Recommendations for assessment and management of pain in cancer patients

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According to the authors, the guidelines contains the most justified principles of diagnostic and therapeutic procedures. They should, however, be interpreted in the context of the individual clinical situation. Recommendations do not always correspond to the current refund rules in force in Poland. In case of doubt, you should be sure of the current refund possibilities of each procedure.

Introduction

Pain is one of the most common symptoms occurring in patients with cancer. Each patient has an inalienable right to receive the most effective analgesic management, and each physician and each nurse has an obligation to provide an appropriate analgesic therapy in order to assure the best possible quality of life to the patient and his/her caregivers [1].

The International Association Study of Pain (IASP) defines pain as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain may be defined by its duration (acute or chronic), pathomechanism (nociceptive, neuropathic or mixed), and location (localised or generalised). Untreated or inefficaciously treated pain may negatively influence the functioning of the organism. Pain is a risk factor of occurrence or exacerbation of shock syndromes, it compromise the immunity of the human organism and decreases patients' quality of life. Pain may also

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impede or even preclude efficient anticancer therapy and lead to a significant increase of cost of the therapeutic management. Inefficaciously or untreated pain may cause emotional and psychotic disorders as well as depression [2]. Pain should be considered and treated in the context of each particular clinical situation. The general patient's status, other symptoms and comorbidities, and the administered anticancer treatment as well as the nonmedical aspects (psychological, social, and spiritual problems of patients and of their caregivers) should also be considered.

The prevalence of pain is estimated to be about 40–50% of patients during oncological therapy and about 60–70% of patients with advanced cancer [3].

The current standards of analgesic management of cancer patients are presented in this section.

Clinical assessment of pain

The assessment of pain is a subjective phenomenon that results from the individual sensitivity of a patient to pain stimuli, and from the multidimensional influence of pain on the physical, psychical, social, and spiritual sphere. Patients' psychical condition and their personality traits influence the perception of pain. The absence of objective pain assessment tools poses another practical problem, and consequently the clinical evaluation of pain is still based on the patient's subjective relation. When self-evaluation is not feasible the pain must be evaluated by caregivers and by health professionals.

A visual analogue scale (VAS) is a simple tool that enables the individual evaluation of pain intensity. In VAS the patient indicates a point representing the intensity of the experienced pain on a 10-cm continuous line (from "no pain" to "the most severe pain intensity"). The numerical rating scale (NRS) is a standard tool used to assess the intensity of pain in daily clinical practice. In the NRS a patient defines the intensity of pain by choosing an adequate number from 0 (no pain) to 10 (the most severe pain). A Likert descriptive scale is also sometimes used to define pain intensity ("no pain" — "weak pain" — "moderate pain" — "severe pain" — "very severe pain"). In the case of children, persons who do not speak the language, illiterates, and patients with cognitive disorders and with dyslexia, pictorial scales are used (e.g. facial expression). The evaluation of the intensity of pain should be done before the onset of therapy, and regular monitoring of the intensity of pain should be continued during the treatment. Some tools, adapted to the situation in Poland, provide more detailed evaluation of pain: the Memorial Pain Assessment Card (MPAC) and the Brief Pain Inventory — Short Form. The fist tool, MPAC, consists of:

— three numeric scales in which the patient evaluates the intensity of pain, pain relief, and general mood as well as the intensity of pain, with use of a verbal scale;
— a section filled out by a physician or a nurse, which includes the pathomechanism, localisation, and type of pain (background and a breakthrough pain) and the administered therapy.

The BPI-SF formulary includes numeric scales evaluating the intensity of the pain and pain relief in the past 24 hours as well as the influence of pain, in the same period of time, on the daily activities of the patients.

In patients with a neuropathic component of pain, some different sensory symptoms may be present, which may coexist in different combinations. That is why a clinical examination should include touch, prick, pressure, low and high temperature, vibration, and temporal summation. Several scales (screening tools) based on the verbal description of pain have been developed in the past few years. These scales may or may not include some elements of the clinical examination, and they significantly improve the recognition of neuropathic pain as well as the implementation of adequate therapy. The Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS), for example, includes five questions concerning pain and two elements of clinical examination; the specificity of this scale reaches 85% and sensitivity 80% — when the number of points exceeds 12/24 it means that the pain has mostly neuropathic character.

Another scale, the Douleur Neuropathique 4 Question scale (DN4), includes seven questions concerning the symptoms and three elements of clinical examination. The specificity of this scale reaches 83% and sensitivity 90%. If the number of points exceeds 4/10 it means that the pain has mostly neuropathic character [4].

Pathophysiology of pain

The pathophysiology of pain includes two main mechanisms. The first is related to the mechanical and/or chemical irritation of the nociceptors and causes nociceptive pain (somatic, visceral). The second mechanism — independent from the activation of the nociceptors — is caused by the injury of the somatosensory nervous system and causes neuropathic pain. Neuropathic pain is characterised by the hyperalgesia phenomena (an increased sensitivity to pain stimuli) and allodynia (pain induced by stimuli that normally do not cause any pain). The characteristics of the neuropathic pain that are often reported by the patients include the sensation of burning, pins and needles, or popping with frequent coexistence of sensation disorders or a sensation similar to an electric shock-like sensations. It should be stressed that the neuropathic

pain is more difficult to manage than the nociceptor pain in which the efficacy of the non-opioid analgesics and of the opioids is significantly higher. It is worth mentioning that that somatic bone pain also presents some features of neuropathic pain and is qualified as a pain with a neuropathic component.

If possible, therapy of the chronic pain should be directed to the underlying pain pathophysiology, which may result in permanent relief and prevent other complications.

The pain experienced by patients, depending on the time of its occurrence, may be divided into background pain and breakthrough pain, also known as episodic pain [5]. Background pain persists for over 12 hours in a day, while a breakthrough pain is defined as an attack of a severe and usually transient pain that increases rapidly and appears despite efficient therapy of the background pain. The time to the maximal intensity of the breakthrough pain ususally equals several minutes, and the median time of its duration is about 30 minutes. However, a breakthrough pain episode may last from several dozen seconds to several hours. Recent publications have shown that episodic pain may also be diagnosed in patients with uncontrolled background pain, when opioids are not administered, and in the absence of background pain. A breakthrough pain may occur without any defined cause (spontaneous or idiopathic pain), but it may also be triggered by a particular factor (incidental pain). End-of-dose pain, which occurs before the administration of the next dose of a regularly used analgesic and which requires modification of the therapy of the background pain, is not classified as breakthrough pain [6].

