INDEX COPERNICUS INTERNATIONAL

ORIGINAL ARTICLE

Pharmacotherapy of pain in cancer patients – recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons

Jerzy Wordliczek[1,2], Aleksandra Kotlińska-Lemieszek[3], Wojciech Leppert[3], Jarosław Woroń[2,4], Jan Dobrogowski[5], Małgorzata Krajnik[6], Anna Przeklasa-Muszyńska[5], Jacek Jassem[7], Jarosław Drobnik[8], Anna Wrzosek[1,2], Marcin Janecki[9], Jadwiga Pyszkowska[10], Magdalena Kocot-Kępska[5], Renata Zajączkowska[1,2], Iwona Filipczak-Bryniarska[11], Krystyna Boczar[12], Joanna Jakowicka-Wordliczek[2], Małgorzata Malec-Milewska[13], Andrzej Kübler[14], Marek Suchorzewski[15], Sylwester Mordarski[16], Adam Dziki[17], Krzysztof Paśnik[18]

[1]Department of Interdisciplinary Intensive Care, Jagiellonian University Medical College, Kraków
[2]Clinical Department of Anesthesiology and Intensive Care, University Hospital in Kraków
[3]Department and Clinic of Palliative Medicine, Poznań University of Medical Sciences, Poznań
[4]Department of Clinical Pharmacology, Chair of Pharmacology, Jagiellonian University Medical College, Kraków
[5]Department for Pain Research and Treatment, Chair of Anesthesiology, Jagiellonian University Medical College, Kraków
[6]Department and Chair of Palliative Care, Nicolaus Copernicus University Medical College, Bydgoszcz
[7]Department and Clinic of Oncology and Radiotherapy, Medical University of Gdańsk
[8]Department and Clinic of Palliative Medicine, Wrocław Medical University, Wrocław
[9]Department of Palliative Medicine and Care, Chair of Nursing, Faculty of Health Sciences, Medical University of Silesia, Katowice
[10]Prof. Kornel Gibiński University Medical Center, Medical University of Silesia, Katowice
[11]Department for Pain Treatment and Palliative Care, Chair of Internal Medicine and Gerontology, Jagiellonian University Medical College, Kraków
[12]Chronic Pain Clinic, Independent Public Healthcare Institution, Tychy
[13]Department of Anesthesiology and Intensive Care, Post-Graduate Medical Education Centre, Warsaw
[14]Pain Therapy and Palliative Care Center, University Clinical Hospital, Wrocław
[15]Department of Anesthesiology and Intensive Care, University Clinical Center, Gdańsk
[16]Department of Anesthesiology and Intensive Care, Pain Therapy Clinic, Wrocław Medical University, Wrocław
[17]Department of General and Colorectal Surgery, Medical University of Łódź
[18]Department of General, Oncological, and Thoracic Surgery, Central Clinical Hospital of the Ministry of National Defense, Military Institute of Medicine, Warsaw

Article history: Received: 10.06.2018 Accepted: 10.08.2018 Published: 31.10.2018

ABSTRACT: Guidelines for the pharmacotherapy of pain in cancer patients were developed by a group of 21 experts of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons. During a series of meetings, the experts carried out an overview of the available literature on the treatment of pain in cancer patients, paying particular attention to systematic reviews and more recent randomized studies not included in the reviews. The search was performed in the EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials databases using such keywords as "pain", "cancer", "pharmacotherapy", "analgesics", and similar. The overviewed articles included studies of pathomechanisms of pain in cancer patients, methods for the assessment of pain in cancer patients, and drugs used in the pharmacotherapy of pain in cancer patients, including non-opioid analgesics (paracetamol, metamizole, non-steroidal anti-inflammatory drugs), opioids (strong and weak), coanalgesics (glucocorticosteroids, α2-adrenergic receptor agonists, NMDA receptor antagonists, antidepressants, anticonvulsants, topical medications) as well as drugs used to reduce the adverse effects of the analgesic treatment and symptoms other than pain in patients subjected to opioid treatment. The principles of opioid rotation and the management of patients with opioidophobia were discussed and recommendations for the management of opioid-induced hyperalgesia were presented. Drugs used in different types of pain experienced by cancer patients, including neuropathic pain, visceral pain, bone pain, and breakthrough pain, were included in the overview. Most common interactions of drugs used in the pharmacotherapy of pain in cancer patients as well as the principles for the management of crisis situations. In the final part of the recommendations, the issues of pain and care in dying patients are discussed. Recommendations are addressed to physicians of different specialties involved in the diagnostics and treatment of cancer in their daily practice. It is the hope of the experts who took part in the development of these recommendations that the recommendations would become helpful in everyday medical practice and thus contribute to the improvement in the quality of care and the efficacy of pain treatment in this group of patients.

KEYWORDS: pharmacotherapy, pain, cancer patients pain, recommendations, oncology, palliative medicine, anesthesiology, adverse effects, drug interactions

Pain is a symptom commonly experienced by cancer patients and posing a significant clinical challenge at every stage of the disease. Pain may be the first symptom of the disease; it may also be present during the diagnostic period, anticancer and symptomatic treatment, as well as in advanced disease. Pain is also experienced during emission in patients "cured" of the cancer with significant consequences, usually due to the causal treatment received [20].

The incidence of pain depends on the stage of the disease and a broad range of estimates is provided in individual literature studies due to the lack of unambiguous and standardized pain definitions and measurement methods. For example, the incidence of pain in patient undergoing oncological treatment, having undergone oncological treatment, and patients with advanced cancer is estimated at: 44–73% (mean 59%), 21–46% (mean 33%) and 58–69% (mean 64%), respectively. The incidence of pain experienced by patients at all disease stages ranges between 43 and 63% (mean 53%).

Differences in the incidence and intensity of pain are also due to the differences in patient populations included in the studies (patients treated in outpatient, inpatient, and hospice settings). According to the World Health Organization (WHO) guidelines, pain therapy should allow to achieve analgesic success in 70–90% of cancer patients [47].

As shown in a 2016 meta-analysis of 117 reports on pain in cancer, this goal is still a distant one, as pain persisted in 39.3% of patients after radical treatment, 55% of patients in the course of cancer treatment, and 66.4% at the advanced stage of the disease. Moderate to severe pain (NRS>5) was reported by 38% of patients [183].

International analyses suggest that in recent years, the percentage of patients receiving insufficient analgesic treatment has been reduced globally by about 25% [58]. However, too many patients still receive inappropriate treatment [36, 163, 178].

This publication, developed by a group of experts of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy, and Association of Polish Surgeons includes the guidelines on the pharmacotherapy of pain in cancer patients.

Pharmacotherapy is a basic method for the treatment of pain in this group of patients, and the management is ruled by a set of general guidelines [19, 122, 150, 194, 195]:

1. The analgesic agent and its dose should be selected individually for each patient and type of pain.

2. Analgesic serum drug levels and continued analgesic effect should be maintained by administration of subsequent doses at regular intervals depending on the drug's pharmacokinetic and pharmacodynamic properties. This means that it is wrong to administer analgesic agents only "in case of pain" (excluding the treatment of break-through pain episodes).

3. If the treatment is inefficient, the analgesic agent is switched to a stronger one according to the WHO analgesic ladder.

4. Pharmacotherapy of pain is supplemented by the use of analgesic adjuvants (coanalgesics).

5. If possible, oral administration route should have the priority, although each route of administration ensuring efficient analgesia and accepted by the patient is considered acceptable.

6. Careful monitoring of the treatment is required.

The treatment of pain and alleviation of physical as well as emotional, social, and spiritual suffering ("total" pain) is an integral part of the management of cancer patients, particularly patients with advanced disease. Each patient has the right to expect efficient pain therapy including pharmacological and non-pharmacological treatment methods.

The latter provides a significant support and frequently increases the efficacy of pharmacotherapy. This is particularly true for palliative radiological treatment, especially radiotherapy and systemic treatment, particularly hormone therapy, chemotherapy, immunotherapy, and molecular therapy. Interventional methods for the treatment of pain (nerve blocks, neurodestructive procedures), physiotherapy, occupational therapy and psychotherapy are also important. Pharmacotherapy of pain in cancer patients is presented in Algorithm 1.

CAUSES OF PAIN IN CANCER PATIENTS

Pain experienced by cancer patients is the result of complex pathological processes involving molecular, tissue, and systemic changes caused by proliferating tumor tissue, changes associated with progressive, debilitating disease such as bed sores, oral mucositis, candidiasis, muscle contractures, herpetic neuralgia, anticancer treatment and concomitant disorders not related to cancer.

