Diagnostic and therapeutic management of cancer patients with pain: recommendations of the Expert Group of the Polish Association for Palliative Care, Polish Association for the Study of Pain, and Polish Association of Clinical Oncology

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Table of contents

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These guidelines contain evidence-based principles of diagnostic and therapeutic procedures, prepared taking into account the value of scientific evidence and categories of recommendations. The rules of conduct should always be interpreted in the context of the individual clinical situation. Recommendations do not always correspond to the current rules of reimbursement in Poland. In case of doubt, current reimbursement possibilities of individual procedures should be determined. Strength of recommendations and quality of scientific evidence:
I A — Strong recommendation, high-quality evidence
I B — Strong recommendation, moderate-quality evidence
I C — Strong recommendation, low-quality evidence
II A — Weak recommendation, high-quality evidence
II B — Weak recommendation, moderate-quality evidence
II C — Weak recommendation, low-quality evidence

ABSTRACT

In order to elaborate diagnostic and therapeutic recommendations regarding the management of cancer patients with pain, a narrative review of the literature in PubMed and Cochrane database was conducted for the period of 2000–2022. An Expert Group of three scientific associations: Polish Association of Palliative Care, Polish Association for the Study of Pain, and Polish Association of Clinical Oncology was appointed, which made a literature review and formulated guidelines with strength of recommendations and quality of evidence.

To achieve optimal effect of pain treatment cancer patients require complex clinical assessment of pain with detailed recognition of pathophysiology, intensity and time frame (baseline and breakthrough — episodic) of pain. Pain evaluation should encompass other symptoms, comorbidities, disturbances in psychological, social, and spiritual dimensions, which may induce patients' suffering and total pain appearance. An important role plays anticancer local and systemic treatment, which may induce or exacerbate pain induced by cancer or comorbidities.

A standard approach in patients with chronic pain in the course of cancer and other diseases is based on World Health Organization (WHO) analgesic ladder algorithm, which is supplemented with non-pharmacological management. It is recommended an individual approach in pain treatment depending on clinical situation of a concrete patient. Efforts should be made to effectively manage other symptoms, which accompany cancer. An introduction of specific treatment taking into account given pathophysiology, time frame and intensity of pain increase effectiveness and significantly shorten time necessary to achieve effective analgesia, and moreover contribute to decrease intensity and frequency of adverse effects of analgesics used.

Keywords: cancer, clinical assessment, pain, pharmacotherapy, treatment

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Introduction

Pain is one of the most common symptoms in cancer patients. Ensuring the most effective pain management, which is an inalienable right of every patient and, at the same time, the basic duty of every doctor and nurse, allows for maintaining the highest possible quality of life (QoL) for patients and caregivers. According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]. The following important characteristics of pain have been distinguished:

— pain is always a personal experience that is influenced to varying degrees by biological, psychological, social, and spiritual factors;
— pain and nociception are different phenomena; pain cannot be inferred solely from activity of sensory neurons;
— through their life experiences, individual learn a concept pain;
— a person's report of an experience as pain should be respected — in Poland, pain therapy is guaranteed by legal provisions ensuring the right to pain treatment for every person;
— although pain usually serves an adaptive role, it may have adverse effects on function, social, psychological and spiritual well-being;
— verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Pain can be differentiated according to its duration (acute *vs*. chronic), pathophysiology (receptor, neuropathic, mixed, nociplastic), and place of sensation (localized *vs*. generalized) [2]. Untreated or ineffectively treated pain is a factor that interferes with proper functioning of the body; pain contributes to the occurrence or intensification of shock symptoms, lowers immunity, and is a factor that significantly reduces patients' quality of life (QoL), which makes effective anti-cancer treatment difficult or impossible and increases the cost of

therapy many times over [3]. Ineffective therapy or lack of pain management can lead to emotional and psychotic disorders as well as depression.

Pain should be considered and treated in the context of a specific clinical situation, taking into account patients' general condition, other symptoms, comorbidities, and anticancer treatment, as well as in the context of non-medical aspects: psychological, social, and spiritual problems of patients and caregivers. The prevalence of pain is estimated at 40–50% of patients undergoing anticancer treatment and 60–70% of patients in an advanced cancer stage [4].

Clinical assessment of pain

Pain is a subjective phenomenon, which is related to individual sensitivity to pain stimuli as well as the multidimensional impact of pain on the physical, mental, social, and spiritual domains. The mental state of patients and their personalities play an important role in the perception of pain [5]. In addition, a significant practical problem is the lack of objective measures of pain; hence its clinical assessment is most often based on the patient's subjective report, and in the absence of self-assessment, on the assessment made by the caregivers and medical staff.

A simple tool for individual assessment of pain intensity is a visual analog scale (VAS), on which the patient indicates the point corresponding to the perceived intensity of pain on a 10-cm continuous line (from no pain to the strongest pain). In clinical practice, the standard tool for assessing pain intensity is the numerical rating scale (NRS), in which the degree of pain severity is defined by the patient with an appropriate number in the range from 0 (no pain) to 10 (the strongest pain). Sometimes a descriptive Likert verbal scale is used to assess pain intensity (no pain, mild pain, moderate pain, severe pain, very severe pain). In children, people who do not know a language, the illiterate, and in patients with cognitive and dyslexic deficits, behavioral pictorial scales are used. Pain intensity should be assessed both before starting treatment and regularly monitored during treatment. A slightly more detailed assessment of pain is provided by the tools adapted to Polish conditions: Memorial Pain Assessment Card (MPAC) and Brief Pain Inventory — Short Form (BPI–SF). The MPAC tool consists of three numerical scales in which the patient assesses pain intensity, pain relief, and general mood and pain intensity is also assessed according to a verbal scale. There is also a section completed by the doctor or nurse, which includes the pathophysiology, location, type of pain (background and breakthrough), and treatment. On the other hand, the BPI–SF contains numerical rating scales for describing pain intensity and pain relief in the last 24 hours, as well as the impact of pain on patients' daily activities during the same period.

Patients with the neuropathic component of pain have various sensory symptoms that may coexist in various combinations. Therefore, clinical examination of patients should include assessment of sensitivity to touch, pricking, pressure, low and high temperature, and vibration, as well as time summation. In recent years, several scales (screening tools) based on verbal description of pain, with or without elements of a clinical examination, have been developed, and they significantly facilitate diagnosis of neuropathic pain and implementation of appropriate treatment. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale consists of five questions about pain and two items of the clinical examination; specificity of the scale is 85%, sensitivity is 80%, and if the number of points is > 12/24, the pain is predominantly neuropathic. Another much simpler Douleur Neuropathique 4 Questions (DN4) scale contains seven symptom questions and three clinical examination items. Specificity of the scale is 83%, and sensitivity is 90%. If the number of "yes" answers is > 4/10, the pain is mainly neuropathic [6].

To assess the nociplastic component, the Central Sensitization Inventory (CSI) questionnaire with 25 questions is used, which has also been translated and adapted to Polish. A score > 40/100 indicates involvement of central sensitization and the nociplastic component of pain [7].

In clinical practice, a useful tool for pain assessment by patients and caregivers can be a diary for regular observation and monitoring of pain treatment, as well as a patient guide on how to manage pain in cancer patients. Both the diary and the guide are available online [8].

Components of pain pathophysiology

The pathophysiology of pain involves two main mechanisms. The first is associated with mechanical and/or chemical activation of pain receptors (nociceptors) and causes nociceptive pain with or without an inflammatory component (somatic, visceral). The second mechanism — independent of the activation of pain receptors — is caused by damage to the somatosensory nervous system and is classified as neuropathic pain. Neuropathic pain is characterized by hyperalgesia (increased sensitivity to pain stimuli) and allodynia (pain caused by stimuli that normally do not cause

pain). Neuropathic pain is often described by patients as burning, stinging, pricking with a tingling sensation, or tearing, often accompanied by sensory disturbances such as hyperesthesia or hypoesthesia or sensations similar to the passage of electric current. It should be emphasized that neuropathic pain is more difficult to treat than nociceptive pain, which is characterized by significantly greater effectiveness of non-opioid and opioid analgesics. It is worth noting that somatic bone pain in cancer patients also shows the characteristics of neuropathic pain; hence it is classified as pain with a neuropathic component. Nociplastic pain is pain that results from changes in the central processes of nociceptive control. It occurs in the absence of clear evidence of actual or impending tissue damage that causes activation of peripheral nociceptors or evidence of disease or damage to the somatosensory system that causes pain [9]. Nociplastic pain is the most difficult to recognize and treat, which may contribute to the ineffectiveness of pain management. In cancer patients, the pathophysiology of pain is usually mixed, with receptor, neuropathic, and nociplastic mechanisms contributing in varying degrees to clinical manifestation.