Incidental pain may be divided into involuntary: independent of the patient's will, or voluntary: triggered by predictable and voluntary patient activity or nursing, diagnostic and therapeutic procedures (procedural pain). The strategy of treatment of spontaneous and incidental involuntary pain consists of using rapid-onset analgesic drugs at the moment of pain occurrence, in order to assure the most effective analgesia in a minimal period of time. Products containing fentanyl, which have rapid onset of action and are absorbed through the mucosa (intranasal, buccal, and sublingual routes), are usually used for this purpose. In the case of occurrence of pain induced by predicted and voluntary activity of patients or by nursing, diagnostic and therapeutic procedures (procedural pain) it should be prevented effectively by pre-emptive use of an appropriate dose of analgesic, which will efficiently prevent or significantly decrease the intensity of the incidental pain. For this purpose, typically immediate-release formulations of opioids are administered by an oral or parenteral routes (subcutaneously — usually at home, intravenously — usually at in-patient units) [7].

The basic rules of analgesic management of cancer patients

Pharmacological treatment

In the analgesic management of cancer patients both pharmacotherapy and nonpharmacological methods are used (II, A).

In the therapy of background pain (continuous pain) the pharmacotherapy should be conducted continuously in order to maintain a stable, therapeutic concentration of the drugs in the blood. The analgesics should be administered at regular intervals, and the route of administration should be comfortable for the patient. However, the oral route of drug administration should be preferred whenever possible. If the patient prefers another route of administration or when oral therapy is not feasible or complicated by some adverse events that are difficult to manage, an alternative route of administration of the analgesic drug should be applied. The efficacy should be monitored and adverse effects of the treatment should be prevented and managed.

The use of analgesic drugs is based on the analgesic ladder developed by the World Health Organisation (WHO), which divides analgesic drugs into three groups [8]:

— step I — non-opioid analgesics (NSAIDs, non-steroid anti-inflammatory drugs) or paracetamol or metamizole;
— step II — so-called "weak" opioids (tramadol, codeine, and dihydrocodeine);
— step III — so-called "strong" opioids (morphine, oxycodone, oxycodone/naloxone, fentanyl, buprenorphine, tapentadol, methadone, hydromorphone).

Treatment is based on the individual choice of analgesic drug that is adequate to the intensity of the patient's pain. The therapy should be started from step I non-opioid analgesics administered alone when pain intensity is rated as 1–3 NRS. In patients with pain of moderate intensity (NRS 4–6), the therapy should be started "weak" opioids of step II or low doses of "strong" (step III) opioids. During the administration of "strong" opioids no ceiling effect occurs, which is observed during treatment with non-opioid analgesics and "weak" opioids. This allows to expect a better analgesic effect after dose escalation in the majority of patients. When WHO pain ladder step II and III opioids are used, a concomitant administration of non-opioid analgesics may be considered (a different mechanism of analgesic action). On the other hand, it is not recommended to combine step II and III opioids. The indication for use of the adjuvant drugs may occur at every step of the therapy. The adjuvant drugs includes the group of co-analgesics (adjuvant analgesics), which increase the analgesic effect of opioids in some types of pain (mostly in neuropathic and bone pain as well as in visceral colicky pain) and of

the drugs used in the prevention of opioid-induced side effects (laxatives and antiemetics).

The basic rules of the pharmacotherapy of pain in cancer patients includes:

— administration of analgesics by an oral or transdermal route if possible;
— regular administration of analgesic drugs in the management of background pain and on an ad hoc basis in episodes of pain exacerbation;
— the choice of analgesics should depend on pain intensity evaluated by the patient;
— the drug dose should be individually adjusted in order to provide efficient analgesia and acceptable adverse effects;
— monitoring should be carried out of the analgesic efficacy, of the side effects, and of patients' and caregivers' quality of life.

Non-opioid analgesics

Non-opioid analgesics are used alone in mild pain intensity (NRS 1–3) and together with opioids in moderate (NRS 4–6) and severe (NRS 7–10) pain intensity.

Non-steroid anti-inflammatory drugs (NSAIDs) block the synthesis of prostaglandins through the inhibition of the cyclooxygenase (COX) activity and, to a lesser degree, through the expression of the induced isoform of the nitric oxide synthase. Because the majority of NSAIDs are weak acids and may damage the gastric and duodenal mucosa, concomitant use of proton pump inhibitors is recommended in the risk group patients. The negative effect of NSAIDs on the liver may be manifested by the usually asymptomatic elevation of the aminotransferases. Nimesulide may demonstrate some more intensified hepatotoxicity. The negative impact of the NSAIDs on the kidneys may lead to the occurrence of peripheral oedemas and in some cases to acute renal insufficiency. In some and up to a dozen or so per cent of patients treated with the acetylsalicylic acid or with NSAIDs, bronchial asthma attacks may occur. Acetylsalicylic acid is an irreversible inhibitor of thromboxane synthesis. There is a diversified risk of vascular complications associated with the use of NSAIDs. Naproxen has the lower risk of this type of complication; however, the drug has a long plasma half-life. The choice of drug from the NSAID group should be based on the individual evaluation of patients regarding the estimated analgesic efficacy and the toxicity profile of each particular drug.

In elderly patients who are chronically treated with NSAIDs a special precaution should be taken due to the increased risk of intensification of heart and renal failure. The parenteral or per rectum administration of NSAIDs does not improve the quality of the analgesia and does not reduce the prevalence of the side effects compared to the oral route. Concomitant use of two NSAIDs is not recommended because it does not improve the analgesic efficacy but significantly increases the risk of damage of the gastrointestinal tract mucosa and of any other side effects. NSAIDs show important efficacy in the therapy of bone pain.

Paracetamol shows analgesic and antipyretic activity but has no peripheral anti-inflammatory effect. At therapeutic doses it does not produce side effects typical for NSAIDs involving the gastrointestinal tract and kidneys. The clinical effect of paracetamol administration is observed in 15–30 minutes depending on the pharmaceutical form of the drug. If paracetamol is used at the recommended doses (the maximal dose of 4 g per day, and in elderly patients 2 g per day), usually no severe adverse effects are observed except for some allergic reactions. In long-term treatment and when higher doses are used adverse events may occur. The liver is often involved. Paracetamol is contraindicated in patients with liver failure. In cases when tretment with paracetamol is long-lasting we should be especially cautious regarding patients with cachexia, who abuse alcohol, and who receive barbiturates. Paracetamol does not induce bronchospasm in asthma patients. The combination of NSAIDs and paracetamol produces a synergic analgesic and antipyretic effect [9].