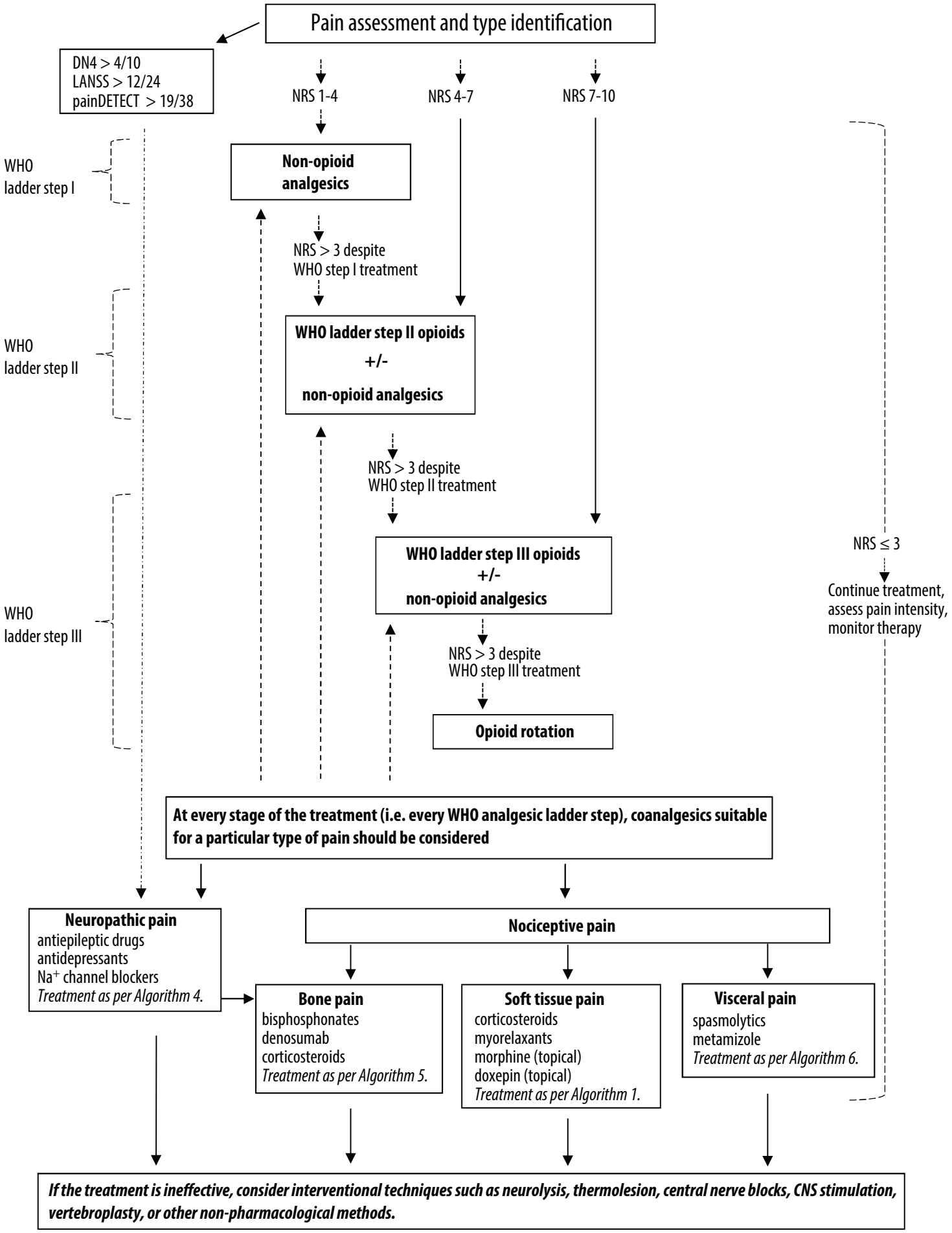
Pain experienced by cancer patients is frequently of a mixed type rather than a "pure", nociceptive (somatic, visceral) or neuropathic pain syndrome. Pain is usually a complex phenomenon resulting from concurrent activity of various mechanisms such as inflammatory, neuropathic, or ischemic mechanisms.

It is also frequently experienced in several locations. Identification of all these factors is very important due to the therapeutic implications and available options for effective treatment [92, 133, 183, 193]. Main causes of pain in cancer patients are presented in Fig. 1.

METHODOLOGY

The guidelines were developed on the basis of the review of available medical literature on the pharmacotherapy of pain in cancer patients. Most recent systematic reviews and randomized studies not included in these reviews or not falling within the scope of available reviews were identified. To this end, EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials databases were queried using the following keywords:

pain, cancer, pharmacotherapy, analgesics and derived terms (in English). In addition, a review was made of the available English and Polish language monographs on the treatment of pain in cancer patients. Guidelines were adapted to Polish conditions, i.e. to the availability of individual drugs as well as binding organizational and legal frameworks.



Algorithm 1. Pharmacotherapy of pain in cancer patients.

PAIN ASSESSMENT

Clinical assessment of pain is of key importance for effective pain therapy. It includes determination of the location and radiation of pain, the nature (quality) of pain, its intensity, alleviating and exacerbating factors, efficacy and tolerance of previous treatment, or presence of break-through pains, facilitating identification of the pathomechanism (type) of pain. Another important element of pain assessment is the assessment of the emotional component. Basic neurological examination facilitates identification of concomitant dysesthesias. Break-through pains require separate assessment, as does the baseline pain.

Currently, most guidelines recommend the use of the numeric rating scale (NRS) with 0 indicating no pain and 10 indicating the worst imaginable pain. Usually, scores in the range of 1–3 (up to 4) are indicative of mild pain, scores of 4–6 (up to 7) are indicative of moderate pain, scores of 7–8 are indicative of severe pain and scores of 9–10 are indicative of extreme pain [17, 126]. The NRS is the standard tool for the assessment of pain intensity and the monitoring of the efficacy of pain treatment [23, 69, 70]. It is believed that the NRS intensity of pain in a patient receiving efficient pain therapy should be ≤ 3.

The NRS scale is much more sensitive than any verbal scale; although verbal scales may be useful in everyday clinical practice, they are not suitable for statistical comparison purposes and are therefore not recommended for comparisons of different types of pain treatment [23]. The NRS scale is presented in Fig. 2.

Chronic pain discomfort may also be assessed using tools involving qualitative assessment of pain and its impact on patient's activity along with the standard assessment of the intensity of pain. Most commonly used tools in this group include Brief Pain Inventory – Short Form, McGill Pain Questionnaire, Pain Assessment Sheet and Doloplus scale. Patients with neuropathic pain component experience various sensory symptoms coexisting in various combinations; therefore, examination should involve the assessment of touch, pin-prick, pressure, low and high temperatures, vibrations, and temporal summation of these aspects. In recent years, several scales (screening tools) were developed which significantly facilitate identification of neuropathic pain and implementation of appropriate treatment. For example, if the DN4 (Douleur Neuropathique 4 Questions) score is > 4/10, the nature of pain is mainly neuropathic. In painDETECT and LANSS scales, presence of neuropathic component is indicated by the score of > 19/38 and ≥ 12/24, respectively [176]. The need for continuous monitoring of pain therapy and other symptoms throughout the treatment period should be highlighted.

PHARMACOTHERAPY OF PAIN

NON-OPIOID ANALGESICS (NOAs)

In cancer patients, non-opioid analgesics are recommended when the pain intensity does not exceed 4 points in the NRS scale. NOAs may be used in monotherapy; at higher pain intensities, there should be components of multimodal analgesia to broaden the spectrum of the analgesic effect of other painkillers and to reduce the total dose of opioid analgesics.

Non-steroidal anti-inflammatory drugs are effective in every type of nociceptive pain. Paracetamol is less efficient in the treatment of nociceptive pain with an inflammatory component due to the lack of inflammatory activity. Metamizole is additionally characterized by spasmolytic effect ensuring its efficacy in colic-type treatment [51].

Additive analgesic effect is observed for combinations of NSAIDs with paracetamol and/or metamizole.

Intramuscular and rectal administration of non-opioid analgesics is not recommended due to the pain/discomfort for the patient, long latency of analgesia and variable profile of the analgesic effect. Analgesic ceilings were determined for all non-opioid analgesics. Above these values, no increase in analgesic effect is observed while the risk of adverse effects increases significantly.

Maximum daily doses of non-opioid analgesics are as follows:

- metamizole: up to 5 g;
- paracetamol: do not exceed 15 mg/kg per oral or intravenous dose. Dose may be repeated at most 4 times in one day (up to 4 g/d)

Combinations of tramadol with dexketoprofen and paracetamol are also available in the pharmaceutical market. Both combinations take advantage of hyperadditive synergy between analgesic components. On the other hand, additive effects are observed for combinations containing ibuprofen and paracetamol [18, 37, 51, 57, 189].

OPIOIDS OF THE SECOND STEP OF THE WHO ANALGESIC LADDER

Opioids of the second step of the WHO analgesic ladder are used most frequently in patients with moderate pain (NRS 4–6) refractory to the drugs of the first step of the WHO analgesic ladder. They are used as single agents or in combination with non-opioid analgesics. Exceeding recommended maximum doses usually does not lead to additional analgesic effect (analgesic ceiling) while potentially increasing adverse effects [150].

In Poland, three drugs are available, including tramadol, codeine, and dihydrocodeine (DHC).

According to the guidelines of the European Association for Palliative Care (EPAC), the second step of the WHO analgesic ladder may also include low doses of third-step analgesics: morphine up to 30 mg/d, oxycodone up to 20 mg/d, hydromorphon up to 4 mg/d, all administered via the oral route [19].