According to the period of occurrence, pain experienced by patients can be divided into constant, i.e., background (baseline) pain and breakthrough pain, also referred to as episodic pain [10]. Background pain occurs for more than 12 hours a day, while breakthrough pain is defined as an attack of strong and usually short-term pain, with rapidly increasing intensity, despite effectively treated background pain. The time to the maximum intensity of breakthrough pain is usually a few minutes, and the median duration is about 30 minutes, although a pain episode can last from several tens of seconds to several hours. In more recent publications, episodic pain is also diagnosed in patients with ineffectively treated background pain when opioids are not administered or in the absence of background pain. Breakthrough pain can occur without a specific cause (spontaneous, idiopathic pain), or can also be triggered by a specific factor (incidental pain). Breakthrough pain does not include end-of-dose pain, which occurs before the administration of the next dose of a regularly used analgesic and requires correction of background pain treatment [11].

Incidental pain can be divided into independent of the patient's will (involuntary) or dependent on the patient's will (voluntary), i.e., caused by the predictable and voluntary activity of patients or care activities (procedural pain). The strategy for the treatment of spontaneous and incidental involuntary pain consists of administration of analgesics with a rapid onset of analgesic action at the onset of pain to ensure effective analgesia in the shortest possible time. The most used for this purpose are fast-acting fentanyl products, applied by the transmucosal route (nasal, buccal, or sublingual). However, in the case of pain caused by predictable and voluntary activity of patients or care activities (procedural pain), the occurrence of pain should be prevented by applying an additional dose of an analgesic in advance, which will effectively prevent or significantly reduce the intensity of incidental pain. For this purpose, immediate-release opioids can be administered orally or parenterally (subcutaneously, usually at home, or intravenously, usually in stationary or outpatient settings) [12].

General principles of cancer pain management

Whenever possible, treatment of chronic pain should target the underlying condition to achieve permanent relief and prevent other complications. If the cause cannot be identified or eliminated, symptomatic treatment should be used, taking into account the clinical manifestation, especially the pathophysiology, intensity, and time pattern of pain.

Pharmacological treatment

Pharmacotherapy and non-pharmacological methods are used in the management of cancer pain (II A).

In the treatment of background (constant) pain, pharmacotherapy should be conducted continuously to maintain a constant therapeutic blood concentration of drugs, and analgesics should be administered at regular intervals in line with their pharmacokinetic profile, the most convenient route for the patient, with a preference for oral administration. However, if the patient prefers a different route of administration, when oral treatment is not possible, when the patient is taking other drugs that change the bioavailability of analgesics, or when side effects are difficult to treat, analgesics are administered by other routes (transdermal, subcutaneous, intravenous, intrathecal, or topical). It is advisable to use drugs with a long duration of action (oral route with controlled release) and, if necessary (breakthrough pain), drugs with a rapid onset and short duration of analgesic effect (immediate-release oral formulations), which is adequate to the characteristics of breakthrough pain. Frequent breakthrough pain (more than 3 episodes a day) is an indication to consider adjusting the treatment of background pain. An effectiveness of pain therapy should be monitored, and side effects of analgesic therapy should be prevented and treated accordingly.

The use of analgesics is based on the analgesic ladder algorithm developed by the World Health Organization (WHO), according to which analgesics can be divided into three groups [13]. Step I included non-opioid analgesics: non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and metamizole. The next group consists of opioids from step II of the WHO analgesic ladder ("weak" opioids): tramadol, codeine, and dihydrocodeine. At step II of the WHO analgesic ladder, low doses of "strong" opioids may also be used: oxycodone or morphine (at a dose of 20 mg and 30 mg/day, respectively, administered orally). The next group consists of opioids from step III of the WHO analgesic ladder ("strong" opioids): morphine, oxycodone, oxycodone/naloxone, fentanyl, buprenorphine, tapentadol, methadone, and hydromorphone (currently unavailable in Poland). Treatment is based on the individual selection of an analgesic adequate to the intensity and pathophysiology of the patient's pain.

Treatment begins with step I drugs (usually with pain intensity corresponds to NRS 1–3). In patients with moderate pain (NRS 4–6), treatment begins with step II or low doses of step III opioids. There is no ceiling effect during treatment with "strong" opioids observed during treatment with step I and II analgesics, which allows the majority of patients to expect a better analgesic effect after increasing the dose of the drug. When using opioid drugs, steps II and III of the WHO analgesic ladder, concomitant administration of non-opioid analgesics may be considered (different mechanism of analgesic effect). However, step II and III opioids should not be combined. At each step of the WHO analgesic ladder, it is advisable to consider the use of supportive agents, which include analgesic adjuvants (co-analgesics) that increase the effect of analgesics and drugs that reduce or prevent their side effects. At each treatment step, there may be indications for the administration of supportive drugs, which include a group of co-analgesics (adjuvant analgesics), increasing the analgesic effects of pain medications in some types of pain (mainly in neuropathic, bone pain and visceral colicky pain) or due to their mechanism of analgesic action in specific types of pain (neuropathic pain, nociplastic pain) and drugs to prevent or alleviate the side effects of opioids (laxatives and antiemetics).

Non-opioid analgesics

They are used alone in mild pain (NRS 1–3) and as supportive agents in pain with moderate (NRS 4–6) and severe (NRS 7–10) intensity, together with opioids.

Table 1. Dosage of non-steroidal anti-inflammatory drugs used in multimodal cancer pain therapy

Drug	Recommended doses
Ketoprofen	100 mg twice a day
Dexketoprofen	3 × 50 mg daily
Ibuprofen	600 mg 4 times a day, the maximum dose is 3200 mg/day
Lornoxicam	First dose 16 mg, then 8 mg 1–2 times a day
Diclofenac	50 mg three times a day or 75 mg twice a day; the maximum daily dose is 150 mg
Nimesulide	100 mg twice daily
Etoricoxib	60–90 mg once daily; the maximum daily dose is 120 mg

Non-steroidal anti-inflammatory drugs (NSAIDs) block prostaglandin synthesis by inhibiting cyclooxygenase (COX) activity and, to a lesser extent, expression of the induced isoform of nitric oxide synthase. They also have non-cyclooxygenase mechanisms of analgesic action; therefore, their choice should be individualized (Tab. 1). Since NSAIDs, except nabumetone, are weak acids and can damage the gastroduodenal mucosa, concomitant use of a proton pump inhibitor (PPI) is recommended in patients at risk. The decision to add a PPI should be individualized, and these drugs should be administered in patients with a clinically significant risk of gastropathy. The use of omeprazole is not recommended due to numerous pharmacokinetic interactions, including with analgesics, and due to the possible side effect on mitochondrial function, which is important in cancer patients. The adverse effect of NSAIDs on the liver is most often manifested by an asymptomatic increase in aminotransferase activity. In particular, administration of diclofenac should be avoided in patients at risk of drug-induced hepatopathy. The adverse effect of NSAIDs on the kidneys may, in turn, lead to peripheral edema and sometimes to acute renal failure. The risk of nephropathy is particularly increased in patients taking concomitant medications that inhibit the activity of the renin-angiotensin-aldosterone system, loop diuretics, and spironolactone. An increased risk of nephropathy may occur with concomitant administration of NSAIDs and paracetamol due to the inhibition of plasma renin activity by paracetamol, and this is of particular importance in dehydrated patients. There is a variable risk of cardiovascular complications associated with the use of NSAIDs; therefore, in this particular group of patients, the choice of NSAIDs should be individualized in relation to the expected analgesic efficacy and

side effect profile. In the case of a clinically significant risk of NSAID-induced adverse effects, especially in the elderly, it is worth choosing drugs with a short peripheral half-life.

Special care should be taken in elderly patients receiving chronic NSAID treatment due to the increased risk of adverse reactions, especially worsening heart failure and renal insufficiency. Rectal administration of NSAIDs is not recommended due to the long latency period of the analgesic effect, and the incidence of side effects is not reduced compared to the oral route. Two systemic NSAIDs should not be administered concomitantly, as this does not increase analgesic efficacy but significantly increases the risk of gastrointestinal mucosa damage and other side effects, but systemic and topical NSAIDs may be combined. NSAIDs are highly effective in the treatment of bone pain, with an inflammatory and receptor component, but are ineffective in neuropathic and nociplastic pain.

Paracetamol has analgesic and antipyretic effects but does not cause peripheral anti-inflammatory effects. At therapeutic doses, NSAIDs class side effects from the gastrointestinal tract and kidneys do not appear; however, paracetamol inhibits plasma renin activity and, especially in dehydrated patients, has a potentially nephrotoxic effect. The clinical effect after administration of paracetamol occurs after 15–30 minutes, depending on the pharmaceutical form of the drug. When using paracetamol in the correct dosage (maximum daily dose 4 g/day), no serious side effects are usually observed, except for allergic skin reactions. At higher doses or with long-term use, side effects may occur, especially in the liver. Paracetamol is contraindicated in patients with liver failure, as well as in patients taking concomitant drugs that are CYP3A4 inducers, e.g., dexamethasone or carbamazepine. When using paracetamol for a long time, special care should be taken in malnourished patients, those abusing alcohol, and using barbiturates and oral anticoagulants. Paracetamol does not cause bronchospasm in people with bronchial asthma. The combination of NSAIDs and paracetamol has a synergistic analgesic and antipyretic effect [14]. Due to its pharmacokinetic and pharmacodynamic profile, paracetamol should not be used in inflammatory pain and visceral pain.