Metamizol is a non-opioid analgesic that has no anti-inflammatory effect. The mechanism of its analgesic activity is mostly based on the inhibition of COX-2 and COX-3 in the central nervous system (CNS) and to a lesser extent on the inhibition of COX-1 and probably also on the activation of opioid system. The drug has a spasmolytic effect, which is important in the therapy of the acute colicky pain. The maximal daily dose of metamizole is 5 g. In cancer patients the drug is mostly used to treat breakthrough pain and colicky pain. Metamizole should not be given continuously for a period longer than seven days due to the increased risk of its side effects, especially concerning the haematopoietic system.

Opioid analgesics

Opioids play a key role in the therapy of the moderate to severe pain intensity in cancer patients through their influence on the three types of opioid receptors: μ, δ, and κ, which are contemporarily defined as MOR, KOR, and DOR, respectively. The opioid receptors are localised in many structures of the central and peripheral nervous system. The effects of opioid activity depends on many factors, including: their affinity to the opioid receptors, their influence on the serotoninergic, adrenergic system as well as on the N-methyl-D-aspartate (NMDA) receptors, on their physicochemical properties, and on their pharmacokinetic characteristics. In the treatment of breakthrough pain the dose of short-acting opioid (immediate-release formulations) administered by an oral route usually equals approximately 10–20% of the

total daily dose of the regularly administered opioid. In the case of use of rapid-onset fentanyl products administered transmucosally, the rule of titration from the lowest dose of a particular product should be always applied. This rule concerns also the switch from one fentanyl product to another one (including products with the same route of administration, e.g. intranasally) and also any important changes in the therapy of the background pain (any important change of the basic opioid dose or rotation of opioids).

WHO analgesic ladder step II opioids ("weak" opioids)

Opioids of step II WHO analgesic ladder are typically used in patients with moderate pain intensity (NRS 4–6) [10]. Exceeding the recommended maximal doses of "weak" opioids usually does not provide any additional analgesic effect, whereas it may intensify the side effects (ceilling effect of analgesia). Tramadol, codeine, and dihydrocodeine are accessible in Poland (Table 1).

Tramadol is the most frequently used WHO analgesic ladder step II opioid, which has a several-times weaker analgesic effect compared to morphine (II, A). Tramadol shows a double mechanism of analgesic action: despite the influence on the opioid receptors (mostly μ) in the CNS, it activates a descendent antinociceptive system through the inhibition of noradrenaline and serotonin reuptake. Tramadol is metabolised in the liver by the cytochrome P-450 enzyme and then excreted 90% (after oral administration) by the kidneys and 10% in stools. The analgesic effect of tramadol depends on the activity of the CYP2D6 enzyme, which catalyses the transformation of the basic substance into the O-desmethyltramadol (M1), which shows a significant analgesic effect through the activation of opioid μ receptors. Nausea, vomiting, and excessive sweating, especially at the beginning of the therapy, are the most commonly observed side effects. The advantage of tramadol is its weak negative influence on propulsive GI motiltity and lower constipating effect compared to other opioids. Tramadol is available in different formulations, also as controlled-release tablets. The tablets, capsules and drops (40 drops = 100 mg) are administered by an oral route, and ampoules may be administered subcutaneously, intravenously, and less frequently intramuscularly. Tramadol should be administered at daily doses of up to 400 mg, every 4–6 h in immediate-release formulations or every 12 h in controlled-release products. In the management of breakthrough pain occurring during the basic analgesic therapy with tramadol, immediate-release tramadol formulations are used. Tramadol is also available in combination with paracetamol, which accelerates the start of the analgesic effect of this drug and provides a synergistic analgesic effect.

Due to the prolonged plasma half-life of tramadol and of its active metabolite, in the case of renal failure it is recommended to reduce the drug dose and to prolong the intervals between the consecutive doses or to switch to another opioid. Prolongation of the time intervals between the consecutive doses of the drug and reduction of the drug dose are also recommended in patients with impairment of liver function. In patients with history of epilepsy, tramadol is not recommended due to an increased risk of occurrence of convulsions. Due to the increase of the concentration of porphyrins, tramadol increases the risk of attacks in patients with porphyria. Tramadol should not be administered together with inhibitors of the reuptake of serotonin and with tricyclic antidepressants because it may induce symptoms of the serotonin syndrome. The combination of tramadol with carbamazepine should also be avoided because it impairs its analgesic effect.

Codeine is a μ opioid receptor agonist the analgesic effect of which is about ten-fold weaker than morphine (I, A). Codeine is a prodrug; it shows an analgesic effect dependant on its transformation to morphine, which is catalysed by CYP2D6 enzyme and from other metabolites (mostly codeine-6-glucuronide). Due to its strong antitussive activity, it is considered a drug of choice in patients with moderate-intensity pain, who concomitantly have a cough. Constipation is a frequent side effect of codeine. Codeine is administered only orally as immediate-release tablets or as a solution. The analgesic effect starts after 15–30 minutes and lasts for about 4–6 hours ($T_{1/2}$ 3–4 hours). The maximal daily dose is 240 mg. Codeine is also available in combination with paracetamol and caffeine, with ASA, and with ibuprofen.

Dihydrocodeine (DHC) is a derivative of codeine. The potency ratio of DHC compared to oral doses of morphine is 5:1. The drug is mostly metabolised to DHC-6-glucuronide and to dihydromorphine. Its side effects are usually weaker compared to codeine. In contrast to codeine and tramadol the analgesic effects of DHC do not depend on the activity of the CYP2D6 enzyme. DHC is only available as controlled released tablets, which should be used every 12 hours. The maximal daily dose of DHC is 240 mg. DHC is recommended in patients with moderate intensity pain frequently with cough and dyspnoea.

A common propriety of the metabolism of codeine and tramadol is the dependence of the analgesic effect and of the side effects on the genetically conditioned activity of CYP2D6 enzyme as well as on renal excretion (the latter also concerns DHC). On the other hand, the analgesic effect and side effects of DHC do not depend on the activity of this enzyme. Step II of the WHO analgesic ladder includes the use of low doses of the "strong" opioids (morphine to 30 mg, oxycodone to 20 mg orally per day) instead of "weak" opioids [11].