Tramadol

It is the most commonly used opioid of the second step of the WHO analgesic ladder; its analgesic effect is about 5–10 times weaker than that of morphine [93]. Tramadol has a dual analgesic mechanism: besides interacting with opioid receptors (mainly μ-receptors) within the CNS, it activates the anterograde antinociceptive system by inhibiting noradrenalin and serotonin reuptake. Most common adverse effects of tramadol include nausea and hyperhidrosis, observed particularly early in the treatment. A benefit of

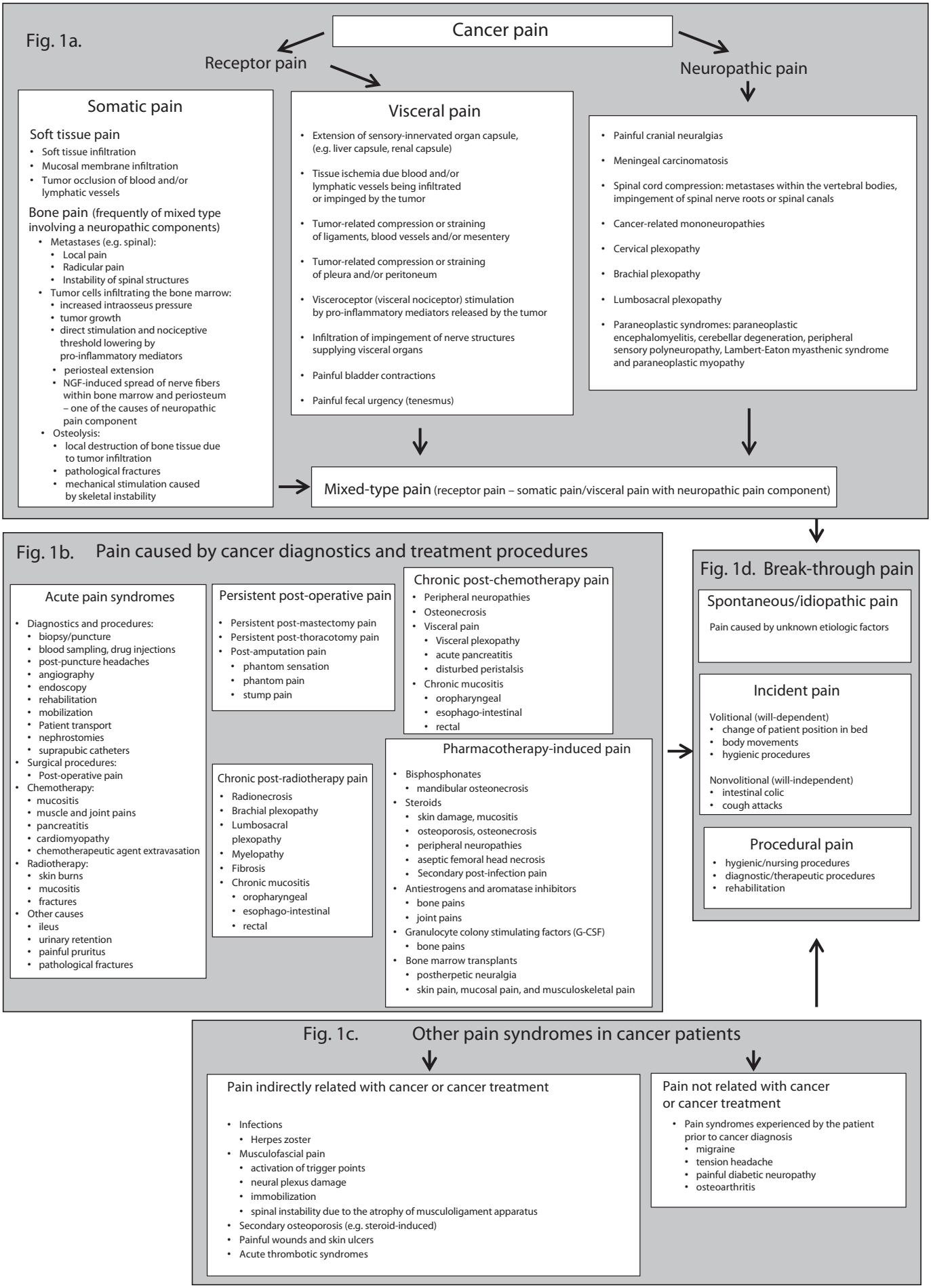


Fig. 1. Causes of pain in cancer patients.

Tab. I. Recommended NSAID daily doses in cancer patients.

DRUG	DAILY DOSE
Dexketoprofen	150 mg – parenteral use; 75 mg – oral use
Ketoprofen	200 mg
Ibuprofen	2400 mg
Naproxene	1000 mg
Nimesulide	200 mg
Diclofenac	150 mg

tramadol consists in its lower adverse impact on gastrointestinal motility and lower incidence of constipation as compared to codeine, dihydrocodeine, and opioids of the third step of the WHO analgesic ladder [93]. It should be highlighted that:

- Due to the extended half-life of tramadol and its active metabolite (M1), it is recommended that patients with renal and hepatic insufficiency receive lower doses of the drug at longer intervals or are switched to another opioid.
- Tramadol is not recommended in patients with the history of epilepsy due to the increased risk of seizures.
- Tramadol should not be used in combination with SSRI or TCA antidepressants as it might lead to serotonin syndrome.
- Simultaneous use of carmabazepine is not recommended as it reduces the analgesic effect of tramadol.

Codeine

Codeine is an agonist of the μ-opioid receptor, its analgesic effect being about 10 times lower than that of morphine. Codeine is a prodrug; its analgesic efficacy depends on its being transformed into morphine. In patients with rapid codeine to morphine metabolism, the analgesic effect of codeine may be accompanied by intense adverse effects (significant risk of respiratory depression as a result of "morphine explosion") [53]. The highest risk of adverse effects of codeine is observed in children and young individuals [65]. Due to its strong antitussive properties, codeine is recommended in patients with moderate pain and concomitant cough. Constipation and increased risk of nausea and vomiting are frequent side effects of codeine [172].

Dihydrocodeine

Dihydrocodeine (DHC) is a derivative of codeine. The strength ratio of oral DHC to oral morphine is about 1:3 [94]. DHC should be considered in patients with moderate pain and accompanying cough and shortness of breath. Equivalent single sustained release doses of tramadol and DHC are 100 mg and 60 mg, respectively [91].

OPIOIDS OF THE THIRD STEP OF THE WHO ANALGESIC LADDER

Opioids of the third step of the WHO analgesic ladder III include morphine, oxycodone, hydromorphon (unavailable in Poland), oxycodone/naloxone, fentanyl, buprenorphine, tapentadol, and methadone.

According to the European Association for Palliative Care (EAPC) and European Society for Medical Oncology (ESMO) guidelines, morphine, oxycodone, and hydromorphon are the first choice of opioids for the treatment of moderate to severe pain in cancer patients [19, 27, 132, 150].

Most frequently, treatment with step III opioids is started:

- After discontinuation of step II analgesics failing to ensure effective analgesia;
- As a continuation of low-dose morphine and oxycodone treatment as part of the WHO step II treatment.

Opioid titration, i.e. gradual increase of doses is recommended until satisfactory analgesic effect and patient-acceptable adverse effect profile is achieved.

Morphine

A pure agonist of opioid receptors (mainly μ-opioid receptors), the standard opioid drug recommended by WHO, ESMO, EAPC, and National Institute of Clinical Excellence (NICE), used as a reference for the comparison of analgesic strength of other opioids [19, 125, 150, 194]. Morphine is recommended in patients suffering from pain and shortness of breath as it is the opioid of choice in the symptomatic treatment of shortness of breath [10]. Moderate liver damage has no significant impact on the metabolism of the drug. In patients with renal dysfunction, a switch to another, "renal safe" opioid (buprenorphine, methadone, fentanyl) should be performed due to the reduced elimination of morphine metabolites; alternatively, the administration route should be changed to parenteral one. Morphine in pain treatment is administered via the oral route as immediate and modified release forms, via parenteral routes (subcutaneous, intravenous, less frequently intrathecal-epidural, subarachnoid) or, sometimes, topically (in the treatment of pain caused by chemo- or radiotherapy-induced skin ulceration or mucositis) [81, 184, 190, 202]. The equivalent oral dose is about 3 times higher than subcutaneous or intravenous dose. Titration of morphine doses is usually performed using oral immediate release formulations (particularly in "unstable" pains due to the possibility of faster assessment of outcomes and selection of appropriate drug dose) or controlled release formulations,

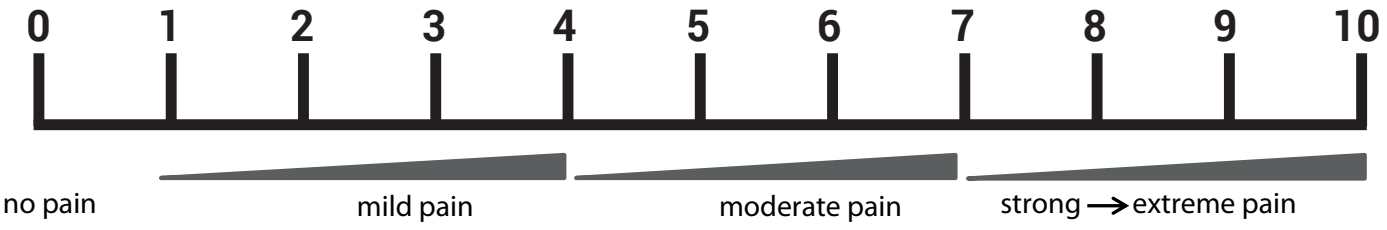


Fig. 2. Numeric rating scale (NRS).

Tab. II. Opioids of the second step of the who analgesic ladder.