Metamizole is a non-opioid analgesic from step I of the WHO analgesic ladder, devoid of anti-inflammatory effect. The mechanism of the analgesic action is mainly COX2 inhibition in the central nervous system (CNS) and, to a lesser extent, COX1 inhibition and possibly activation of the opioidergic system. This agent has a spasmolytic effect resulting from the central inhibition of adenosine reuptake, which is important in the treatment of acute colic pain and visceral pain. The maximum daily dose of metamizole is 5 g. In cancer patients, the drug is most often used in the treatment of breakthrough, colic and visceral pain. Metamizole should not be administered regularly for more than 7 days due to an increased risk of side effects, especially from the hematopoietic system.

Opioid analgesics

Opioids play a key role in the treatment of moderate to severe cancer pain by affecting three types of opioid receptors: μ, κ and δ, currently referred to as MOR, KOR, and DOR, respectively, and the nociceptin receptor NOR. Opioid receptors are located in numerous structures of the central and peripheral nervous system. The effects of opioids depend on many factors, including an affinity for opioid receptors, effects on the serotonergic, adrenergic, and N-methyl-D-aspartic (NMDA) receptors, as well as on physicochemical properties and pharmacokinetic characteristics. In the treatment of breakthrough pain, the dose of short-acting (immediate-release) opioids administered via an oral route is usually 10–20% of the total daily dose of regularly administered opioids. When using fentanyl with a rapid onset of analgesia via the transmucosal route, the principle of titration from the lowest available dose of a given product always applies. The above rule also applies to the replacement of one fentanyl product with another (also administered by the same route, e.g., intranasally), as well as to significant changes in the treatment of background pain (significant change in the dose of the background opioid or rotation of opioids).

Step II opioid analgesics of the WHO analgesic ladder ("weak" opioids)

Step II opioids of the WHO analgesic ladder are most often used in patients with moderate pain (NRS 4–6) [15]. Exceeding the recommended maximum doses usually does not cause an additional analgesic effect but may intensify side effects ("ceiling effect"). Tramadol, codeine, and dihydrocodeine are available in Poland (Tab. 2).

Tramadol is the most commonly used step II opioid of the WHO analgesic ladder, with an analgesic effect several times weaker than that of morphine (II A). Tramadol exhibits a dual mechanism of analgesic action: in addition to acting on opioid (predominantly μ) receptors in the CNS, it activates the descending antinociceptive system by inhibiting the reuptake of norepinephrine and serotonin. Tramadol is metabolized in

Table 2. Most commonly used opioids in the treatment of cancer pain

Drug	Route of administration, drug form	Starting dose, comments	Duration of action [hours]
Morphine	Oral: Divisible tablets 20 mg, aqueous solution	Primarily intended for dose titration and treatment of breakthrough pain Patients not treated with opioids: 2.5–5 mg every 4–6 h Patients treated without effect with "weak" opioids: 5–10 mg every 4–6 h In the treatment of breakthrough pain, usually 10–20% of morphine daily dose	4–6
	Controlled-release tablets 10, 30, 60, 100, and 200 mg	Opioid-naïve patients: usually 10 mg every 12 hours Patients treated without effect with "weak" opioids usually 20–30 mg every 12 hours	12
	Subcutaneous and intravenous: morphine sulphate ampoules 20 mg/1 mL	Subcutaneous route: Usually 2–3 mg every 4–6 h in patients not treated with opioids, most often 4–6 mg every 4–6 h in patients treated without effect with "weak" opioids	4–6
		Intravenous route: Usually 1–2 mg every 4–6 h in patients not treated with opioids, most often 3–5 mg every 4–6 h in patients treated without effect with "weak" opioids If necessary, the dose may be increased and repeated every few minutes until pain subsides or sedation occurs. Usually used to quickly obtain analgesia both in hospital and outpatient settings	4
Oxycodone	Oral: 1 mg/1 mL aqueous solution (100 mL and 250 mL), 5 and 10 mg tablets	Primarily intended for dose titration and treatment of breakthrough pain Patients not treated with opioids: 2.5–5 mg every 4–6 h Patients treated without effect with "weak" opioids: 5–10 mg every 4–6 h In the treatment of breakthrough pain, usually 10–20% of oxycodone daily dose	4–6
	Controlled-release tablets 5, 10, 20, 40, 60, and 80 mg	Patients not treated with opioids usually 5–10 mg every 12 hours Patients treated without effect with "weak" opioids usually 10–20 mg every 12 h	12
	Subcutaneous and intravenous: oxycodone hydrochloride 10 mg/1 mL and 20 mg/2 mL ampoules	Subcutaneous route: Usually 2–3 mg every 4–6 h in patients not treated with opioids, most often 4–6 mg every 4–6 h in patients treated without effect with "weak" opioids	4–6
		Intravenous route: Usually 1–2 mg every 4–6 h in patients not treated with opioids, most often 3–5 mg every 4–6 h in patients treated without effect with "weak" opioids If necessary, the dose may be increased and repeated every few minutes until pain subsides or sedation occurs. Usually used to quickly obtain analgesia both in hospital and outpatient settings	4
Tramadol	Oral: Drops (40 drops = 100 mg, drops with dispenser 1 dose = 5 drops)	Drops are useful, especially during the titration period and for the treatment of breakthrough pain 5–20 drops (12.5–50 mg) every 4–6 hours For breakthrough pain, usually 10–20 drops, depending on the dose administered regularly, for the treatment of background pain	4–6
	50 mg capsules Controlled-release tablets and capsules of 50, 100, 200 mg	Controlled-release tablets or capsules of 50–100 mg every 12 h	12
	Subcutaneous and intravenous: tramadol hydrochloride (50 mg/1 mL, 100 mg/2 mL ampoules)	Subcutaneous route: usually 20–50 mg every 4–6 h	4–6

→

Table 2 cont. Most commonly used opioids in the treatment of cancer pain

Drug	Route of administration, drug form	Starting dose, comments	Duration of action [hours]
		Intravenous route: usually used both in hospital and outpatient settings, the most common dose is 50–100 mg in slow infusion The maximum dose of tramadol is 400 mg/day Dual (opioid and non-opioid) analgesic mechanism, less frequent constipation as compared to other opioids Prophylactic addition of an antiemetic drug (haloperidol or tiethylperazine) is recommended when starting treatment with tramadol. Analgesia and side effects (mainly related to the opioid component) dependent on CYP2D6 polymorphism	4
Codeine	Oral: 20 mg tablets, aqueous solution	The maximum dose of codeine is 240 mg/day Codeine is largely a prodrug: partially metabolized to morphine by CYP2D6 Analgesia and side effects of codeine are dependent on CYP2D6 polymorphism	4–6
Dihydro-codeine	Oral: Controlled-release tablets of 60 and 90 mg	The starting dose is usually 1–2 × 60 mg, the maximum dose of dihydrocodeine is 240 mg/day Analgesia and side effects of codeine are dependent on CYP2D6 polymorphism	12
Fentanyl	Transdermal: 12.5, 25, 50, 75, and 100 μg/h patches	The starting dose is 12.5–25 μg/h in patients not treated with opioids and 25 μg/h in patients treated with "weak" opioids; the maximum dose is 200 μg/h No active metabolites, drug metabolized by CYP3A4	72
Bupreno-rphine	Transdermal: 35, 52.5, and 70 μg/h patches	The starting dose is usually 17.5 μg/h in opioid-naive patients and 35 μg/h in patients treated with "weak" opioids; the maximum dose is 140 μg/h Drug metabolism mainly by glucuronic acid conjugation, excreted mainly via the gastrointestinal tract, preferred in stable neuropathic pain, in elderly patients, and in renal impairment	72–96
Oxycodone/ /naloxone	Oral: Controlled-release tablets 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20mg	Patients not treated with opioids 5 mg/2.5–10 mg/5 mg every 12 h. Patients treated without effect with "weak" opioids 10 mg/5 mg every 12 h In the treatment of breakthrough pain, usually 10–20% of oxycodone daily dose Patients treated with other "strong" opioids: the dose is determined individually through equivalent dose converters and titration. The maximum dose is 80 mg/40 mg twice a day	12
Tapentadol	Oral: Controlled-release tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	Patients not treated with opioids 50 mg every 12 h Patients treated without effect with "weak" opioids 50–100 mg every 12 h The maximum dose is 250 mg twice a day	12

the liver by cytochrome P–450, and then approximately 90% (after oral administration) is excreted via the kidneys, with approximately 10% excreted in feces. The analgesic effect of tramadol depends on the activity of the CYP2D6 enzyme. It catalyzes the conversion of the parent compound to O-desmethyltramadol (M1), which has a significant analgesic effect by activating μ-opioid receptors. In the Caucasian population, 7–10% of people do not metabolize of tramadol to M1 (poor metabolizers), then the analgesic effect may be much weaker, while 1–2% excessively metabolize tramadol to M1 (ultrarapid metabolizers). This results in a higher risk of side effects, including nausea and vomiting, sedation, and respiratory depression.