Table 1. Opioids commonly used in the therapy of patients with cancer pain

Drug	Route of administration, formulation	Initial dosing, remarks	Duration of drug action (hours)
Tramadol	Oral: drops (40 drops = 100 mg, drops with dropper 1 dose = 5 drops), capsules 50 mg	Drops are especially useful during the titration period and in the therapy of the breakthrough pain; 5–20 drops (12.5–50 mg), every 4–6 hours; in the therapy of the breakthrough pain, usually 10–20 drops depending on the dose regularly administered to control the background pain	4–6
	Controlled release tablets and capsules 50, 100, 200 mg	Controlled release tablets or capsules 50–100 mg, every 12 hours	12
	Subcutaneous and intravenous: Tramadol hydrochloride — ampules 50 mg/1 ml, 100 mg/2 ml	Subcutaneous route: usually from 20–50 mg, every 4–6 hours Intravenous route: usually used on the ward or in the clinic, usually a dose of 50–100 mg in a slow infusion A maximal dose of tramadol equals 400 mg per day; a double (opioid and non-opioid) mechanism of analgesia, less frequent constipation compared to other opioids; at the beginning of therapy with tramadol a prophylactic administration of antiemetic drug (haloperidol or thiethylperazine) is recommended; analgesia and side effects (mostly concerning the opioid component) depend on the polymorphism of the CYP2D6 enzyme	4–6 4
Codeine	Oral: tablets 20 mg, water solution	Maximal dose of codeine is 240 mg per day; codeine is mostly a pro-drug: it is partially metabolised to morphine by the CYP2D6 enzyme; analgesia and side effects of codeine depend on the polymorphism of the CYP2D6 enzyme	4–6
Dihydro-codeine	Oral: controlled release tablets 60 and 90 mg	The initial dose is usually 2 × 60 mg, maximal dose of dihydrocodeine is 240 mg per day; analgesia and side effects of dihydrocodeine do not depend on the polymorphism of the CYP2D6 enzyme	12
Morphine	Oral: dividable tablets 20 mg, water solution	It is mostly dedicated to titrating the dose and to treating the breakthrough pain; opioid-naive patients about 2.5–5 mg, every 4–6 hours; patients with no effect of "weak" opioids about 5–10 mg, every 4–6 hours; in the therapy of the breakthrough pain usually 10–20% of daily morphine dose	4–6
	Controlled release tablets 10, 30, 60, 100, and 200 mg	Opioid-naive patients usually 10 mg, every 12 hours Patients with no effect of "weak" opioids usually 20–30 mg, every 12 hours	12
	Subcutaneous and intravenous: morphine sulphate ampules 20 mg/1 ml	Subcutaneous route: usually 2–3 mg, every 4–6 hours in opioid-naive patients, usually about 4–6 mg, every 4–6 hours in patients with no effect of "weak" opioids Intravenous route: usually 1–2 mg, every 4–6 hours in opioid-naive patients, usually about 3–5 mg, every 4–6 hours in patients with no effect of "weak" opioids If necessary, a drug dose may be increased and repeated every several minutes until the pain relief or to the sedation. Usually used on the ward or in an outpatient clinic in order to achieve a rapid analgesia	4–6 4

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Table 1 cont. Opioids commonly used in the therapy of patients with cancer pain

Drug	Route of administration, formulation	Initial dosing, remarks	Duration of drug action (hours)
Oxycodone	Oral: water solution 1 mg/1 ml (100 ml and 250 ml)	Dedicated mostly to titrate the dose and to treat the breakthrough pain; opioid-naive patients approximately 2.5–5 mg, every 4–6 hours; patient with no effect of "weak" opioids approx. 5–10 mg, every 4–6 hours; in the therapy of the breakthrough pain usually approx. 10–20% of the daily dose of oxycodone	4–6
	Oral: controlled release tablets 5, 10, 20, 40, 60, and 80 mg	Opioid-naive patients approximately 5–10 mg, every 12 hours Patient with no effect of "weak" opioids approx. 10–20 mg every 12 hours	12
	Subcutaneous and intravenous: Oxycodone hydrochloride ampules 10 mg/1 ml and 20 mg/2 ml	Subcutaneous route: usually 2–3 mg, every 4–6 hours in opioid-naive patients, mostly approx. 4–6 mg, every 4–6 hours and in patients with no effect of "weak" opioids Intravenous route: usually 1–2 mg, every 4–6 hours in opioid-naive patients, usually approx. 3–5 mg, every 4–6 hours in patients with no effect of "weak" opioids If necessary the dose may be increased and repeated every several minutes until the pain relief or to the sedation. Usually used on the ward or in the outpatient clinic in order to achieve a quick analgesia	4–6 4
Fentanyl	Transdermal: transdermal systems (patches) release: 12, 25, 50, 75, and 100 mcg/hour	Usually recommended in patients in whom the efficient dose had been previously established with use of "strong" opioids administered orally or parenterally — the initial dose of fentanyl should be individually defined, depending on the previous dose of the opioid; in selected cases, used in patients previously treated with "weak" opioids. Less frequently in opioid--naive patients — the initial dose is 12 mcg/hour; strict monitoring of patients is mandatory	72
	Transmucosal: intranasal, buccal, sublingual	Used in the management of the breakthrough pain in opioid-tolerant patients: those receiving the therapy of the background pain with at least 60 mg of morphine daily by an oral route or an equivalent daily dose of morphine administered by other routes or an equivalent daily dose of another opioid. Often, if there is no effect of immediate-release formulations of opioids (e.g. morphine, oxycodone) administered orally or through any other route; an individual titration from the lowest available dose of a particular product is always mandatory; no active metabolites, the drug is metabolised by the CYP3A4 enzyme	
Bupre-norphine	Transdermal: transdermal systems (patches) release 35, 52.5, and 70 mcg/hour	The initial dose usually equals 17.5 mcg/hour in opioid-naive patients and 35 mcg/hour in patients if no effect of "weak" opioids; maximal dose is 140 mcg/hour The metabolism of a drug mostly through the conjugation with glucuronic acid, it is mostly eliminated through the gastrointestinal tract, and it is preferred in the stable neuropathic pain and in elderly patients as well as in patients with impaired renal function	72–96
Oxycodone/ /naloxone	Oral: controlled release tablets 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/ /10 mg, 40 mg/20 mg	Opioid-naive patients 5 mg/2.5 mg–10 mg/5 mg, every 12 hours Patients with no effect of "weak" opioids 10 mg/5 mg–20 mg/10 mg, every 12 hours In the therapy of the breakthrough pain, usually about 10–20% of the daily dose of oxycodone Patients treated with "strong" opioids — a dose established individually with use of the equivalent dose conversion factors and titration The maximal dose of product is 2-times daily 80 mg/40 mg	12
Tapentdol	Oral: controlled release tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	Opioid-naive patients 50 mg, every 12 hours; patients with no effect of "weak" opioids 50–100 mg, every 12 hours A maximal dose of the drug is 2-times daily 250 mg	12
Methadone	Oral: syrup 1 mg/1 ml	Individual dosing; a drug is recommended in second- or third-line therapy if when other opioids are ineffective. Methadone should be used by palliative medicine specialists or physicians experienced in pain therapy Numerous drug interactions. Potential cardiotoxicity and hypoglycaemic effect especially with higher doses of the drug	Variable 8–24

WHO analgesic ladder step III opioids ("strong" opioids)

The WHO analgesic ladder step III opioids that have no ceiling effect are recommended in the therapy of a severe and very severe pain (NRS 7–10) [12]. Morphine, oxycodone, oxycodone/naloxone, fentanyl, buprenorphine, tapentadol, and methadone are available on the Polish market, while hydromorphone is not available in Poland. According to the recommendations of the European Association for Palliative Care (EAPC), morphine, oxycodone, and hydromorphone are first-line opioids in the therapy of moderate and severe pain intensity in caner patients (I, A). In the therapy of a chronic pain it is not recommended to use pethidine and pentazocine due to the toxic effects of their metabolites.