DRUG	ADMINISTRATION ROUTE, FORMULATION	DOSAGE, COMMENTS	EFFECT DURATION (HOURS)
Tramadol	Oral: drops (40 drops = 100 mg), drops with dispenser (1 dose = 5 drops), capsules 50 mg	Drops are particularly useful for dose titration and treatment of break-through pain: 5–30 drops (= 12.5–75 mg) every 4–6 h. One additional single dose (= 10–20% of daily dose) in the treatment of break-through pain.	4–6
	Extended release tablets 50, 100, 200 mg	Primary pain treatment: extended release tablets 50–200 mg every 12 hours One additional single dose (= 10–20% of daily dose, usually 10–20 drops, depending on regular dose) in the treatment of break-through pain. Parenteral vs. oral administration dosage calculation ratio is 1:1.	12
	Subcutaneous and intravenous: tramadol hydrochloride 50 mg/1 ml, 100 mg/2 ml	Subcutaneous route: usually 20–75 mg every 4–6 h. Intravenous route: usually used in inpatient/one-day setting. Most common dose 50–100 mg in slow infusion. Maximum daily dose of tramadol is 400 mg. Double (opioid and non-opioid) mechanism of analgesic activity, reduced incidence of constipation compared to codeine and dihydrocodeine. When initiating tramadol treatment, inclusion of antiemetic prophylaxis is also recommended.	4–6
Codeine:	Oral: Codeine phosphate active substance for preparation of aqueous solution and other formulations, e.g. 2.0/100.0 (2%)	Initial dose 10–30 mg every 4–6 h. One additional single dose (10–20% of daily dose) in the treatment of break-through pain. Maximum daily dose of codeine is 240 mg..	4–6
	Combination products containing paracetamol	Codeine is largely a prodrug, being partially metabolized into morphine by CYP2D6.	
Dihydrocodeine	Oral: Modified release tablets 60 and 90 mg	The usual initial dose is 2 x 60 mg; maximum daily dose of dihydrocodeine is 240 mg. Codeine doses corresponding to 10–20% of daily dose may be used in the treatment of break-through pain. Analgesia and side effects are independent of CYP2D6 polymorphism.	12

always with the immediate release formulation being available for "rescue" use (usually at doses corresponding to 10–20% of daily dose of morphine) [125, 179]. In patients with very strong pain, optimum management consists in titration of morphine administered via parenteral, subcutaneous, or intravenous route. Morphine may also be administered subcutaneously in patients with swallowing disorders; other routes include intravenous, epidural, subarachnoid as well as topical administration [44].

Some patients consider it necessary to reduce the morphine dose determined by the titration method, particularly in weak and cachectic patients. However, it should be highlighted that morphine is the most hydrophilic of all opioid drugs. This has a significant impact on its dosage as the most important efficacy-determining parameter upon chronic use of morphine is the area under the blood drug concentration vs. time curve (AUC). Cachectic patients are characterized by reduced volume of distribution (Vd) within the adipose tissue which requires a reduction in the doses of lipophilic drugs (e.g. fentanyl). At the same time, hypoalbuminemia and edemas present in cachectic patients may increase the Vd of hydrophilic drugs to reduce their levels and cause secondary AUC reduction. This means that reduced morphine doses in patients with increased Vd may significantly reduce the efficacy of the drug.

Oxycodone

A semi-synthetic agonist of μ- and κ-opioid receptors administered via the oral or parenteral route (subcutaneous or intravenous). In the light of current knowledge, oxycodone, like morphine, may be used as the first-line drug for the treatment of moderate to strong pain in cancer patients [158]. No significant differences are observed in the incidence of most adverse effects of oxycodone and morphine [15, 148, 158, 199]. However, some clinical studies showed that somnolence, hallucinations and intense myoclonies were less frequent in patients receiving oxycodone as compared to those receiving morphine [27, 99]. It is suggested that oxycodone's ability to interact with κ-opioid receptors prevalent within the visceral area may determine the higher efficacy of the drug in the treatment of visceral pain being observed in comparison to other opioids [131]. Clinical studies have also demonstrated the efficacy of oxycodone in the treatment of neuropathic pain component in cancer patients [52, 129, 50] as well as bone pain in the same population [61, 165]. Oxycodone and its metabolites are mainly subject to renal elimination and thus caution should be exercised when using the drug in patients with renal impairment. The equivalence coefficient for oral morphine and oral oxycodone ranges from 1.5:1 to 2:1 [179]. When switching from oral to parenteral oxycodone, the equivalence coefficient is 1:2 which means that the oral dose is twice higher than the parenteral dose. When oxycodone is used as the primary drug, break-through pains may be treated with oxycodone or morphine in immediate release formulations or with transdermal fentanyl formulations.

Oxycodone/naloxone

Oxycodone/naloxone combines oxycodone with another opioid receptor agonist, naloxone, in a 2:1 ratio, in a single controlled-release tablet. In clinical studies, the drug was shown to be efficient in the treatment of chronic pain in patients with cancer and other disorders while simultaneously leading to an improvement of preventing opioid-induced bowel dysfunction [2, 3, 4]. The drug maintains the desired effects of oxycodone. Naloxone blocks the

Oral morphine (p.o.) treatment may be started using:

- Immediate release formulations (IR tablets or aqueous solution),
- Modified/sustained release formulations (SR tablets).

In patients naïve to WHO ladder step II opioids:

- Start with 2.5–5 of IR morphine every 4 hours (dose before sleep to be increased by 50%) or with 10 mg of SR morphine every 12 hours.
- Prescribe antiemetic drug (to be used during the first 5–7 days of opioid treatment) + laxative(s).

In patients previously treated with WHO ladder step II opioids:

- Start with 5–10 of IR morphine every 4 hours (dose before sleep to be increased by 50%) or with 20–30 mg of SR morphine every 12 hours.
- In case of elderly patients, patients with poor performance status, dehydration, or cachexia, treatment should be started using the dose recommended for patients naïve to WHO ladder step II opioids.
- In elderly patients, intervals between doses should be increased – morphine IR to be administered every 6-8 hours.
- Increasing the evening dose by 50% should ensure analgesic effect lasting until next morning (eliminating the need of waking the patient to receive a dose in the night).
- Prescribe an interventional dose of IR morphine corresponding to 10-20% of daily dose.
- Prescribe antiemetic drug (to be used during the first 5–7 days of opioid treatment) + laxative(s).
- Oral morphine should be avoided in patients with impaired renal function – replace oral morphine with parenteral morphine or another opioid, such as buprenorphine, fentanyl, or methadone (Table IV).

In patients previously treated with WHO ladder step III opioids:

- Use opioid rotation – start with a dose calculated using equivalence coefficients, e.g. 1:1.5 to convert oral dose of oxycodone to oral dose of morphine or 1:2 to convert oral dose of oxycodone to the subcutaneous dose of morphine (Table V).
- Remember that the highest the converted dose, the more cautious should be the drug switching proceedings: most frequently, the initial dose of the new opioid should be 25–75% of the calculated dose, with optimum total dose being subsequently titrated (gradually increased until optimum analgesia is obtained) on the basis of the observed results and number of interventional doses.
- Continue administration of laxatives (if required).
- Oral morphine should be avoided in patients with impaired renal function – replace oral morphine with parenteral* morphine or another opioid, such as buprenorphine, fentanyl, or methadone (Table IV).

NOTE: patients may receive interventional treatment with morphine as an immediate release formulation (usually corresponding to 10–20% of daily dose), usually not more frequently than once every 4 hours, or with transmucosal fentanyl provided that they have received ≥ 60 mg of oral morphine/day or an equivalent daily dose of another opioid analgesic for ≥ 7 days (starting from the lowest dose of 50-100 µg as per the pharmacokinetic profile of particular formulation.

Monitor the treatment – assess the outcome

If the outcome is satisfactory continue the treatment.

If the patient received IR morphine, switching to SR formulations may be considered (provided there are no contraindications such as ileostomy).

If pain control is insufficient and the patient received > 2 interventional doses per day, the regular morphine should be increased by the total of interventional doses (corresponding to 30–50% of the previous regular dose).

- **If the interventional dose is insufficient,** increase the dose (usually by 50%) and assess the efficacy of the new dose.
- If the interventional dose is efficient but causing excessive somnolence, reduce the dose (usually by 30–50%).

Monitor the treatment – reassess the effect after 1–2 days

If the outcome is satisfactory continue the treatment.

If pain control is insufficient:

- Reassess pain intensity;
- Increase the regular opioid dose by the sum of interventional doses (usually by 30–50%) unless patient experiences adverse effects;
- Consider changing the opioid drug, adding another opioid and/or adding a coanalgesic.

Algorithm 2. Analgesic treatment of cancer patients using oral morphine.

Tab. III. Characteristics of available transmucosal fentanyl formulations [29, 108, 118, 201].

FORMULATION	TIME UNTIL ANALGESIC EFFECT (MIN.)	BIOAVAILABILITY (%)	TIME UNTIL PEAK BLOOD CONCENTRATION (MIN.)	HALF-LIFE (HOURS)
FBT	15	65	35–45	2,6–12
SLF	10–15	70	30–60	5–10
INFS	5–10	80–90	12–15	elimination time 3–4
FPNS	5–10	60	19–21	15–25

FBT – buccal tablets; SLF – sublingual tablets; INFS – intranasal aqueous solution; FPNS – intranasal pectin solution.

activity of oxycodone in the intestinal wall. The recommended daily dose should not exceed 160 mg/80 mg [179]. Due to the presence of naloxone, contraindications include significant hepatic impairment and portal circulation disorders, renal impairment, allergies to product ingredients, and diarrhea.

Fentanyl

A pure agonist of μ-opioid receptors characterized by analgesic strength 100 times higher than that of morphine. Due to its significant lipophilicity, the drug may be administered by transdermal and transmucosal routes. Fentanyl is metabolized in the liver to inactive norfenantyl for subsequent renal elimination as inactive metabolites (> 90% of the starting dose). It is well tolerated by patients with moderate hepatic or renal impairment. Fentanyl may be administered via subcutaneous and intravenous route in patients with advanced (stage 4–5) chronic kidney disease with GFR of < 30 ml/min [40]. Compared to morphine, constipation is less commonly observed during fentanyl use [60]. In the treatment of pain, fentanyl is administered via transdermal, transmucosal, and parenteral routes.

Transdermal therapeutic systems are usually applied every 72 hours with close monitoring. Since analgesic effect is observed 12 hours after first application, efficient analgesia is required during this period and should be provided by other analgesic drugs. Full analgesic efficacy is achieved after 1–2 transdermal system changes.