The most commonly observed side effects associated with the use of tramadol are nausea and hyperhidrosis, especially at the beginning of treatment. The advantage of tramadol is a lower impact on the motility of the gastrointestinal tract and a weak constipation-inducing effect, as well as a lower risk of causing respiratory

depression compared to other opioids. Tramadol is available in many formulations, including a controlled release form. Tablets, oral drops (40 drops = 100 mg), and ampoules are used, which can be administered subcutaneously and intravenously. The drug should be used in doses up to 400 mg/day, administered in the immediate-release formulations every 4–6 hours, or in prolonged-acting forms every 12 hours. In breakthrough pain during treatment with tramadol as a background drug, immediate-release preparations of tramadol are used. Tramadol is available as a fixed-dose combination (FDC) with paracetamol and dexketoprofen, which accelerates the onset of action of the drug and causes a synergistic analgesic effect.

Due to the prolonged half-life of tramadol and its being an active metabolite in patients with renal failure, it is recommended to reduce its dose and to extend the intervals between subsequent doses or to switch to another opioid. Extending the dosing intervals and reducing the dose is also recommended in patients with hepatic impairment. In patients with a history of epilepsy, tramadol is not recommended due to an increased risk of seizures, and in patients without a history of epilepsy, the drug does not increase the risk of seizures. Due to an increase in the concentration of porphyrins, tramadol raises the risk of attacks in patients with acute porphyria. Tramadol should not be administered together with antidepressants that inhibit the reuptake of serotonin, as well as serotonin and norepinephrine, and tricyclic antidepressants, as it may lead to symptoms of serotonin syndrome. The use of tramadol with CYP3A4 inducers (mainly carbamazepine or dexamethasone) is contraindicated because an increased amount of N-desmethyltramadol is synthesized, which has no analgesic effect but has a proconvulsant effect. In the case of concomitant use of CYP2D6 inhibitors with tramadol, the risk of nausea and vomiting increases significantly, and the simultaneous administration of tramadol and carbamazepine worsens its analgesic effect.

Codeine is an agonist of the μ-opioid receptor, with an analgesic effect approximately 10 times lower than that of morphine. Codeine is a prodrug with an analgesic effect dependent on the conversion to morphine determined by the activity of CYP2D6, as well as other metabolites (mainly codeine-6-glucuronide). Due to its strong antitussive properties, it is considered the drug of choice in patients with moderate pain and cough. A common side effect of codeine is constipation. Codeine is only administered orally in the form of immediate-release tablets or solution. The analgesic effect occurs after 15–30 minutes and lasts for 4–6 hours ($T_{1/2}$ 3–4 hours). The maximum daily dose of codeine is 240 mg. Codeine is also available in FDC with paracetamol, paracetamol and caffeine, acetylsalicylic acid and ibuprofen. Due to its pharmacokinetic profile and genetically variable metabolism, codeine is not recommended for the treatment of pain.

Dihydrocodeine (DHC) is a derivative of codeine. The analgesic potency of DHC is approximately 5 times weaker than that of morphine administered via an oral route. The drug is metabolized mainly to DHC-6-glucuronide and dihydromorphine, and side effects are usually less severe compared to codeine. Unlike codeine and tramadol, the analgesic effects of DHC do not depend on CYP2D6 activity. Dihydrocodeine is only available as controlled-release tablets to be taken every 12 hours. The maximum daily dose of DHC is 240 mg. DHC is recommended in patients with moderate pain, often accompanied by cough and shortness of breath.

A common feature of tramadol and codeine metabolism is the dependence of the analgesic effect and side effects on the genetically determined CYP2D6 activity, as well as renal excretion (the latter also applies to DHC), while the analgesia and side effects of DHC do not depend on CYP2D6 activity. At step II of the WHO analgesic ladder, low doses of "strong" (morphine up to 30 mg, oxycodone up to 20 mg per day orally) can be used instead of "weak" opioids [16].

Step III opioid analgesics of the WHO analgesic ladder ("strong" opioids)

Opioids without the ceiling effect from step III of the WHO analgesic ladder are recommended for the treatment of severe and very severe pain (NRS 7–10) [17]. Morphine, oxycodone, oxycodone/naloxone, fentanyl, buprenorphine, tapentadol, and methadone are available in Poland, and hydromorphone is not available yet [18]. According to the European Association for Palliative Care (EAPC) guidelines, morphine, oxycodone, and hydromorphone are the first-choice opioids in the treatment of moderate to severe cancer pain (I A) [13]. In the treatment of chronic pain, the use of pethidine and pentazocine is contraindicated due to the toxic effects of their metabolites.

Morphine is the standard opioid recommended by the WHO and the European Society for Medical Oncology (ESMO). The strength of the analgesic effect of other opioids is compared to morphine (I A). It is a pure agonist of opioid (predominantly μ) receptors. The main metabolites are morphine-3-glucuronide and morphine-6-glucuronide, and, like the parent compound, they are excreted by the kidneys. Morphine is a hydrophilic opioid of choice in the treatment of pain and in patients with dyspnea [19]. Concomitant use of

morphine and benzodiazepines, and other CNS depressants increases the risk of sedation, hypotonia, and respiratory depression. Constipation may be a significant problem during treatment with morphine [20]. Many drugs taken concomitantly with morphine, including drugs with anticholinergic effects (e.g., pridinol and tizanidine) and serotonin receptor antagonists, also increase defecation disorders.

In the treatment of pain, morphine is used orally with immediate- and controlled-release formulations or parenterally (subcutaneously, intravenously), rarely intrathecally and topically. The equivalent oral dose is approximately 3-fold higher than the parenteral dose due to limited absorption from the gastrointestinal tract and significant hepatic first-pass effect. Treatment usually starts with low single doses (tablets, less often water solution with immediate release), usually 5 mg (patients not previously treated with "weak" opioids) or 10 mg (patients previously treated with "weak" opioids), administered every 4–6 hours. In the case of starting morphine treatment with controlled-release tablets in patients previously untreated with "weak" opioids, a single dose of morphine of 10 mg every 12 hours is most often used (20 mg daily), while treatment of patients previously receiving "weak" opioids usually starts with a single dose of 20 or 30 mg every 12 hours (daily dose is 40 mg and 60 mg, respectively). Sometimes administration of controlled-release morphine is recommended every 8 hours. The initial doses given in patients with renal impairment, severe cachexia, and the elderly are usually half as low. In these groups of patients, due to reduced elimination of morphine metabolites, close monitoring is required, and sometimes also prolongation of the intervals between subsequent administrations of the drug, change of administration route to parenteral, or switch (rotation) to another opioid. Moderate liver damage does not significantly affect the metabolism of the drug.

Morphine product, dose, and administration route are determined individually, using the principle of gradually increasing doses until a satisfactory analgesic effect with side effects acceptable to the patient is obtained (titration). During the treatment of background pain with controlled-release morphine, immediate-release morphine products are used in the treatment of breakthrough pain, usually in a dose equal to approximately 10–20% of the daily dose. During the treatment of background pain with immediate-release morphine, the dose administered in the treatment of breakthrough pain is usually equal to a single dose administered every 4–6 hours [21]. In patients in whom morphine is regularly used subcutaneously or intravenously, the rescue dose is most often administered by the same route and is usually equal to a single dose.

Oxycodone is a semi-synthetic μ and k receptor agonist (I A). Unchanged oxycodone and its metabolites are mainly excreted via the kidneys, which requires careful use of the drug in cases of impaired renal function [22]. Oxycodone is administered orally or parenterally (subcutaneously or intravenously) [23]. The morphine-to-oxycodone equivalent dose ratio is 1.5–2:1 for the oral route. When switching from parenteral to oral oxycodone administration, a 3:4 ratio is applied, i.e., the oral dose is slightly higher than the parenteral dose. Controlled-release oxycodone tablets are given every 12 hours. During oxycodone treatment, oxycodone or immediate-release morphine or transmucosal fentanyl products can be used as the primary treatment for breakthrough pain.

Oxycodone/naloxone is a 2:1 combination of oxycodone and naloxone in one controlled-release tablet (I B). In clinical trials, the product was shown to be effective in the treatment of chronic cancer pain and pain in the course of non-cancerous diseases while improving or preventing opioid-induced constipation [24]. The recommended daily dose cannot exceed 160 mg/80 mg and should be achieved gradually by titration [25]. Contraindications to the use of oxycodone/naloxone are typical of opioids; however, hepatic, renal, and portal circulation disorders, allergy to the product's ingredients, and diarrhea are also important.