Morphine is a standard opioid recommended by the WHO and by the European Society of Medical Oncology (ESMO). The analgesic potential of other opioids is compared to that of morphine (I, A). Morphine is a pure opioid receptor agonist, mostly of type μ. The main metabolites are: morprhine-3-glucuronide and morphine-6-glucuronide. Morphine is a hydrophilic opioid used by choice in the therapy of pain in patients with dyspnoea [13]. Moderate liver impairment does not significantly influence the metabolism of the drug. Patients with impaired renal function require strict monitoring, dose reduction, prolongation of the intervals between consecutive drug doses, changing the administration route to parenteral, or rotation to another opioid, due to the reduced elimination of the morphine metabolites. Constipation may be a significant problem during therapy with morphine.

In the therapy of pain morphine is used by an oral route as immediate-release and controlled-release formulations as well as parenterally (subcutaneously, intravenously) and rarely intrathecally. The equivalent dose of a drug administered orally is three-fold higher than the parenteral dose due to lower absorption. The therapy is most frequently started from low doses, usually single dose 5 mg (patient previously not treated with "weak" opioids) or 10 mg (patients previously receiving "weak" opioids) administered every 4–6 hours (immediate-release tablets or less frequently water solution). The use of controlled-release morphine tablets is usually started from a dose of about 20–40 mg daily, fractionated every 12 hours. The type of the morphine formulation, its dose, and route of administration should be individually determined using the rule of dose titration to achieve a satisfactory analgesic effect and acceptable (for the patient) side effects (titration). During the therapy of the background pain with an oral controlled-release morphine formulation the therapy of the breakthrough pain usually involves immediate-release morphine products administered by an oral route. In patients who regularly receive a subcutaneous morphine formulation, a rescue dose of the drug is usually given in the same way. Concomitant use of morphine and benzodiazepines or other drugs that have a depressive influence on the CNS increase the risk of sedation, hypotony, and respiratory depression. Many drugs taken together with morphine, including anticholinergic drugs and serotonin receptor antagonists, intensify constipation

Oxycodone is a semisynthetic agonist of the μ and κ receptors (I, A). The parent compound as well as metabolites are mostly excreted by kidneys. That is why the drug should be used carefully in cases of renal impairment. Oxycodone is administered orally or parenterally (subcutaneously or intravenously). The equivalent dose ratio of morphine and oxycodone is 1.5–2:1 for the oral route. In the case of switch from the parenteral administration of oxycodone to the oral route, a 1:2 ratio should be applied, which means that the oral dose should be two times higher than the parenteral dose. Controlled release oxycodone tablets are administered every 12 hours. During the therapy of baseline pain with controlled-release oxycodone tablets, breakthrough pain episodes may be treated with immediate-release oxycodone and morphine oral formulations as well as rapid onset fentanyl transmucosal products.

Oxycodone/naloxone is a combination of oxycodone with naloxone in the proportion 2:1 in a single controlled-release tablet. The efficacy of this formulation in the therapy of chronic pain in cancer patients and with other diseases, as well as the concomitant improvement or prevention of opioid-induced constipation, have been shown in clinical trials [14]. The recommended daily dose of the formulation should not exceed 160 mg/80 mg and should be implemented gradually by titration. The contraindication for use of oxycodone/naloxone are typical as for all opioids. The drug should also be avoided in patients with severe liver impairment, portal vein circulation disturbances, renal failure, allergy, and diarrhea.

Fentanyl is a pure agonist of the opioid μ receptor. Its analgesic potential is about 100:1 compared to morphine. A significant lipophilicity of the drug is used in transdermal therapy. Fentanyl is metabolised by the CYP3A4 enzyme in the liver to the inactive norfentanyl and then excreted by kidneys in 90% as inactive metabolites. It is well tolerated by patients with moderate liver and renal insufficiency. The transdermal and intravenous use of fentanyl is relatively safe in the case of advanced chronic renal disease (grades 4–5) with glomerular filtration rate below 30 ml/min. In comparison to morphine, fentanyl has a weaker sedative effect, releases low amounts of histamine, and more rarely induces constipation.

Fentanyl is administered through transmucosal and parenteral routes. Fentanyl patches can be used transdermally, which are changed every 72 hours; however, the analgesic effect of the first patch occurs within 12 hours and a complete analgesic effect is reached after 2–5 changes of the patches (II, B). Transdermal fentanyl

Table 2. Fentanyl products used in the therapy of the episodes of the breakthrough pain

Selected pharmacokinetic parameters	Administration route			
	Sublingual (Vellofent)	Buccal (Effentora)	Intranasal (Instanyl)	Intranasal (PecFent)
Absolute bioavailability (%)	70	65	89	60
Time to maximal serum concentration (minutes)	50–90	47	9–15	15–21
Half-life (hours)	12	22	3–4	15–25
Onset of the analgesic effect (minutes)	5–10	10–15	5–7	5–10

patches are usually recommended in patients previously treated with other WHO pain ladder step III opioids and less frequently in patients who do not achieve efficient analgesia with the use of "weak" opioids. It is rarely recommended in opioid-naive patients. If fentanyl is administered to "strong" opioid-naïve patients, it is recommended to use the lowest therapeutic dose of the drug (12 mcg/hour) and to monitor carefully the clinical condition of the patients. Patients with elevated body temperature should be specially monitored due to the possibility of an extended release of the drug.

Breakthrough pain that occur during the therapy with transdermal fentanyl or with other opioids may be managed by rapid-onset fentanyl formulations administered intranasally or tablets delivered via buccal or sublingual route (Table 2). The basic rule for correct use of transmucosal fentanyl formulations is titration from the lowest available dose, which is mandatory at the beginning of the therapy of the breakthrough pain as well as at the change of the fentanyl product (e.g. from buccal formulation into an intranasal product or inversely, or of different intranasal products), after the change from the previously used, traditional opioids in the therapy of the breakthrough pain (e.g. of the short acting morphine or oxycodone products) and in cases of important changes of dosage of the opioid used to treat the background pain, e.g. rotation (switch) of the opioid. It should also be stressed that according to the Summary of Product Characteristics, the rapid-onset fentanyl formulations can only be recommended in opioid-tolerant patients (a daily oral morphine dose equals at least 60 mg or an equivalent morphine dose administered through a different route or equivalent dose of another opioid, used for at least seven days). During the therapy of the breakthrough pain with transdermal fentanyl, immediate-relase morphine may also be administered orally or through another route (subcutaneously, intravenously).