It is convenient to perform the first application in the morning so as to facilitate patient monitoring and reduce the risk of nocturnal overdose. Transdermal systems should not be changed to higher-dose systems more frequently than after application of 1-2 patches. For fentanyl, which binds mainly to the receptors present within the CNS, more frequent modifications may involve increased risk of adverse effects.

Excessive sweating may disturb drug absorption and application of transdermal systems whereas fever and other situations involving vasodilation (use of thermophores, warm compresses, hot tubs) increase the absorption of fentanyl and the risk of adverse effects and drug overdose [42, 85, 161, 167, 179]. The transdermal systems (patches) with fentanyl may contain trace amounts of ferrite elements, and thus the physician should inform the patient to remove the patch before MRI procedures and reapply it once the scan is completed [46].

In cachectic patients (lacking appropriate amounts of adipose tissue), variable fentanyl levels and clinical outcomes may be observed following transdermal system application [66, 173]. Patients with low albumin levels are at risk of toxic effects due to elevated levels of the free fentanyl fraction [11].

Transmucosal fentanyl formulations in the treatment of break-through pains

Transmucosal fentanyl formulations are used in patients who experience break-through pains despite treatment with WHO ladder step III opioids [179]. The most important principle of the treatment with transmucosal fentanyl formulations for rapid analgesic onset is the titration of the dose starting from the lowest available dose until efficient analgesia is achieved with acceptable adverse effects (Table III). Formulation choice should depend on the clinical situation, patient's preference, and pharmacokinetic profile of the drug matching the characteristics of break-through pain:

- Intranasal formulations of fentanyl are recommended in cases of rapid-onset, short-lasting pain.
- Buccal or subnlingual formulations are indicated for rapid-onset and longer-lasting pain episodes.
- Oral immediate release opioids are recommended for slow-onset, longer-lasting pain episodes.

Buprenorphine

A partial agonist of μ-opioid receptors and agonist of κ-opioid receptors, presenting with an analgesic effect about 75 times stronger than that of morphine. In line with current recommendations, maximum dose of transdermal buprenorphine should not exceed 140 μg/h. Drug metabolites are excreted in 70–80% via the gastrointestinal tract; low quantities are eliminated by the kidneys. Buprenorphine is recommended in patients with chronic renal insufficiency and hemodialyzed patient [120, 179]. Due to its high lipophilicity, the drug is administered from transdermal patches applied on the skin every 72–96 hours. The analgesic effect of the first buprenorphine patch is observed after about 12–24 hours. Due to the long time to pharmacokinetic equilibrium, the first dose may be increased (if necessary after 72–96 hours as per the relevant summary of product characteristics.

Buprenorphine is sometimes used as sublingual tablets (usually every 6–8 hours in the treatment of baseline pain and on a per need basis in the treatment of break-through pain in selected patients). During transdermal buprenorphine therapy, breakthrough pain is usually treated using immediate release oral morphine or oxycodone, sublingual buprenorphine or transmucosal fentanyl in fast-acting formulations [90, 110, 112, 159, 160, 181].

Tapentadol

An analgesic characterized by a complex mechanism of action: an agonist of μ-opioid receptor and selective noradrenalin reuptake inhibitor within the central nervous system (CNS). Analgesic strength of tapentadol is about three times lower than that

Oral oxycodone (p.o.) treatment may be started using:
- Immediate release formulations (1 mg/1 ml oral solution),
- Sustained release formulations (SR tablets).

In patients naïve to WHO ladder step II opioids:
- Start with 2.5–5 of IR oxycodone every 4 hours (dose before sleep to be increased by 50%) or with 5 mg of SR oxycodone every 12 hours.
- Prescribe antiemetic drug (to be used during the first 5–7 days of opioid treatment) + laxative(s).

In patients previously treated with WHO ladder step II opioids:
- 5 mg every 4–6 hours or 10 mg every 12 as SR formulation,
- In case of elderly patients, patients with poor performance status, dehydration, or cachexia, treatment should be started using the dose recommended for patients naïve to WHO ladder step II opioids.
- Prescribe an interventional dose of oxycodone corresponding to 10–20% of daily dose or an equivalent dose of morphine (dose increased by 50% relative to the oxycodone dose),
- Prescribe antiemetic drug (to be used during the first 5–7 days of opioid treatment) + laxative(s).
- In patients with impaired renal function: start with the dose recommended for patients recommended for patients naïve to WHO ladder step II opioids. Use with caution and monitor the outcomes or consider switching the drug to another opioid, e.g. buprenorphine, fentanyl, or methadone (Table IV).

In patients previously treated with WHO ladder step III opioids:
- Use opioid rotation – start with a dose calculated using equivalence coefficients, e.g. 1.5:1 to convert oral dose of morphine to oral dose of oxycodone or 2:1 to convert subcutaneous dose of morphine to oral dose of oxycodone (Table V).
- Remember that the highest the converted dose, the more cautious should be the drug switching proceedings: most frequently, the initial dose of the new opioid should be 25–75% of the calculated dose, with optimum total dose being subsequently titrated (gradually increased until optimum analgesia and an acceptable adverse effects profile is obtained) on the basis of the observed results and number of interventional doses.
- Continue administration of laxatives (if required).
- In patients with impaired renal function: use with caution and monitor the outcomes or consider switching the drug to another opioid, e.g. buprenorphine, fentanyl, or methadone (Table IV).

NOTE: patients may receive interventional treatment with morphine or oxycodone as an immediate release formulation (usually corresponding to 10-20% of daily dose), or with transmucosal fentanyl provided that they have received ≥ 40 mg of oral oxycodone /day or an equivalent daily dose of another opioid analgesic for ≥ 7 days (starting from the lowest dose of 50-100 µg as per the pharmacokinetic profile of particular formulation.

Monitor the treatment – assess the outcome

If the outcome is satisfactory:
- Continue the treatment.
- If the patient received IR oxycodone, switching to SR formulations may be considered (provided there are no contraindications such as ileostomy).

If pain control is insufficient and the patient received > 2 interventional doses per day, the regular oxycodone should be increased by the total of interventional doses (corresponding to 3050% of the previous regular dose).
Adjust the interventional dose of oxycodone simultaneously.
If the interventional dose is insufficient, increase the dose (usually by 50%) and assess the efficacy of the new dose.
If the interventional dose is efficient but causing excessive somnolence, reduce the dose (usually by 3050%).

Monitor the treatment – reassess the effect after 1–2 days

If the outcome is satisfactory continue the treatment.

If pain control is insufficient:
- Reassess pain intensity;
- Increase the regular opioid dose by the sum of interventional doses (usually by 30–50%) unless patient experiences adverse effects;
- Consider changing the opioid drug, adding another opioid and/or adding a coanalgesic.

Algorithm 3. Analgesic treatment of cancer patients using oral oxycodone.

Tab. IV. Opioid analgesic of WHO III analgesic ladder step III.