Fentanyl is a pure μ-opioid receptor agonist. Its analgesic strength compared to morphine is approximately 100:1. The significant lipophilicity of the drug is used in transdermal and transmucosal therapy. Fentanyl is metabolized in the liver by CYP3A4 to the inactive norfentanyl and then excreted by the kidneys mostly (90%) as inactive metabolites. It is well tolerated by patients with moderate hepatic and renal insufficiency. The use of transdermal and intravenous fentanyl is quite safe in advanced chronic kidney disease (grades 4–5) with a glomerular filtration rate below 30 mL/min. Compared to morphine, fentanyl has a less pronounced sedative effect, releases histamine to a small extent, and less frequently causes constipation [26].

For the treatment of pain, fentanyl is administered by the transdermal, transmucosal, and parenteral routes. Transdermal patches are applied every 72 hours, with the analgesic effect about 12 hours after applying the first patch, and full analgesic effectiveness is achieved after 2–5 changes of patches (II B). Particular care should be taken in patients with fever due to the increased rate of absorption and release of the drug and, consequently, the increased risk of side effects.

Table 3. Fentanyl products used to treat breakthrough pain episodes

Selected pharmacokinetic parameters	Route of administration			
	Sublingual (tablets)	Buccal (tablets)	Intranasal (nasal spray)	Intranasal (nasal spray with pectin)
Absolute bioavailability [%]	70	65	89	60
Time to peak serum concentration [minutes]	50–90	47	9–15	15–21
Half-life [hours]	12	22	3–4	15–25
Onset of analgesic effect [minutes]	5–10	10–15	5–7	5–10

In the treatment of breakthrough pain during therapy with transdermal fentanyl and other opioids, intranasal formulations, or buccal/sublingual fentanyl tablets with a rapid onset of analgesic effect can be used (Tab. 3) [27]. The general principle of use of transmucosal fentanyl products is dose titration, which also applies when changing the type of fentanyl formulation (e.g., from intranasal to buccal or vice versa or between different intranasal products) and after switching from using other traditional opioids for breakthrough pain (e.g., short-acting morphine or oxycodone). According to SPC rapid-onset fentanyl products can only be recommended to cancer patients who are using opioids to treat their background pain (daily dose of oral morphine of 60 mg or equivalent dose of morphine administered by other routes or an equivalent dose of other opioids, used for at least 7 days). During therapy with transdermal fentanyl, oral immediate-release morphine or morphine administered by other routes (subcutaneous, intravenous) may also be used for breakthrough pain management. The choice of transmucosal administration route of fentanyl for the treatment of breakthrough pain should be based on clinical assessment of pain exacerbation characteristics, condition of the nasal and oral mucosa, and the patient's preferences. Fentanyl has a serotonergic effect, which is worth remembering, especially in polytherapy.

Buprenorphine is a partial agonist of μ-opioid and nociceptin receptors and an antagonist of the κ-opioid receptor. The potency of buprenorphine is approximately 75 times greater than that of morphine. In the analgesic therapeutic dose range, buprenorphine acts as a pure μ-opioid agonist and shows no ceiling effect. Drug metabolites are excreted in 70–80% by the digestive tract and a small amount by the kidneys. Buprenorphine is a safe opioid in patients with chronic renal failure and in dialysis patients. It is rapidly absorbed through the oral mucosa and is used in the form of sublingual tablets administered every 6–8 hours as it is poorly absorbed from gastrointestinal tract. Due to its high lipophilicity, the drug is administered transdermally as patches applied to the skin every 72–96 hours (II B). The analgesic effect of the first buprenorphine patch occurs after about 12 hours [28]. Oral or subcutaneous morphine or fentanyl fast-acting products are most commonly used for the treatment of breakthrough pain during background therapy with transdermal buprenorphine [29]. Buprenorphine patches are the only "strong" opioid available on Rp prescriptions.

Tapentadol is a representative of a new group of opioid analgesics with a complex mechanism of action: agonistic effect on opioid receptors, predominantly μ, and inhibition of norepinephrine reuptake in the CNS (I B). Due to the complex mechanism of analgesia, tapentadol has an analgesic effect typical of opioids and antidepressants from the group of norepinephrine reuptake inhibitors [30]. In addition to effective analgesia, including in patients with neuropathic pain, tapentadol is characterized by good treatment tolerance. Compared to other opioids, it is associated with limited side effects related to the influence on opioid receptors (particularly important in terms of the adverse impact on the gastrointestinal tract), low risk of interactions with other drugs (metabolism outside the cytochrome P–450 enzyme system), and lower potential for addiction [31].

Methadone is a synthetic μ and κ opioid receptor agonist, NMDA receptor antagonist that increases monoamine levels (I A). The analgesic potency, compared to oral morphine, is 4–12-fold higher. Methadone causes less severe constipation, nausea, and vomiting and it can be safely used in chronic renal failure and dialysis patients. Due to the complex pharmacokinetics, significant risk of drug interactions, and prolongation of the QT interval, it is recommended that methadone treatment should be conducted by a physician experienced in pain management. The drug is used orally in the form of syrup (concentration 1 mg/1 mL),

administered every 12 hours at a single initial dose of 2.5–5 mg. It is recommended not to exceed the initial daily dose of 10 mg in patients who have not previously been treated with other strong opioids. In patients who fail to achieve an adequate analgesic effect or experience severe side effects during treatment with other opioids, it is suggested to consider switching to methadone [32]. Methadone is used not only in the treatment of chronic pain but also in the treatment of opioid addiction and withdrawal syndromes.

Side effects of opioid analgesics

An individual system of opioid receptors in each person may be the cause of a different analgesic effect of opioids and different profiles and severity of side effects [33]. The most commonly observed side effects of opioids include constipation and other post-opioid gastrointestinal disorders. From the beginning of treatment with opioids, it is usually necessary to use prophylactic osmotic laxatives orally: macrogol or, less frequently, lactulose (due to it having more side effects) alone or in combination with irritants: senna derivatives, bisacodyl, and sometimes rectal irritants, e.g., glycerin suppositories.

The drugs of choice in the treatment of opioid-induced bowel dysfunction (OIBD) are peripherally acting μ-opioid receptor antagonists (PAMORA), such as naldemedine, N-methylnaltrexone, and naloxegol. Nausea and vomiting are less frequently observed side effects of opioids, and metoclopramide, haloperidol, and thiethylperazine are the most commonly used in their treatment. Metoclopramide, due to the inhibition of CYP2D6 activity, should not be administered in patients taking tramadol concomitantly and other drugs with hepatic clearance dependent on cytochrome P450 isoenzyme. Other side effects of opioids include drowsiness, dry mouth, balance disorders, skin itching, excessive sweating, hallucinations, respiratory depression (rare, most often associated with improper opioid dosing), urinary symptoms (urinary retention), myoclonus, and very rarely seizures. In the case of respiratory depression, intravenous naloxone should be administered (1 amp = 400 μg should be diluted in 10 mL of saline and administered 40–80 μg, i.e., 1–2 mL, every 30–60 seconds until opioid overdose symptoms subside).

In the case of opioid side effects, four strategies are commonly used: reducing the dose of systemically administered opioids, symptomatic treatment adequate to complication pathophysiology, changing the route of opioid administration, and rotation (switching) of opioids. The concept of opioid rotation means changing the currently used opioid analgesic to another opioid. Opioid replacement enables the elimination of metabolites, which may be important in patients treated with morphine who suffer from deterioration of renal function or dehydration. Similarly, in the case of analgesic inefficacy during treatment with one opioid, a switch to another opioid should be made. Due to incomplete cross-tolerance, care should be taken when converting the corresponding doses of different opioids, and lower converters should be used than those resulting from tables of equivalent doses of opioids, whose usefulness in clinical practice is limited. In each case, the patient requires determination of additional dose — single and daily — and close monitoring during titration to achieve an effective dose. In most patients, switching to opioids improves the effectiveness of pain management and reduces side effect intensity. Occasionally, two-step III opioids are administered simultaneously (e.g., morphine or oxycodone with fentanyl or buprenorphine), which is based on slightly different binding to receptor subtypes and differences in physicochemical properties of different opioids. There are no guidelines in this regard due to the small number of clinical trials conducted so far.