Buprenorphine is a partial agonist of the μ opioid receptors and an antagonist of the κ opioid receptor. The analgesic potency of the buprenorphine is about 75-fold higher than that of morphine. At therapeutic doses (up to 15 mg per day) buprenorphine acts as a pure agonist of the μ opioid receptors and shows no ceiling effect. The metabolites of this drug are excreted in 70–80% through the gastrointestinal tract and in a small percentage by the kidney. Buprenorphine is a safe opioid in patients with chronic renal disease and in dialysis patients. It is quickly reabsorbed through the buccal mucosa and is used in the form of sublingual tablets administered every 6–8 hours. Due to its lipophilicity, the drug is also used as transdermal patches changed every 72–96 hours (II, B). The analgesic effect of the first buprenorphine patch is observed within about 12 hours. During therapy of baseline pain with buprenorphine, brakthrough pain episodes should be managed with oral immediate-release or subcuteneous morphine products or by rapid-onset fentanyl formulations. Buprenorphine patches are the only "strong" opioids available as an Rp. prescription medicine in Poland (all other "strong" opioids are prescribed on special Rpw. receipts).

Tapentadol represents a new group of opioid analgesic drugs that have a double mechanism of action: they act as agonists of mu opioid receptors and inhibit the reuptake of the noradrenaline in the CNS. Due to its double mechanism of action, tapentadol is characterised by an analgesic effect typical for opioids and for the antidepressants that are inhibitors of the reuptake of the noradrenaline. As well as the efficient analgesia, also in patients with neuropathic pain, therapy with tapentadol is well tolerated due to the (limited in comparison with other opioids) side effects related to its interaction with the opioid receptors (especially important in the context of the negative impact on the gastrointestinal tract) and due to a low risk of interactions with other drugs (the drug is metabolised outside the cytochrome P-450 system) as well as due to its lower addictive potential.

Methadone is a synthetic agonist of the μ and κ opioid receptors, an antagonist of the NMDA receptors, and it increases the level of monoamines. Its analgesic potential compared to oral morphine equals about 4–12:1. Compared to morphine, methadone induces less intensive constipation, nausea, and vomiting. Methadone may be safely used in chronic renal insufficiency and in dialysis patients. Due to its complex pharmacokinetics and serious risk of drug interactions and of QT interval propongation, and the possibility of hypoglicaemia (especially at daily doses over 40 mg), it is recommended that the therapy with methadone should

be supervised by physician experienced in analgesic therapy. The drug is used as an oral syrup (concentration 1 mg/1 ml) every 8–12 hours, in single doses of 2.5–5 mg. It is recommended not to initially exceed the daily dose of about 10 mg of drug in patients previously untreated with other "strong" opioids. In patients who do not achieve a satisfactory analgesia or who experience severe side effects during the therapy with other opioids, the switch to methadone is suggested. Besides the therapy of chronic pain, methadone is also used to treat opioid addiction and abstinence syndromes.

Adverse effects of opioid analgesics

An individual distribution of the opioid receptors in each human may result in a different analgesic effect of opioids and of different toxicity profile and intensity. The most common side effect induced by opioids is opioid-induced constipation (OIC) and other symptoms of opioid-induced bowel dysfunction (OIBD). The prophylactic use of oral laxatives (osmotic — macrogol or lactulose — solo or in combination with irritants — senna derivatives or bisacodyl) and in some cases per rectum (e.g. glycerine suppositories) is usually necessary from the beginning of the therapy. Nausea and vomiting are less frequently observed side effects of opioid use — the therapy usually includes metoclopramide, haloperidol, and thiethylperazine. Other side effects of opioids are: sedation, dry mouth, balance dosorders, itch, excessive sweating, hallucinations, respiratory depression (occurs rarely and usually due to the inappropriate dosing of the opioid), urinary tract syndromes (urine retention), myoclonic jerks, and very rarely epileptic attack. In the case of occurrence of respiratory depression it is recommended that naloxone (1 ampule = 400 μg should be diluted in 10 ml of the 0.9% NaCl and then infused by 40–80 μg = 1–2 ml every 30–60 seconds until resolution of the opioid overdose symptoms) should be administered by an intravenous route.

In the case of occurrence of opioid side effects four therapeutic approaches are used: to decrease the dose of the opioid which is systemically administered, symptomatic treatment, change of the route of opioid administration, and rotation (switch) of opioids. The concept of opioid rotation means a change of the currently used opioid analgesic to another opioid. A switch of opioids enables the elimination of the metabolites, which may be important in patients treated with morphine, with deterioration of kidney functioning and dehydration. Also, if the therapy with one opioid is inefficient, the drug should be changed to another opioid. Due to incomplete cross tolerance, the equivalent doses of opioids should be carefully calculated. It is recommended that lower doses should be applied rather than the ones suggested in the tables of equivalent doses of opioids, which have limited usefulness in clinical practice. In each case, an individual single and daily opioid dose must be calculated for a particular patient and strict monitoring of the therapy during the period of the opioid dose titration is required. In the majority of patients, a switch of opioids improves the analgesic efficacy and decreases the intensity of the side effects. The combination of two step III opioids is currently quite frequent in clinical practice (e.g. morphine or oxycodone with fentanyl or with buprenorphine). This attitude is based on a slightly different binding of different opioids to the particular subtypes of opioid receptors and differences in physicochemical properties. Nevertheless, there are no univocal recommendations due to the small number of the clinical trials involving this issue [15].