ADMINISTRATION ROUTE, FORMULATION	STARTING DOSE, COMMENTS
MORPHINE Oral: Immediate release formulations: 20 mg divisible tablets, morphine hydrochloride aqueous solution (usually 0.5–1%)	Intended mainly for dose titration and break-through pain treatment. Opioid-naïve patients: 2.5–5 mg every 4 hours. WHO ladder step II-refractory patients: 5–10 mg every 4 hours Patients with cachexia and/or elderly patients: start with the dose recommended for WHO ladder step II-naïve patients. Treatment of break-through pain: usually 10–20% of daily morphine dose (with individual dosage adjustments).
Extended/controlled release tablets 10, 30, 60, 100, and 200 mg	Opioid-naïve patients: usually from 10 mg every 12 hours. WHO ladder step II-refractory patients: usually 20–30 mg every 12 hours. SR formulations are sometimes used at 8-hour intervals when high fluctuations in the levels of analgesia and the intensity of adverse effects (somnolence) are observed for b.i.d. dosage.
Subcutaneous and intravenous: morphine sulfate ampoules 10 and 20 mg/1 ml	Subcutaneous route: continuous subcutaneous infusion or divided doses administered usually every 4 hours; usually, 1/3 to 1/2 of the morphine dose is administered orally. Intravenous route is used usually in patients with central or peripheral venous ports in an inpatient setting. Usually: 1/3 of the daily dose (of morphine administered as continuous i.v. infusion compared to oral morphine); Doses determined in a titration procedure; Used also as for emergency titration aimed at quick analgesia (boluses of e.g. 1–2 mg every 10 minutes until pain reduction or adverse eUsed also as for emergency titration aimed at quick analgesia (boluses of e.g. 1–2 mg every 10 minutes until pain reduction or adverse effects become evident). Example titration of parenteral morphine: 1. Morphine 1–2 mg i.v. every 5–10 min or 2–5 mg s.c. every 10–20 min until effective analgesia or development of adverse effects (somnolence); 2. Record the total dose of morphine administered; 3. Then, use: a. the titrated (effective) dose every 4 hours as s.c. or i.v. Injections; of course, calculated dose may have to be adjusted due to inter-individual differences; b. continuous (i.v. or s.c.) infusion; infusion rate should be adjusted so as to administer the recorded dose over 4–6 hours. The choice of appropriate dose depends on the individual; in addition, the treatment requires strict monitoring and naloxone being available at hand. In patients with significant impairment of peripheral perfusion (e.g. dehydration, shock, hypothermia), absorption of drugs administered via the subcutaneous route may be delayed; when perfusion improves, morphine "deposited" within the subcutaneous tissue may be absorbed rapidly to cause adverse effects. In addition, significant impairment of peripheral circulation in end-of-life patients subcutaneous opioids may no longer be effective and the administration route may need to be changed to i.v. administration.
OOXYCODONE Oral: 1 mg/1 ml oral solution (100 and 250 ml)	Intended mainly for dose titration and break-through pain treatment. Opioid-naïve patients: start from 2.5–5 mg of aqueous oxycodone solution every 4–6 hours. WHO ladder step II-refractory patients: 5 mg every 4–6 hours. Patients with cachexia and/or elderly patients: start with the dose recommended for WHO ladder step II-naïve patients.
extended/controlled release tablets 5, 10, 20, 40, and 80 mg	Treatment of break-through pain: usually 10–20% of daily oxycodone dose (individual dosage adjustments required). Patients naïve to low-strength opioids: start from 5 mg every 12 hours. Low-strength opioids-refractory patients: start from 10 mg every 12 hours (patients with cachexia, elderly patients, patients with mild impairment of hepatic or renal function: start from 5 mg every 12 hours).
Subcutaneous and intravenous route: Oxycodone hydrochloride ampoules 10 mg/1 ml and 20 mg/2 ml	Subcutaneous and intravenous route: Ca. two-fold reduction in daily dose compared to oral oxycodone
OXYCODONE/NALOXONE Oral: 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg extended release tablets	Opioid-naïve patients: - from 5 mg/2.5 mg every 12 hours. Low-strength opioids-refractory patients: e.g. from 10 mg/5 mg every 12 hours. Patients treated with other high-strength opioids: dose to be determined individually using equivalence coefficients and titrations. In opioid-naïve patients: · Start with 5 mg of oxycodone /2.5 mg of naloxone every 12 hours; · In elderly patients, patients with renal impairment, advanced disease, and poor performance status: start with 5 mg of oxycodone/2.5 mg of naloxone every 12 hours' · Monitor the outcomes for another two days, then reassess the outcome (until satisfactory); · Maximum recommended daily dose of oxycodone/naloxone combination (as determined by titration) is 160 mg of oxycodone/80 mg of naloxone; although this does not mean that larger doses should not be used, upper clearance limit may be achieved for oral naloxone. Oxycodone/naloxone combination may be used with other step III opioids, including oxycodone. Patients previously treated with morphine or another opioid: · start with a dose calculated using equivalence coefficients, e.g. 1:1.5 to convert oral dose of oxycodone to oral dose of morphine. Adhere to opioid titration rules as described for other strong opioids. Oxycodone/naloxone is contraindicated in patients with moderate to severe hepatic impairment and/or severe renal impairment.
FENTANYL Transdermal: Transdermal systems with release rates of 12.5, 25, 50, 75, and 100 µg/h.	Recommended in patients following previous determination of opioid demand usually using an oral opioid. In low-strength opioid-refractory patients, fentanyl may be started from the dose of 12.5 µg/h. The dose of 12.5 µg/h may also be recommended in selected opioid-naïve patients on the condition of treatment being strictly monitored.
Transmucosal formulations administered by intranasal, buccal, and sublingual routes in the treatment of break-through pain	These formulations are used in the treatment of break-through pains in patients who had continuously received an equivalent of at least 60 mg of oral morphine per day over at least 7 days. Individual dose titration is required, starting from the lowest dose of a particular fentanyl formulation.

Tab. IV. Opioid analgesic of WHO III analgesic ladder step III.

ADMINISTRATION ROUTE, FORMULATION	STARTING DOSE, COMMENTS
BUPRENORPHINE Transdermal: transdermal systems with release rates of 35, 52.5, and 70 µg/h.	The usual initial dose is 17.5–35 µg/h or is adequately calculated when switching from another high-strength opioid. Maximum dose is 140 µg/h.
Sublingual: sublingual tablets (0.2 mg, 0.4 mg)	Used at the dose of 0.2–0.4 mg administered regularly every 6–8 hour up to the maximum daily dose of 2.4 mg/day, and interventionally in the treatment of break-through pain.
TAPENTADOL Oral: extended release tablets 50, 100, 150, 200, and 250 mg	Low-strength opioids-refractory patients: usually from 50 mg every 12 hours. When switching from another strong opioid, dose should be determined individually. Maximum dose is 250 mg twice a day (total daily doses greater than 500 mg were not studied and are not recommended).
METHADONE Syrup (1 mg/ml)	Individual dosage. The drug is recommended as a second or third line treatment in patients refractory to other WHO ladder step III opioids. Methadone treatment should be initiated by a palliative medicine specialist or physician with experience in the medicine of pain.
HYDROMORPHONE (unavailable in Poland) Oral: immediate release tablets: 2 or 4 mg; sustained-release tablets: 2, 4, 8, 16, 24 mg	The starting dose is 4 mg/d; dose may be increased every 2 days.

of morphine and about five times lower than that of oxycodone (when administered via the oral route) [162, 179]. Besides effective analgesia, particularly in patients with neuropathic pain, tapentadol is characterized by good tolerance due to the limited (as compared to other opioids) adverse effects related to interactions with opioid receptors (particularly as regards negative impact on gastrointestinal system function) and low risk of interactions with other drugs (metabolism not involving the cytochrome P450 enzyme system) [21, 83, 154].

Methadone

Synthetic agonist of µ- and δ-opioid receptors, an antagonist of NMDA receptor. Its strength ratio relative to oral morphine ranges from 4:1 to 12:1. In patients treated with high doses of WHO step III opioids, caution and lower methadone doses are recommended due to the stronger analgesic effect of the product. Methadone may be used safely in chronic renal insufficiency and in hemodialyzed patients [120, 149]. Due to its complex pharmacokinetic profile, significant risk of interactions with other drugs, and QT segment elongation, methadone should be used by physicians with experience in pain therapy [6, 75, 82, 146].

Hydromorphon (unavailable in Poland)

A semi-synthetic opioid, a ketone analog of morphine. It is a strong analog of µ-opioid receptor with no effect on κ- and δ-opioid receptors. Compared to morphine, it is 3–5 and 8.5 times stronger when administered by oral and parenteral route, respectively. It is assumed that a 2 mg dose of hydromorphon corresponds to ca. 10 mg of oral morphine. Following subcutaneous administration, analgesic effect is usually achieved within 15 minutes and maintained over about 4–5 hours. Following oral administration, analgesic effect is achieved within 30 minutes. Hydromorphon may be an efficient alternative to morphine in the treatment of pain. Due to its higher solubility in water, doses may be administered in lower volumes. Hydromorphon may be administered by oral, parenteral, and rectal routes. A metabolite of hydromorphon, hydromorphon-3-glucuronide is neurotoxic and may be accumulated in patients with renal insufficiency [9, 138, 187].

Concluding highlights:

- WHO ladder step III opioids are the first choice of drugs for the treatment of strong pain in cancer patients. Morphine and oxycodone are particularly preferred.
- Oxycodone or oxycodone/naloxone is recommended as the first line of treatment of cancer pain including a visceral component.
- Oxycodone or tapentadol are recommended in the treatment of cancer pain including a neuropathic component.
- Combinations of WHO ladder step II and III opioids is not recommended.
- Buprenorphine is recommended as the first line of opioid treatment of cancer pain in patients with renal insufficiency, renal and hepatic insufficiency, as well as elderly patients.
- Buprenorphine or methadone are recommended in the first line of treatment of cancer pain with diagnosis or history of opioid dependence.

Transdermal opioid formulations are not recommended in patients with fever (a strong recommendation). Patients experiencing fever while treated with transdermal opioid should be carefully monitored due to the risk of drug absorption being increased at high body temperatures or the transdermal patch being detached upon extensive sweating.

- Additional opioid doses are recommended in patients undergoing additional painful procedures.
- Prophylactic administration of antiemetics is recommended when starting opioid therapy.

A comment to Table IV: According to the EAPC guidelines for the choice of the first WHO step III opioid: There are no significant differences between morphine, oxycodone, and hydromorphon.

Transdermal fentanyl and buprenorphine are an alternative for oral opioids; they are particularly recommended in patients unable to receive medications via the oral route.

ROTATION (SWITCHING) OF OPIOIDS

Rotation (switching) of opioids means that the opioid drug is switched to another one so as to improve the analgesic effect and/or the tolerance of treatment's adverse effects [35]. Three main management routes may be considered in such cases, including a change in the administration route, concomitant use of 2 or more opioids, and opioid rotation (switching). The first of these methods involves the administration route of the opioid drug being switched from oral to subcutaneous (in home care setting) or intravenous and, less frequently, intrathecal (the two latter routes are used in an inpatient setting). In most cases, opioids are delivered via the aforementioned routes as continuous infusions [113].

Opioid rotation is based on the assumption of different analgesic effects if individual opioids being due to the differences in their affinities to receptors, lipophilicity, ability to permeate through tissue barriers, pharmacokinetic parameters, and incomplete cross-tolerance. This means that when no effect is achieved using a particular drug, one may expect an improvement following the use of another opioid. This also pertains to the tolerance of the treatment in relation to its adverse effects [185]. Calculation coefficients are also important when changing the administration route.

For example:

60 mg of morphine p.o. = 20 mg of morphine s.c. = 40 mg of oxycodone p.o. = 25 μg/h of fentanyl = 35 μg/h of buprenorphine

One should keep in mind that when administering a new, hitherto not used opioid drug (to which no tolerance was developed by the patient), the calculated dose should be reduced by 25–75%. In patients with peripheral edemas and/or ascites, morphine doses should not be translated to other lipophilic opioids since the high dose of morphine may be due to the large volume of distribution [5].