Supportive agents and adjuvant analgesics

Supportive agents are recommended at every step of the WHO analgesic ladder and include adjuvant analgesics (co-analgesics) that relieve pain or enhance the analgesic effect of other analgesics as well as drugs that prevent or treat side effects of opioids (laxatives, antiemetics). While analgesics are selected according to the intensity of pain, in the selection of adjuvant analgesics, attention is paid mainly to the specific pathophysiology of pain. Adjuvant analgesics are particularly useful in the treatment of pain with neuropathic, nociplastic, and bone components (Tab. 4) [34]. Antiepileptic drugs are most commonly used — mainly gabapentinoids (gabapentin, pregabalin, mirogabalin), less often older drugs: valproic acid, clonazepam, carbamazepine (I A). In addition, antidepressants, norepinephrine and serotonin reuptake inhibitors (venlafaxine in a daily dose of 150–225 mg, duloxetine, milnacipran), some of selected selective serotonin reuptake inhibitors (SSRIs) — vortioxetine and tricyclics (amitriptyline) are frequently used (I A). Other classes of medications used to treat neuropathic pain include topical medications (lignocaine and capsaicin) (II C) and systemic NMDA blockers (ketamine and dextromethorphan) (II B). In bone pain, NSAIDs (II A), bisphosphonates, and denosumab are most often used; moreover, due to the frequent component of neuropathic pain, antiepileptic drugs (usually pregabalin and gabapentin) are sometimes considered [35]. In the treatment of neuropathic

Table 4. Most commonly used adjuvant analgesics in the treatment of cancer pain

Drug group	Drug	Dosage, comments	Duration of action [hours]
Anticonvulsants	Pregabalin	Initially, 2 × 25–75 mg, maximum dose 2 × 300 mg, the starting dose depends on the patient's age and treatment tolerance in terms of emerging potential side effects The drug of first choice from the group of analgesic adjuvants due to the pharmacokinetic and pharmacodynamic profile most often added to opioids because of the lack of a full analgesic effect. Used to treat general anxiety	9–12
	Gabapentin	Initially 3 × 100–200 mg, most often the dose is gradually increased to 900––2400 mg/day; doses > 3600 mg/day are not recommended	8
	Valproic acid	Initially, 2 × 300 mg, recommended doses are 2 × 500 mg, do not exceed a daily dose of 1500 mg; the drug is available in liquid oral form and intravenous form	16–24
Anti-depressant	Duloxetine	The starting dose is usually 1 × 30–60 mg (effective doses 60–120 mg), if necessary, increased to 1 × 120 mg. Due to CYP1A2 induction, lower efficacy may be required, and higher doses may be required in smokers (AUC lower by 50%). Co-administration of CYP1A2 and CYP2D6 inhibitors with irreversible MAOIs is not recommended. It may increase blood pressure	16–24
	Venlafaxine	The starting dose is 1 × 37.5–75 mg; it should be increased to 150–225 mg (in this range, it inhibits the reuptake of serotonin and norepinephrine; in lower doses, it is only SSRI). Metabolized by CYP2D6 to the major active metabolite O-desmethylvenlafaxine and CYP3A4 to N-desmethylvenlafaxine. In combination with sympathomimetic drugs has a cardiotoxic effect	12
	Amitriptyline	Starting dose 1 × 25 mg, titrated up to 1 × 75 mg if necessary. Metabolized by CYP2D6 to the active metabolite nortriptyline, which has a long and variable half- life (20–100 h). It has a strong antimuscarinic and antihistamine effect and numerous side effects	24
Glucocorticoids	Dexamethasone	Dosage is usually 4–16 mg once a day or in two divided doses, an anti-inflammatory effect most often used in the short-term treatment of bone pain and nerve compression, numerous indications in emergencies and supportive therapy, given as a component of anticancer treatment in some tumors	36

AUC — area under the curve; MAO — monoamine oxidase inhibitor; SSRI — selective serotonin reuptake inhibitor

pain caused by nerve compression and bone pain, glucocorticoids are used, especially in the case of involvement of the respiratory system and the coexistence of dyspnea, liver tumors, and brain metastases [36]. Due to the pharmacokinetic-pharmacodynamic profile, dexamethasone is particularly indicated. Attention should be paid to observing the rules of careful dosing (titration) of adjuvant analgesics, especially in combination with opioids, which allows for avoiding or at least significantly reducing the risk of side effects.

Non-pharmacological pain management

In some cancer patients, severe pain is not always effectively relieved by pharmacological treatment alone. In these patients, non-pharmacological methods are used, including anticancer treatment (systemic and local: radiotherapy and surgery), interventional methods, physiotherapy, acupuncture, physical exercise, and psychological support [37]. Radiation therapy is effective in bone pain, which in 60–80% of patients causes a significant reduction or complete resolution of pain, and the analgesic effect often lasts for many months. In some patients different procedures are used, including orthopedic operations, surgical immobilization (stabilization), vertebroplasty (in the case of pathological fractures of vertebral bodies), blocks of musculoskeletal system structures, nerve plexuses and peripheral nerves, neurodestructive procedures (neurolysis, cryolesia, thermolesion) within the nervous system and the administration of analgesics and/or adjuvant analgesics by intrathecal route (subarachnoid or extradural). Due to the complex etiology of pain and occurrence of total pain, many patients require psychological, social, and spiritual support.

Physiotherapy

Physiotherapy should be considered at every stage of cancer pain management as an element of multimodal therapy. In some patients, especially the elderly, the type of physiotherapy should be adapted to their physical capacity and capabilities [38]. Most often, indications for the use of physiotherapy include:

— myofascial pain — after treatment (changes in body posture, scars), abnormal movement patterns, immobilization, increased muscle tension caused by pain;
— bone pain caused by metastases;
— neuropathic pain during and after anticancer treatment.

Techniques used to treat myofascial pain in cancer patients include:

— trigger point therapy (palpable points present within a tense muscle band, hypersensitive to mechanical stimulation);
— mechanical methods — joint mobilization, neuromobilization;
— physical treatments;
— techniques of proprioceptive neuromuscular facilitation (PNF);
— kinesiotaping.

Therapeutic techniques used in patients with bone pain and the role of the physiotherapist include:

1. patient and family education:
— learning to change positions, belying while moving,
— assistance in the selection and use of rehabilitation equipment;
2. neuromodulation techniques — transcutaneous electrical nerve stimulation (TENS).

Transcutaneous electrical nerve stimulation is a cheap and easily accessible method, which can also be performed at home, and side effects are rare (allergic skin reactions, skin burns, edema, pain intensifying). Contraindications to the use of TENS include pacemakers, epilepsy, and mental illness. TENS may be a useful option in the treatment of cancer pain, especially resistant to standard treatment and significantly reducing quality of life. It also has an analgesic effect on musculoskeletal and neuropathic pain [39]. Concerns regarding the safety and effect of TENS on cancer relate to the possible increased local blood supply to tissues due to electrical stimulation. However, the increased blood supply is due to muscle contraction; therefore, electrical stimulation below the motor threshold should not increase blood flow in a given body area.

Acupuncture

Acupuncture can be used to treat cancer pain, especially caused by tumors and surgery; analgesic effects are also possible in other pain syndromes that are difficult to treat, such as neuropathy after chemotherapy and joint pain induced by hormone therapy [40]. Clinical use of acupuncture in cancer patients may improve the effectiveness of standard pharmacotherapy in accordance with WHO recommendations and the quality of life of cancer patients [41].

Acupuncture is recommended by the American College of Chest Physicians for the treatment of pain in patients with lung cancer, especially when standard methods are ineffective or intolerable. Acupuncture is also recommended by the American Society of Clinical Oncology for the treatment of chronic pain in women during and after breast cancer therapy and in cancer survivors. Acupuncture is also recommended for elderly patients due to its effectiveness, low invasiveness, and significant safety [42].

Physical exercise

Many patients believe that rest and stillness can relieve pain. However, cancer patients can safely perform exercises both during and after cancer treatment. These exercises can reduce the intensity of anxiety, depression, and fatigue associated with cancer, as well as improve the quality of life and functioning of patients after anticancer treatment. The lower credibility of this evidence relates to beneficial effects of exercise on sleep quality. The exercise program should be selected individually according to the patient's preferences and performance status (PS) according to the Eastern Cooperative of Oncology Group (ECOG) scale. According to the recommendations, cancer patients with ECOG PS 0–2 can do moderate aerobic exercise (brisk walking, light cycling, water exercises) three times a week for 30 minutes and muscle strengthening exercises twice a week for 20–30 minutes. For patients with ECOG PS 3–4, programs individually selected by physiotherapists are recommended.

In elderly patients, in particular, moderate physical activity for a total of 150 minutes per week is recommended, but also shorter physical activities, such as slow walking and light housework. According to the WHO recommendations, elderly people with reduced mobility can perform physical activity 3 or more days a week to improve balance and prevent falls. When elderly people cannot perform the recommended physical activity due to their health condition, physical activity adapted to their capabilities is recommended [43].

Psychological support

Psychological methods used in the treatment of pain include meditation, hypnotherapy, relaxation, cognitive-behavioral therapy, biofeedback, visualization,

and music therapy [44]. The assumption is to influence various functions of the body through proper brain training. However, there are no studies evaluating the effectiveness of psychological methods in patients suffering from pain. The results of studies conducted in cancer patients indicate that psychological techniques can not only reduce the intensity of pain but also have a positive impact on other quality-of-life components, including reducing anxiety and improving the quality of sleep and mood [45]. In elderly cancer patients, psychoeducation methods are also effective, which include education about pain and its treatment, relaxation, training, and group support.

