cyanosis, hemodynamic instability, hypotension until shock and death [63].

4.3 Adjuvant analgesics

They are drugs with indications different than analgesia. Today is known that adjuvants in combination with some analgesic drugs produce efficient analgesia. In use are several groups of medicines: antidepressants, antiepileptic drugs, corticosteroids, NMDA receptor antagonists and others [78].

The *tricyclic antidepressants* (TCA) adjuvant agents are very well accepted by patients with cancer pain due to their positive effects on the mood and sleep. Amitriptyline 1–2 mg/kg oral is a useful agent for treatment of children with nocturnal pain, neuropathic pain or sleeping difficulties. Amitriptyline, imipramine, doxepin, and clomipramine are also useful and attractive drugs for MMA of the patients in PC and for treatment of neuropathic pain. Because of common side effects of TCA, is advised the use of *Nontricyclic* compounds as safer [79]. Some authors suggest that the use of secondary amines desipramine and nortriptyline, are less anticholinergic and could be better tolerated than tertiary amines [80]. It has been also shown that trazadone, a nontricyclic antidepressant, has the same effectiveness as amitriptyline [81].

Antiepileptic drugs (AED) can offer a remarkably effective treatment strategy in combination with opioids and non-opioids in MMA. It has been proposed that pregabalin and gabapentin, which are effective in neuropathic pain, target accessory α2δ subunits of Ca^{2+} channels. An alternative mechanism of action has also been suggested - that additionally gabapentin blocks spine morphogenesis [82]. The initial daily dose of 100–300 mg of gabapentin can be increased every 3 days. The usual maximum dose is 3600 mg daily. It was reported that carbamazepine, lamotrigine, levetiracetam have been efficacious in alleviating different neuropathic pain syndromes and cancer pain. Precautions must be taken at liver function and bone marrow: suppression is possible to develop.

Corticosteroids are frequently used in PC as an adjuvant therapy for cancer related pain syndromes, which include bone pain, neuropathic pain from infiltration or metastatic compression of neural structures, headache due to increased intracranial pressure, or if the pain is from inflammatory origin (nerve, bone). If the pain is aggravated by tension or muscle spasms, the use of muscle relaxants can play an important role in relieving the pain [83], sedation and anti-cholinergic are present as side effects.

*Bisphosphonates*as adjuvant can help control the pain in certain situations such as: cancer-related neuropathic pain [84], in prevention of fractures in people whose cancer has spread to the bone, in metastatic bone pain, bone pain, breast cancer, bone fractures, osteoporosis with past fracture, etc.

NMDA antagonists has been shown that play an important place and are efficient modulators of the pain in postoperative allodynia and hyperalgesia. A representative of this group is *Ketamine,* a dissociative anesthetic which is used for analgesia as well. It produces, sedation, amnesia, and as an adjuvant sufficient analgesia.

It is used for treatment of severe acute and chronic pain. Its mechanism of action is complex but acts mainly as an antagonist of the NMDA receptor.

Ketamine is given through IV, IM, SC, oral, rectal, nasal, transdermal, epidural, and intrathecal way. It is a safe drug, without effects on respiration at analgesic doses, and less nausea and vomiting compared to opioids [85]. It is used with success in treatment of postoperative pain, refractory neuropathic pain syndromes, and severe Hyperalgesia as well. Its use in PC is controversial and is based on few un-homogeny studies and with a variety of obtained results. Recent study examining refractory cancer pain showed that ketamine used at moderate doses provides efficient analgesia [86].

Canabis still is with limited evidence of its use. The recent controlled trials and studies are unable to answer to the questions about its analgesic efficacy [87].

5. Invasive analgesic techniques

When the pain is refractory to pharmacological treatment, it is advised the use of *invasive analgesic techniques*. The use of local anesthetics provides a novel therapeutic approach in the treatment of pain. It is now established that neuraxial administration of drugs and use of neurolytic blocks are efficient in reduction of intractable cancer pain [88].

The analgesic effect of local anesthetics (procaine, bupivacaine, and lidocaine) is enabled by blocking the voltage sensitive Na^+ channels, preventing the generation and conduction of nerve impulses. It has been also shown that chemical neuromodulation produces effective pain relief. For this purpose, intrathecally can be administered as local anesthetic, opioids, and adjuvant medications (alpha-adrenergic agonists, eg, clonidine), baclofen, and ziconotide. Baclofen is a GABA-B agonist who intrathecally inhibits both monosynaptic and postsynaptic reflexes at the spinal level producing muscle relaxation useful in some neuropathic pain syndromes [89]. Neuroaxial blocks as the epidural/intrathecal application of opioids (in low-dose) and non-opioids drugs (low concentration local anesthetic 0.125–0.25% levo-bupivacaine) increases the analgesic effects with few side effects [90].

Also, directly to the area of pain intrathecal pumps for small doses of medication can be used. The peripheral nerve blocks techniques, catheterization, and tumor infiltration prevent and reduce the bad memories of pain. The quality, duration, and safety of epidurally applied opioids have been intensively studied and compared [91]. It was suggested that sufentanil is a drug with the most promising profile [92]. Agents may be delivered via variety of catheters and ports. The implantation of a self-contained pump delivers medication at a specific rate into the subarachnoid space by a subcutaneously tunneled intrathecal catheter.

Neurolytic blocks or neurolysis of peripheral nerves or plexuses (celiac plexus or superior hypogastric plexus blocks), with phenol or alcohol, can be used for treatment of neoplasm pain, refractory to pharmacological treatment [93].

6. Non-pharmacological therapy

In recent years, due to the advancement of medical techniques and technology, other forms of treatment such as vertebroplasty, spinal cord stimulation, and prolo therapy are being used. The integration of the use of *interventional* medical and rehabilitative techniques improves the patients' lifestyle and helps reduce the pain. The use of surgical procedures is very rare for treatment of pain. There are some cases where surgery was used for relieving a nerve from compression, or at

the disseminated metastatic cancer, a kyphoplasty was used at painful vertebral compression fractures [94].

The other alternative forms of nonpharmacological therapy such as chiropractic therapy, acupuncture, music, movement therapies or yoga in integration with the standard analgesic techniques also provide effective pain relief [95].

Transcutaneous electrical nerve stimulation (TENS) therapy involves the use of low-voltage electric currents to treat pain. This small device delivers the current at or near nerves producing electro-neuromodulation. It is widely used for treatment of intractable neuropathic and central pain but not for cancer pain and is advised in PC [96].

In CONCLUSION, pain management is an especially important part of improving the quality of life in terminal patients. Because of the complexity of pain, the treatment must be multidisciplinary. Aggregation of PC with other settings, the use of MMA, could only permit better prevention of suffering at the end of the life. In the conclusion the next message will be greatly beneficial: undertreated or untreated pain at the end of the life may be cause patients' discomfort, stress, and suffering, which is a message to the clinicians to increase their awareness for pain control during the terminal phase of the life with a liberal use of opioids and non-opioids.

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Conflict of interest

The authors declare no conflict of interest.

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Author details

Marija V. Sholjakova[1*] and Vesna M. Durnev[2]

1 The University "Ss. Cyril and Methodius" Medical School, Skopje, Republic of North Macedonia

2 University Clinic of Anesthesiology, Campus Mother Theresa Skopje, University "Ss. Cyril and Methodius" Medical school, Skopje, Republic of North Macedonia

*Address all correspondence to: msoljakova@yahoo.com

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