Opioid rotation may be performed [104, 117]:

- Immediately/on a one-time basis, e.g. after toxic effects of an opioid drug are experienced by the patient. The drug causing the adverse effect should be replaced by a new opioid analgesic;
- Gradually, with the dose of the first opioid being reduced by 1/3 and the difference being replaced by the new drug (3-step rotation). The latter method may be safer and batter tolerated.

An example of opioid rotation may be the switch from hydrophilic opioids (morphine or oxycodone) to oxycodone/naloxone, tapentadol, transdermal opioids (fentanyl, buprenorphine) and methadone. Drugs replacing hydrophilic opioids have a significantly lower negative impact on the gastrointestinal system due to the presence of naloxone (oxycodone, naloxone), are characterized by a double mechanism of analgesic activity (tapentadol), or have different physicochemical properties (significant central and slight peripheral effect of fentanyl, buprenorphine, and methadone) [119].

In most patients, opioid rotation improves analgesic efficacy and reduces the intensity of adverse effects. The efficacy of opioid rotation with regard to the improvement of analgesia and treatment tolerance is estimated to be in the range of 60–80% [106]. Currently, it is a more common practice to administer two or, less commonly, more step III opioids (e.g. morphine or oxycodone with fentanyl or buprenorphine).

Tab. V. Equianalgesic doses of opioid analgesics.

OPIOID DRUG	ORAL DOSE EQUIANALGESIC TO ORAL MORPHINE 10 MG
Morphine	10 mg
Codeine	90 mg
Dihydrocodeine	60 mg
Tramadol	50 mg
Oxycodone	7.5 mg
Hydromorphon	2 mg
Oxymorphone	1.5 mg
Methadone	1 mg
Fentanyl	0.1 mg
Buprenorphine	0.13 mg
Tapentadol	25–30 mg

Simultaneous use of two opioids usually facilitates more efficient analgesia being achieved with lower doses; however, it mat also increase the risk of adverse effects and interactions between individual opioids as well as between opioids and other drugs. This approach, frequently used in practice, has been poorly documented in clinical trials [77].

Most common combinations include morphine with fentanyl or buprenorphine or various opioids with low doses of methadone added in cases of insufficient anesthesia [145].

There is no rationale for simultaneous use of WHO step II and III opioids [179].

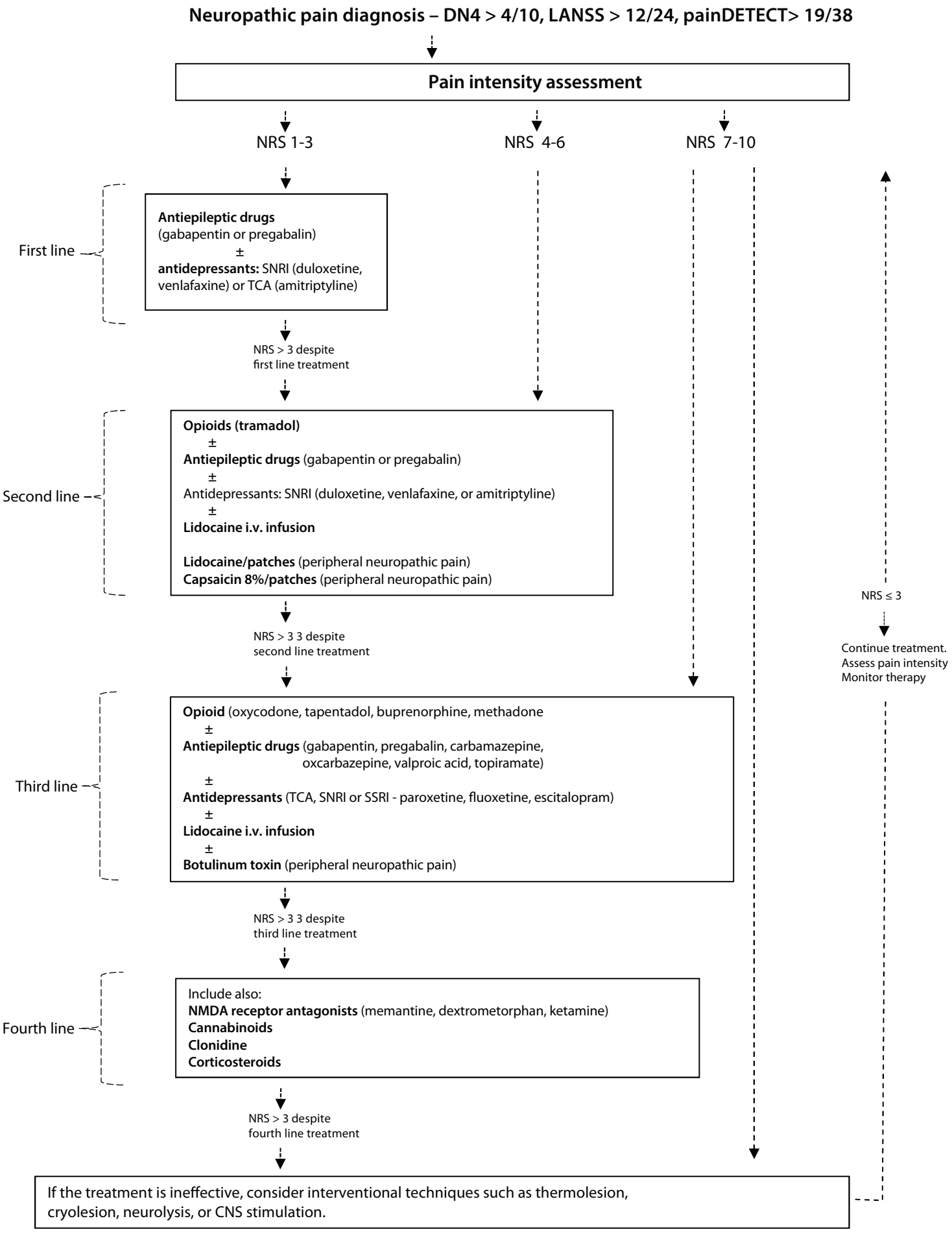
OPIOID-INDUCED HYPERALGESIA

Opioid-induced hyperalgesia is defined as a paradoxical reaction to the administered opioid drugs consisting in that sequential , increasing doses of drug lead to intensification of pain and lower the pain threshold to the level of stimuli usually unable to trigger pain sensations [41, 98, 101, 156].

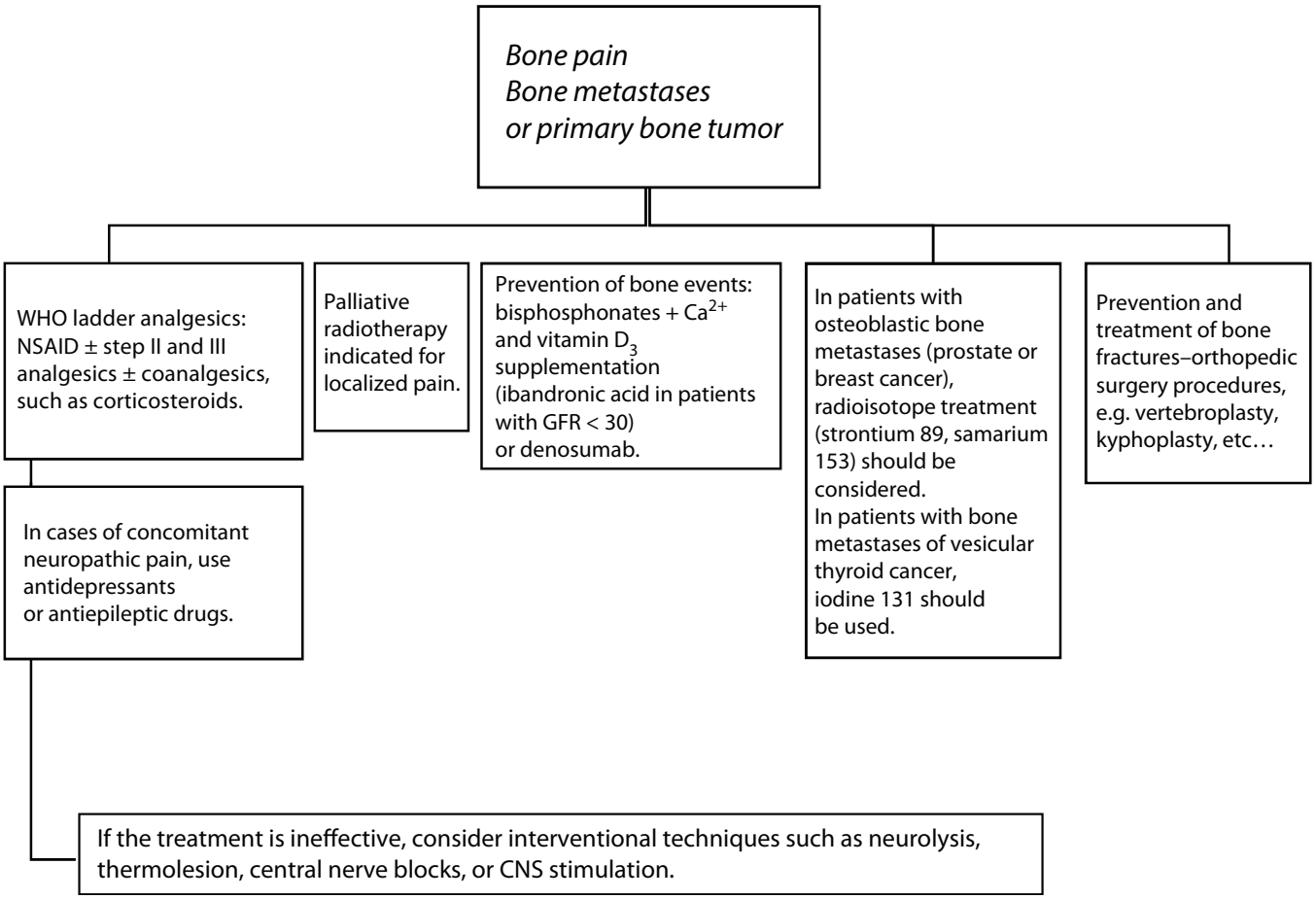
The mechanism of hyperalgesia has not been examined in detail; it is believed to be due to synergistic neuronal overexcitation and activation of glial cells (both astrocytes and microglia). Pathological, paradoxical oversensitivity caused by opioids may have a genetic background [151].