Interventional methods of pain management

Interventional methods include various techniques, from simple injections into tender points within the muscles to invasive neurodestructive methods and intrathecal implantation of catheters and stimulators (Tab. 5). The development of pharmacotherapy, and

Table 5. Therapeutic use of blockades/neurolysis/thermolesion/cryolesia

Type of pain	Blockades/neurolysis/ /thermolysis/cryolesia	Comment
I. Somatic pain:		
Myofascial	Trigger point blockades, injecting muscles and their fascia with LAs, peripheral nerve blocks	Technically simple, safe, and worth trying and propagating, it is advisable to monitor needle position under ultrasound guidance
Osteoarticular	Blockades of intervertebral and facet joints	Technically difficult, they require monitoring of needle/electrode position under the X-ray or US vision track
II. Visceral pain:		
Cancer-related	Stellate ganglion, plexuses: celiac, hypogastric superior The lumbar section of the sympathetic trunk, Walter's ganglion	Technically difficult, they require monitoring needle/electrode position under the X-ray or US vision track
Colicky pain	Epidural blockade in the lumbar or sacral region	Alternative/complement to systemic opioids
III. Vascular pain	Stellate ganglion, the lumbar section of the sympathetic trunk	The effect is very dependent on disease stage, high efficiency in rest pain, and requires monitoring the needle/electrode position under the X-ray or US vision track
IV. Neuropathic pain:		
Pancoast syndrome	Stellate ganglion, cervical epidural block, chordotomy	An alternative to ineffective pharmacotherapy of neuropathic pain, requires monitoring the needle/electrode position under the X-ray or US vision track Technically simple, effective in early stages of disease
Cranial nerve neuralgia	Blockades of peripheral branches of cranial nerves. Blockades of Gasser's ganglion, pterygopalatine ganglion. Gamma KNIFE/surgical decompression of neuro-vascular conflict	Technically difficult, high efficacy rate, monitoring the needle/electrode position under the X-ray or US vision track, in the case of Gamma KNIFE or surgical treatment it requires a neurosurgical center
PHN	Blockades of the sympathetic system. Epidural blockades	Technically difficult, requires monitoring the needle/electrode position under the X-ray or US vision track, effective up to 6 months from disease onset
Radiculopathies	Paravertebral blockades with LAs with addition of glucocorticosteroids	Effective in the acute disease phase
Stump pains	Blockades of trigger or tender points	Technically simple, the therapy of choice in early stages of disease, thermolesion/cryolesia requires monitoring the needle/electrode position under X-ray or ultrasound guidance
Phantom pains	Thermolesion/cryolesia of the stump Blockades of the sympathetic system	Technically difficult, require monitoring the needle/electrode position under the X-ray or US vision track

LA — local anesthetics; PHN — postherpetic neuralgia; US — ultrasonography

especially the introduction of many opioids and adjuvant analgesics, has significantly reduced the importance of interventional methods in recent years, although they are considered in 5–10% of patients. Interventional procedures in cancer patients should be considered at every stage of disease. The main indications for the use of interventional methods are pain that is resistant to pharmacological treatment, with a limited extent and clear localization, e.g., metastasis to the rib, compression of the intercostal nerve, or treatment-resistant side effects of pharmacotherapy [46]. Neurodestructive procedures can also be used in the early stages of the disease, especially neurolysis of the celiac plexus (II B) or the superior hypogastric plexus (II C) before the tumor causes significant anatomical distortions. Interventional methods of treatment should not be regarded as step IV of the WHO analgesic ladder but should be performed early enough when the patient begins to experience pain. This approach allows for a significant reduction in complex pharmacological treatment and/or delay in its initiation. The following minimally invasive intervention methods can be performed in cancer patients:

— blockade of tender trigger points in muscles;
— periarticular and intra-articular blockades;
— peripheral nerve, nerve plexus, and interfascial blocks.

In selected patients, more invasive interventional procedures can be performed in specialized units, such as:

— sympathetic blockades: celiac plexus, hypogastric plexus, Walther's ganglion;
— central blocks: epidural, subarachnoid;
— neurodestructive techniques: thermolesion, cryolesia, neurolysis, surgical procedures;
— intrathecal administration of drugs;
— invasive neuromodulation — stimulation of the spinal cord, peripheral nerves (Tab. 6).

Patients with multiple pain locations, a complex pain mechanism (central), dynamically intensifying pain, and poor general condition are carefully qualified for interventional methods. The patient's age is not a contraindication to the use of interventional methods.

The premise for the use of interventional techniques is the possibility of acting directly at the site of pain. An early and sometimes just one block may prevent the development of potential pain syndrome (phantom pain after limb/breast amputation, pain after thoracotomy/mastectomy). Blockades have a special role in pain syndromes, in which the modulating factor is the excessive activity of the sympathetic nervous system. A classic example of pain that may be dependent on the sympathetic nervous system is neuropathic pain, which occurs in 7–10% of the general population and in over 30% of cancer patients. Therefore, blocks are an important element of therapy for this type of pain [47]. Another possibility of using interventional techniques is their application to inject drugs into the immediate surroundings affected by the disease process: into joint and epidural space (opioids and steroids). In cancer patients, the positive effect of continuous epidural (II C) or subarachnoid (II B) blockade is especially related to neuropathic and bone pain, sometimes also inflammatory, by reducing swelling around the spinal cord.

Blockades are also used as an important diagnostic and prognostic method. A positive but short-term effect of a blockade may confirm the indication for neurodestructive surgery. In cancer patients, not only all advantages but also potential adverse effects of therapeutic treatment should be carefully considered. In each case of using interventional techniques, there is a risk of complications and side effects. Permanent damage to the nervous structures, especially the peripheral nerve, may be associated with unpleasant consequences, such as paresthesia, numbness, and motor deficits; therefore, before performing a neurodestructive procedure, patients should be informed about the possibility of side effects and potential complications. It is also necessary to obtain the patient's informed written consent for the procedure. Performing a neurodestructive procedure may be preceded by a diagnostic and prognostic block with the use of local anesthetics (LAs). This procedure helps to determine the source of pain and its mechanism and also indicates the patient the advantages and disadvantages of future neurolysis/thermolesion. It should be remembered that LAs are always stronger than neurodestructive agents, and the patient is exposed to the same procedure twice. It is always worth thinking carefully about performing a diagnostic block.

Elderly patients may be considered for an invasive procedure if they meet the following criteria:

— patient understands the purpose of the procedure and gives informed consent to the proposed procedure;
— the nature of pain corresponds to indications for use of a given method;
— safety aspects, e.g., use of anticoagulants, coagulation disorders, and local skin infection, are covered.

In cancer patients, one of the most frequently performed invasive procedures is neurolysis within the structures of the sympathetic nervous system:

— celiac plexus — in pain accompanying cancer of the pancreas, liver, and other organs in the epigastrium;
— the superior hypogastric plexus and ganglion impar (Walther) — in pain associated with pelvic tumors and in perineal pain.

Table 6. Most frequently performed interventional techniques in cancer patients

Interventional technique	Indications	Comment
Spinal/epidural neurolysis	Localized, unilateral, severe cancer pain, limited to 1–3 dermatomes, difficult to control with pharmacotherapy	Due to the properties gives a local anesthetic effect and hyperbaricity in relation to the cerebrospinal fluid; the preferred neurolytic agent is phenol Catheter insertion allows the administration of phenol in a fractionated manner, and the anesthetic properties of the drug allow for controlling blockade extent and improving procedure safety High risk of serious neurological complications (muscular weakness of lower limbs, damage to the sphincter function) The reason for incomplete effectiveness may be fibrosis in the spinal canal, e.g., after radiotherapy, which isolates the nerve roots from the administered drug
Neurolysis/ /thermolesion/ /cryolesia of peripheral nerves: intercostal, suprascapular, occipital, intercostobrachial	Cancer pain due to rib metastases or chest wall invasion, chest wall pain syndromes, pain after mastectomy/thoracotomy Painful shoulder syndrome, bone pain resulting from metastases to the scapula, shoulder joint, or humerus Suprascapular neuralgia, occipital neuralgia, headaches: tension, Horton's migraine, post-puncture Intercostobrachial neuralgia after mastectomy	Simple techniques, however, require ultrasound-guided monitoring of the needle/electrode position to reduce the risk of complications (hematoma/intravascular administration/pneumothorax in the case of intercostal blockage) Due to the overlap of dermatomes, two adjacent intercostal spaces must be destroyed to achieve a good intercostal block effect Intercostal nerve neurolysis has been completely replaced by the thermolesion/cryolesia technique
Intrapleural neurolysis	Pleural and chest wall pain due to lung, breast, kidney, and pancreatic tumors	Simple blockade technique, identical to intrapleural LA blockade based on loss of resistance technique Insertion of the needle above the upper rib edge in a lateral position in the mid-scapular line
Neurolysis/ /thermolesion/ /cryolesia of the pterygopalatine ganglion, thermolesion of Gasser's ganglion	Neuralgia, trigeminal neuropathy, atypical facial pain, trigeminal autonomic headache, migraine, post-puncture headache, PHN of 1 branch of the trigeminal nerve, facial pain due to craniofacial tumors	Technically difficult due to significant variability of the anatomical structure of the facial skeleton They require experience and monitoring of the needle/electrode position under the X-ray vision track with the C-arm and contrast administration, which in pterygopalatine ganglion block should be placed in points against maxillary sinus background, and in Gasser's ganglion block, monitoring under the X-ray vision track helps to localize the foramen ovale Side effects in pterygopalatine ganglion blockade result from technical errors and incorrect depositing of the neurolytic agent: corneal ulceration (agent infiltration into the orbit), facial nerve palsy (agent infiltration into the styloid process)
Neurolysis/ /thermolesion/ /cryolesia of stellate ganglion	Upper limb vascular pain, pain after thoracotomy and mastectomy, phantom pain, lymphedema pain, PHN, Pancoast syndrome, CRPS	Neurolysis has been replaced by the thermolesion/cryolesia technique Technically difficult, require experience and monitoring of the needle/electrode position under the X-ray vision track with the C-arm and contrast administration Complications: intravascular or intrathecal administration with generalized toxic reaction/total spinal anesthesia, pneumothorax, recurrent laryngeal, and phrenic nerve palsy, Horner's syndrome
Celiac plexus neurolysis	Cancer-related visceral pain in the upper abdominal cavity (cancer of the pancreatic head, stomach, gallbladder, liver), CP	Technically difficult, require experience and monitoring of the needle/electrode position under the X-ray vision track with the C-arm, TC-arm in the transdiaphragmatic peri- or transaortic approach or ultrasound in the anterior approach and contrast administration, which should be placed linearly on the anterior wall of the abdominal aorta at Th12 level It causes a high sympathetic blockade; therefore, it requires prophylaxis of blood pressure drop