Supportive drugs and adjuvant analgesics (co-analgesics)

Supportive drugs are recommended at every step of the WHO analgesic ladder. They may be divided into co-analgesics (adjuvant analgesics), which have an analgesic effect or which intensify the analgesic effect of analgesic drugs, and drugs that prevent or treat the side effects of opioids (laxatives, antiemetics). While the choice of analgesic is based mostly on pain intensity, a choice of adjuvant analgesic is mostly based on underlying pain pathomechnism. The analgesics are tailored to the intensity of pain. The adjuvant analgesics are adjusted to the pathomechanism of pain. The co-analgesics are especially useful in the therapy of pain with neuropathic and bone components (Table 3) [16]. **Antiepileptic drugs** are the most frequently used group of drugs (gabapentin and pregabalin), and rarely some older products: valproic acid, clonazepam, carbamazepine (I, A). Moreover, **antidepressant drugs** are also frequently used — serotonin and noradrenaline reuptake inhibitors (venlafaxine, duloxetine), and tricyclic antidepressants (amitriptyline, nortriptyline) (I, A). The other groups of drugs that are used to treat neuropathic pain involve drugs administered locally (lignocaine and capsaicin) (II, C) and systemically: NMDA receptor antagonists (ketamine ad dextromethorphan) (II, B). In bone pain NSAIDs are usually used (II, A) as well as bisphosphonates and denosumab and, due to frequent coexistence of neuropathic pain, antiepileptic drugs. Glucocorticosteroids are used in the therapy of neuropathic pain induced by pressure on the nerves, or in therapy of bone pain, especially when there are symptoms of involvement of the respiratory tract and dyspnoea, in liver tumors and in brain metastases. Careful dosing (titration) of adjuvant analgesics is recommended, which allows avoiding or at least limiting risk of toxicity that may be especially prevalent, when combining with opioids [17].

Non-pharmacological methods of pain management

In some cancer patients severe pain cannot be efficiently managed by pharmacological methods. In these patients some **non-pharmacological methods**

Table 3. The analgesic adjuvants commonly used in the therapy of patients with cancer pain

Group of drugs	Drug	Dosing, remarks	Duration of drug activity (hours)
Anticonvulsants	Gabapentin	Initially 2–3 × 100–200 mg, usually the dose is gradually increased up to 900–2400 mg per day, it is not recommended to exceed the daily dose of 3600 mg	8 9–12
	Pregabalin	Initially 2 × 75 mg, if necessary the dose may be gradually increased, maximal dose 2 × 300 mg. The drug is used in the therapy of the generalised anxiety	
Antidepressants	Duloxetine	The initial dose usually equals 1 × 60 mg, if necessary increased to 1 × 120 mg; the parallel use of CYP1A2 and CYP2D6 inhibitors and of the reversible MAO inhibitors is not recommended; may increase blood pressure. Cigarette smoking decreases the AUC by 50%	16–24
	Venlafaxine	Dosing of 1 × 75 mg, if necessary the dose may be increased to 1 × 150 mg. The therapy of neuropatic pain is off label. Metabolites by CYP2D6 to a main active metabolite O-desmethylvenlafaxine and by CYP3A4 to N-desmethylvenlafaxine. It has cardiotoxic activity when combined with sympathomimetics	12
	Amitriptyline	Initial dose is 1 × 25 mg, if necessary the dose may be gradually increased to 1 × 75 mg. Therapy of the neuropathic pain is off label. Metabolised by CYP2D6 to an active metabolite nortriptyline, which is characterised by a long and variable (20–100 hours) plasma half-life. It shows a strong antimuscarinic and antihistaminic effect as well as many side effects	24
Glucocorticosteroids	Dexamethasone	Dosing: usually 4–16 mg daily in 2 doses, the anti-inflammatory effect is used in the short-term therapy of bone pain and of pain induced by pressure to the nerve, many indications in urgent situations and in supportive therapy, as well as anticancer activity in some tumors	36

are used: **radiotherapy, surgery, physiotherapy, and psychotherapy**. For bone pain, radiotherapy is highly efficient. It results in improvement or even in complete resolution of pain in 60–80% of treated patients and the analgesic effect persists for many months. In some patients surgical procedures are applied: orthopaedic surgery, surgical immobilisation — stabilisation, vertebroplasties — in case of the pathologic fractures of the vertebral bodies, peripheral nerves and autonomic plexus blockades, sympathetic plexus blocks, and intrathecal (subarachnoid or epidural) analgesics administration. Due to the complex aetiology of pain and the existence of total pain, many patients require psychotherapy and social and spiritual support.

Interventional methods of pain management

Advances in pharmacology, especially the introduction of many opioids and adjuvant analgesics, has resulted in a significant decrease of the use of the interventional methods in recent years (currently estimated at 5–10% of patients). A localised, limited pain resistant to pharmacotherapy or occurrence of intractable side effects of the pharmacotherapy constitutes the main indication for the use of interventional methods [18]. **Neurodestructive procedures** may also be used in the early phase of the disease (especially the celiac plexus block — II, B or the upper hypogastric plexus block — II, C) before the occurrence of tumor-induced, significant anatomical deformations. *The interventional methods should not be considered as step IV of the WHO analgesic ladder, but they should be performed adequately early, when the patient starts to have pain complaints. This approach allows significantly limit the need of combination pharmacotherapy and/or delay the need of its implementation.*

Another logical argument for using these methods is the possibility of a direct intervention to the area where pain is generated. Performed early, in some case only one blockade, it may prevent the development of a potential pain syndrome (phantom pain after amputation of a limb/breast, pain after thoracotomy/mastectomy). The blockades are especially effective in the pain syndromes modulated by the hyperactivation of the sympathetic system. Neuropathic pain constitutes a classical example of pain that may depend on the sympathetic system. It occurs in 5–8% of the general population and in more

than 30% of cancer patients. That is why the blockades constitute an important element of therapy of this type of pain. Another possible use of interventional techniques is the injection of the drugs (opioids, clonidine, baclofen, and corticosteroids) to the local area of the structures involved in the neoplastic process (intraarticular or to the epidural space) [19]. In cancer patients a positive effect of the continuous epidural (II, C) or subarachnoid (II, B) blockade is observed, especially in neuropathic and bone pain, and sometimes also in inflammatory pain due to the reduction of paraspinal cord oedema.

The blockades are also used as an important diagnostic-prognostic method. A positive but short-lasting effect of the blockade may confirm the indication for a neurodestructive procedure. In cancer patients, all potentially positive as well as potential side effects of the proposed therapeutic method should be carefully considered. Every application of the interventional techniques is associated with a risk of complications and side effects. Permanent impairment of the nerve structures, especially of the peripheral nerve, may result in distressing cosequences such as paraesthesia, numbness, or motoric deficit. That is why the patient must be informed about the potential complications and side effects before performing the procedure. A patient must also sign an informed consent form for this procedure. A neurodestructive procedure may be proceeded by a diagnostic-therapeutic blockade with use of local anaesthetic dugs (LAD). This approach helps to define the source of pain and its mechanism, and it also 'shows' the patients the advantages and disadvantages of the planned block/thermolysis. We should not forget that the LAD has a stronger effect than the neurodestructive measure. Moreover, the patient is exposed to the same procedure two times. That is why the performance of a diagnostic blockade should always be carefully considered.