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Table 6 cont. Most frequently performed interventional techniques in cancer patients

Interventional technique	Indications	Comment
		High (70–85%) effectiveness in the treatment of visceral pain for pancreatic head cancer (II A)
		Ineffective in cancers of the pancreatic body and tail due to the large size of tumors located in this area, which prevents good coverage of the celiac plexus with a neurolytic agent
Thermolesion of visceral nerves at Th11 level	As above	Technically difficult, require experience and monitoring of the needle/electrode position under the X-ray vision track with the C- or TC-arm
Celiac plexus radioablation	As above	Technically difficult, requires experience to select an ionizing radiation dose that is safe for organs
Bilateral thoracoscopic splanchnicectomy	Cancer-related visceral pain in the course of the pancreatic body and tail, CP	Bilateral transection of visceral nerves under visual control should be performed by an experienced endoscopic surgeon
		The procedure requires the patient's prone position so that the surgeon has free access to both pleural cavities without the need to change the patient's position during the procedure and intubation with a double-lumen tube (DLT) and alternate deflation of both lungs
		With no risk of serious complications, including neurological ones associated with classic neurolysis of visceral nerves
		Effective in large pancreatic tumors
Neurolysis of the lumbar section of the sympathetic trunk	Pain in the lower abdomen and lower limbs dependent on the sympathetic system: vascular, neuropathic (CRPS, PHN, FBSS, phantom), cancer, post-traumatic, degenerative pain	Technically easy, but requires monitoring the correct position of the needles using X-ray vision track with C-arm and contrast administration, which should be placed linearly along the iliopsoas muscle
		Due to the considerable length of the lumbar section of the sympathetic trunk, the technique with use of two needles inserted at L2 and L4 levels is recommended
Neurolysis of superior hypogastric plexus	Visceral pain in the course of pelvic cancer: uterus, prostate, rectum, bladder	Technically very difficult, requires a lot of experience and monitoring the correct position of the needle using X-ray vision track with C-arm (two AP and lateral projections are necessary to ensure that the contrast and then the neurolytic agent are administered to the anterior surface of L5–S1 vertebral bodies)
Neurolysis of Walter's ganglion	Cancer pain in the perineal and anal area, phantom pain after rectal resection, perineal pain in the course of pelvic pain syndrome	Technically easy, requires monitoring the correct position of the needle tip using the X-ray vision track and contrast administration or ultrasound
		The sacrococcygeal area can be reached with a bent needle or via the sacrococcygeal junction
Drugs administered intrathecally	Cancer pain resistant to treatment or intolerable side effects of pharmacotherapy, inability to use other interventional methods	About 2% of patients with cancer pain require the use of intrathecal drugs (LAs, opioids, corticosteroids, ketamine, baclofen, magnesium, ziconotide)
		An epidural or subarachnoid catheter is connected to an external or implantable pump
		Contraindications: infection at the puncture site, coagulation disorders, tumor in the spinal canal, anticipated difficulties in pump operation
Vertebroplasty/ /kyphoplasty	Metastases to the vertebral body, pathological or osteoporotic fracture	Bone cement injection to stabilize the vertebral body
		An experienced orthopedist or a neurosurgeon should perform the procedure
		It effectively relieves pain with a relatively low complication rate and an acceptable benefit/risk ratio

AP — anterior-posterior; CP — chronic pancreatitis; CRPS — complex regional pain syndrome; FBSS — frontal behavioral spatial complex; LA — local anesthetics; PHN — postherpetic neuralgia

Neurodestructive procedures can be conducted by physical or chemical factors or surgical incisions (mechanical factors). The physical factors that damage nerve fibers include low (cryolesia) and high temperature (thermolesion) and hypo- and hyperosmotic solutions. Chemical agents that damage nerve fibers include

primarily ethyl alcohol and, less often, phenol and glycerol. Nervous tissue, such as the celiac plexus, can also be damaged by ionizing radiation (radioablation of the celiac plexus), which consists of the destruction of the celiac plexus and pancreatic tumor with a safe dose of ionizing radiation. The procedure is used in patients with pancreatic neoplasms, in whom neurolysis of the celiac plexus cannot be performed (due to too large tumor dimensions, especially located within the body and tail of the pancreas, or vascular infiltration). It is one of the most modern interventional techniques used in the treatment of pain in patients with pancreatic cancer. Poland was the first country in Europe where such procedures were performed [48].

The neurodestructive mechanism of a chemical compound with a neurolytic effect includes inducing Wallerian degeneration of nerve fibers, i.e., the disintegration of protein and lipid substances in axons and changes in myelin sheaths. The increase in fluid pressure inside the nerve fiber impairs blood flow in the blood vessels supplying the nerve. Shortly after the destruction of nerve structures, the regeneration process begins, the duration of which depends on the extent of neurodestruction — usually, the nerve fiber regenerates at a rate of about 1 mm/day. The drug is administered near the nerve without affecting its structure.

Ethyl alcohol is the oldest and most commonly used neurolytic agent with low toxicity, used in a concentration of 50–100% (usually about 65%). Alcoholic neurolysis occurs rapidly and lasts for 5–7 months. Factors limiting the use of alcohol include rapid tissue diffusion, which requires the use of large volumes, making it more difficult to obtain a spatially limited neurolytic effect. During alcohol injection, the patient may experience pain, and alcoholic neuritis may occur. Tissue irritation caused by alcohol can be reduced by using a mixture with LAs, the alcohol concentration is then about 65%; it is also beneficial to rinse the needle with 1–2 mL of 0.9% NaCl or lignocaine. Accidental entry of alcohol into the tissues can cause local neuralgia.

In clinical practice, neurodestructive procedures within sympathetic fibers and/or ganglia, neurodestruction of the sensory roots of the spinal cord, and, selectively, mixed nerves are mainly performed [49]. The most commonly performed celiac plexus neurolysis reduces the intensity of pain in 90% of patients with pancreatic cancer, while complete pain relief is reported by up to 60% of patients. Neurolysis allows reducing the dose of systemically administered opioids, but it does not completely replace pharmacological treatment. An alternative to celiac plexus neurolysis may be celiac nerve neurolysis/thermolesion. The most common use of blockades and neurolysis in cancer patients is presented in Tables 4 and 5. Interventional methods of pain treatment may be associated with serious complications; therefore, they should be performed in specialized units after a thorough analysis of indications and contraindications [50].

Conclusions

In order to obtain the optimal effect of analgesic therapy, cancer patients require a comprehensive clinical assessment of pain, with the recognition of the pathophysiology, intensity, time pattern of pain, other symptoms, comorbidities, and disturbances in the psychological, social and spiritual dimension that may contribute to the patient's suffering and occurrence of total pain. The standard treatment is based on the WHO analgesic ladder algorithm and individualization of pain therapy, depending on the patient's clinical situation, taking into account non-pharmacological methods. Efforts should also be made to ensure effective treatment of other symptoms associated with cancer. Palliative and supportive care improves the quality of life of cancer patients by increasing overall survival and improving the quality of life for families and caregivers. The basic principles of pain pharmacotherapy in cancer patients include:

— oral and transdermal administration of analgesics, if possible and acceptable by patients;
— administration of analgesics at regular intervals and rescue agents in episodes of pain intensification (breakthrough, episodic pain);
— the choice of an analgesic depends mainly on pain intensity assessed by patients;
— drug dosage is selected individually: the optimal dose provides effective analgesia with acceptable side effects;
— attention to detail, monitoring of analgesic effectiveness, side effects, and quality of life of patients and families.

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Conflict of interest

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