The neurodestructive procedures may be done with use of the physical, chemical or mechanical factors. The physical factors that injure the neural filaments are low (cryolysis) and high temperature (thermolysis), and hypo- and hyperosmotic solutions. The chemical factors that injure the neural filaments involve ethanol, phenol, and glycerol. The mechanical factor is a surgical intersection.

The neurodestructive mechanism of a chemical substance that has neurolytic activity is based on induction of so-called Wallerian degeneration of the nerve fibers, which results in disintegration of proteins and lipids in the axons as well as in some changes in the myelin sheaths. The increased pressure of the fluids inside the nerve fiber impairs the blood circulation in the blood vessels supplying a given nerve. In a short period of time after the destruction of the nerve structures a regeneration process is induced, the duration of which depends on the extension of the neurodestruction. Usually a nerve fiber is regenerated by 1 mm per day. The drug should be injected to the area of the nerve without causing any damage to the nerve structure.

Ethyl alcohol is the oldest and the most frequently used neurolytic agent. It has a low toxicity. Ethanol is used at concentration of 50–100% (usually 65%). Alcohol-induced neurolysis is quick and persists for about 5–7 months. The factors that limit the use of alcohol include its quick diffusion in the tissues, which requires the use of high volumes, which in turn impedes the achievement of a space-limited neurolytic effect. Moreover, during the injection of the alcohol, a patient may feel pain or develop alcohol-induced neuritis. The irritating effect of alcohol onto the tissues may be minimalised by using 65% alcohol in combination with LAD. Irrigation of the needle with 1–2 ml of 0.9% NaCl or with lignocaine may also be helpful. Incidental administration of alcohol into the tissues may induce local neuralgia.

Phenol solubility in water is very poor. Only a concentration of 6–7% can be achieved at room temperature. However, it dissolves well in glycerol and a higher concentration of phenol (10–15%) may be achieved with use of this solvent. An advantage of using a solution of phenol in glycerol is the slow release of phenol, which assures a better neurolytic effect. A high density of glycerol is a disadvantage because it is difficult to inject this solution through a long, thin needle. The effect of phenol administration is biphasic: a local anaesthetic effect appears several seconds after the injection and abates in several to a dozen hours. A proper neurolytic effect develops slowly over a period of two weeks. Phenol has a neurolytic effect in the concentration over 5%. The total dose should not exceed 600–800 mg. The most important disadvantage of phenol is its toxicity. Incidentally, intravenously administered phenol may cause the patient's death due to acute renal failure. The period of the neurolytic activity of phenol is difficult to predict, usually lasts 2–4 months.

Glycerol has an analgesic effect, but in contrast to alcohol and phenol it does not totally abolish the sensation of touch. Alcohol- and glycerol-induced touch disorders are poorly tolerated by many patients. The mechanism of glycerol activity are unclear. It probably mostly interacts with the pathological changes, myelinated axial fibres. Another disadvantage of glycerol is its high velocity, which impedes the injection.

In clinical practice neurodestructive procedures are mostly applied to the sympathetic nerves or plexus, to the sensory fibres of the spine, and selectively to mixed nerves [20]. The most common uses of blockades and blocks in cancer patients are presented in Table 4.

Summary

Achievement of the optimal analgesic effect in cancer patients requires a complex clinical evaluation of the pain, with a detailed analysis of its pathomechanism, intensity, and time pattern of pain complains

Table 4. The use of blockades and of blocks in cancer patients

Type of pain	Blockade/block/thermolysis	Commentary
I. Somatic pain		
Muscular-facial	Trigger-points blockades, muscles and their fascia injections, peripheral nerves blockades (e.g. suprascapular nerve, intercostal nerves)	Technically very easy method, safe, worth to try and to propagate
Bone-articular	Blockades of the intravertebral and interapophyseal joints	Technically difficult procedure, demands experience, a blockade may give a long-lasting effect
II. Visceral pain		
Induced by cancer	Stellate ganglion or (C7-Th3) Coeliac plexus Superior hypogastric plexus Lumbar part of the sympathetic trunk	Technically difficult procedure, demands experience, the methods are efficient; however, supportive therapy and the monitoring of the position of the end of the needle by RTG or USG imaging are necessary.
Colicky	Epidural blockade of the lumbar section	Alternative to systemically administered opioids
Myocardial infarct	Blockade of the stellate ganglion, epidural blockade of the thoracic section (Th1–Th4)	Good analgesic effect, decreases blood pressure in the pulmonary artery
III. Vascular pain	Stellate ganglion or C7-Th3 Lumbar section of the sympathetic trunk	Effect depends on the clinical stage of the disease, highly effective in pain at rest
IV. Neuropathic pain		
A complex regional pain syndrome	Stellate ganglion Th2 Lumbar section of the sympathetic trunk Segmental intravenous sympathectomy	A therapy by choice in the early phase
Pancoast syndrome	Stellate ganglion Epidural blockade of the cervical segment	Alternative in case of an ineffective pharmacotherapy of neuropathic pain
Neuralgias of the cranial nerves	Blockades of the peripheral branches of the cranial nerves Blockade of the Gasser's ganglion Blockade of the pterygopalatine ganglion	Technically uncomplicated procedure, efficient in the early phase of the disease Technically difficult procedure, demands the monitoring of the position of the end of the needle by RTG or USG imaging
Postherpetic neuralgia (PHN)	Blockades of the sympathetic system	Efficient during the first 6 months from the onset of the disease
Radiculopathies	Epidural blockade Paravertebral blockades with addition of steroid	Efficient in the acute phase of the disease
Stump pain	Trigger points blockade	Technically simple procedures, demand at least two stimulations; a therapy by choice in the early phase of the disease
Phantom pain	Blockades of the sympathetic system	Demands the monitoring of the position of the end of the needle by RTG or USG imaging

(background and breakthrough-episodic pain). The evaluation of pain should also include other symptoms, comorbidities, and psychological, social, and spiritual dimensions, which may influence patients' suffering and the occurrence of total pain. Local and systemic cancer therapy is also important because it may induce or increase the pain induced by cancer or by any other diseases. Implementation of the recommended therapy, which involves the mechanism of pain, time pattern, and intensity of pain, increases the efficacy and significantly shortens the time necessary to achieve an effective analgesia. It also decreases the intensity and the frequency of occurrence of opioid-induced side effects. In cancer patients and in different types of chronic pain a standard management should be based on the algorithm of the WHO analgesic ladder. Individualisation of the pain therapy is recommended depending on the patient's clinical situation. The efficient management of other

cancer-induced symptoms should also be assured. Palliative and supportive care significantly improve well-being of cancer patients, may prolong overall survival time, and positively influence the quality of life of patients and their caregivers.

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