Therapeutic management

If the successive doses of the opioid drug lead to intensification of pain and lower the pain threshold to the level of stimuli usually unable to trigger pain sensations, one should aim at gradual discontinuation of the particular opioid drug. Gradual discontinuation helps in prevention of withdrawal symptoms. Relief in spontaneous and evoked pain was observed following opioid dose reduction. A switch to methadone, buprenorphine, or other non-phenanthrene opioid (e.g. fentanyl) is recommended. One should also consider treatment with NMDA antagonists (ketamine, dextromethorphan, memantine), valproate, gabapentin or pregabalin [7, 156].



Algorithm 4. Treatment of neuropathic pain.



Algorithm 5. Bone pain treatment diagram.

ANALGESIC ADJUVANTS (COANALGESICS)

Adjuvant (supporting) drugs are used at every stage of pain treatment in cancer patients [19, 109, 141, 150, 194, 195]. These include:

- Analgesic adjuvants (coanalgesics – drugs not classified as analgesics but found to exert analgesic effects in certain types of pain (Table VII).
- Drugs used in prevention and treatment of adverse effects associated with the use of analgesics (usually opioid analgesics) as well as in the treatment of symptoms other than pain.

Several categories of coanalgesics were identified, including those used in every type of pain, those used in neuropathic pain, bone pain, spasticity, visceral pain, or pain caused by increased intracranial pressure. However, the quality of available evidence supporting the efficacy of coanalgesics in alleviating pain in cancer patients is low. On the other hand, the treatment of pain accompanying cancer should, if possible, take into consideration personal preferences of patients [182].

Multidirectional coanalgesic agents

Glucocorticosteroids

The mechanism of the analgesic activity of glucocorticosteroids is associated with their anti-inflammatory and anti-edemic effect (reduced compression of tender structures, such as spinal nerve roots,, by swollen tissues, reduced intracranial pressure) and, probably, also with indirect inhibition of the electric activity of the affected nerve [54, 64, 136].

Glucocorticosteroids are used in many types of pain, including neuropathic pain (caused by compression and infiltration of nervous system structures), bone pain, visceral pain, lymphoedema-related pain, or pain associated with the growth of intracranial tumors. An additional effect of glucocorticosteroids consists in improved mood and appetite as well as in their antiemetic activity [115, 137, 197].

α2 Adrenergic receptor agonists

Clonidine

The efficacy of clonidine is low when administered via the oral route. The drug is also applied topically or intrathecally (subarachnoid/epidural administration) [43, 86, 196].

Dexmedetomidine

Administered intravenously at intensive care and palliative medicine units to evoke analgosedation. Analgesic efficacy comprises a central component (stimulation of receptors with in the brain stem and posterior horns of the spinal cord) as well as a peripheral component (stimulation of receptors within the dorsal root ganglia) [142].

Tab. VI. Factors which may reduce opioidophobia in patients [55].

FACTORS ARE LISTED IN DESCENDING IMPORTANCE ORDER
1. Patient's trust
2. Highlighting that adverse effects may be managed (prevented or effectively alleviated once they occur)
3. No opioidophobia on the physician's side (physicians must cope with their own anxieties first)
4. Highlighting that if the pain is reduced in the course of the treatment or as the result of additional therapeutic measures (e.g. Nerve block, neurolysis, radiotherapy), the strong opioid dose may (and should) be reduced, or even discontinued if pain is resolved
5. Physician's competence
6. Explaining that the drug will be administered starting from a small dose which will be gradually increased and individually adjusted depending on the need
7. Highlighting that opioids may be discontinued (under physician's supervision) should any adverse effects be difficult to treat and at any time should the patient demand such discontinuation
8. Ensuring the patient that should they poorly tolerate the treatment with a particular opioid, the treatment may be modified or switched to another drug
9. Preparing written patient materials (and appropriate drug prescriptions) containing detailed recommendations for prevention and treatment of adverse effects and the physician's contact details
10. Asking the patient about their opinions or beliefs on the use of opioids; listening and correcting/responding to any misbeliefs or anxieties
11. Identification of patient's anxieties (by the patient themselves), physician's help in separating opinions based on prevalent myths from actual facts
12. Inclusion of patient's guardians in the aforementioned strategy.
13. Patient noticing that the treatment leads to good therapeutic outcomes.

N-Methyl-D-aspartate (NMDA) receptor antagonists

Many observational studies suggested the efficacy of NMDA receptor antagonists in prevention and reduction in the development of central hypersensitivity and thus in the reduction of pain intensity and inhibition of opioid tolerance development [72]. To this end, non-competitive antagonists of NMDA receptors are used, including ketamine, dextropethorphan, amantadine, and mementine [105]. Ketamine is used most frequently, usually in the treatment of neuropathic pain in combination with opioid analgesics. In palliative care, ketamine is used, usually combined with an opioid, in the treatment of difficult and refractory pain syndromes [13, 62, 143, 155, 168]. However, the results of studies on the use of ketamine and other NMDA receptor antagonists (memantine, amantadine, and dextrometorphan) in the treatment of neuropathic pain in cancer patients are ambiguous [24].

Cannabinoids

Cannabinoids are organic active substances interacting with metabotropic cannabinoid receptors CB1 and CB2 [12].

As shown in randomized, controlled studies, cannabinoids may be effective in the treatment of patients with chronic neuropathic pain and chemotherapy-induced nausea or vomiting [34, 68, 73, 100, 140, 188].

Cannabinoids may be efficient adjuvants in the treatment of cancer patients with pain that can't be relieved efficiently using opioid analgesics; However, good quality clinical studies are lacking to support strong recommendations for the use of cannabinoids. Cannabinoids seem to be safe when used at low or medium doses [127, 177]. Results of preclinical studies also suggest that cannabinoids may be efficient in the treatment of chemotherapy-induced peripheral neuropathy [1].

Drugs used in the treatment of neuropathic pain

Neuropathic pain in cancer patients may be caused by a damage to the somatosensory part of the nervous system being caused by the primary tumor or its metastases. Neuropathic pain may also be an outcome of surgical treatment, radiotherapy, or chemotherapy. Characteristics of neuropathic pain include:

- Pain experienced on the surface of the skin within the range corresponding to the area supplied by the affected nerve; the pain is reported by the patients to be burning, stinging;
- Paroxysmal shooting pain (electric shock-like sensations);
- Sensory disorders such as hypoesthesia or hyperalgesia, allodynia.

Antidepressants

Antidepressants are used in the treatment of neuropathic pain and chronic pain symptoms with concurrent depression. They are also used in the treatment of other symptoms such as anxiety, sleep disorders, or skin itching.

The mechanism of action of antidepressant drugs consists, among others, in inhibition of the reuptake of monoamines (noradrenalin and/or serotonin) from the synaptic cleft, resulting in intensified inhibition of nociception as the result of activation of endogenous antinociceptive systems. Antidepressants used in the treatment of neuropathic pain in cancer patients included mainly amitriptyline, duloxetine, venlafaxine [49, 128, 166].

Combinations of antidepressants and antiepileptic drugs reduce the intensity of neuropathic pain in cancer patients [59].

Antiepileptic drugs

The class of antiepileptic drugs consists of substances of various chemical structures and diverse mechanisms of action. On the molecular level, drugs of this group reduce the concentrations of sodium and/or calcium levels in pre-or postsynaptic cells within the CNS. Drugs recommended for use in the first line treatment of neuropathic pain in cancer include gabapentin and pregabalin [8, 39, 49, 59, 76, 144, 175].

Topical drugs

Lidocaine, doxepin, and capsaicin are used mainly in the treatment of localized peripheral neuropathic pain in cancer patients [74, 134, 196]. The treatment of neuropathic pain in cancer patients is presented in Algorithm 4.

Drugs used in the treatment of bone pain

Bone pain is usually well-localized and intensified upon compression. It is usually present while resting and moving alike. Due to the partially inflammatory nature of bone pain, NSAIDs play an important role and present with high efficacy in the treatment of bone pains and should therefore be used (in monotherapy or adjuvantly with opioids) unless contraindicated. Adjuvant drugs for

Tab. VII. Most common coanalgesics.

CATEGORY	GROUP	DRUG	DOSAGE	COMMENTS
Multidirectional drugs	Corticosteroids	Dexamethasone	2–16 mg/d	Preferred for long duration of effects (36–54 hours) and only slight mineralcorticoid effect. Higher doses (up to 16 mg) may be used in spinal cord compression. Steroid nerve blocks in the metastatic region (4–8 mg).
		Prednisone	5–10 mg bid	Intravenous infusions in spinal cord compression.
		Methylprednisolone	4–32 mg 40 mg – blocks	In pain caused by bone metastases, steroid nerve blocks are used in the region of metastasis (methylprednisolone acetate).
		Betamethasone	7 mg	Steroid nerve blocks in the metastatic region
	NMDA antagonists	Ketamine	Oral: 10–25 mg 4–6 times a day; epidural: 30 mg per day; continuous i.v. Infusion: 1–2 µg/kg bw/min	Different doses are used in clinical practice depending on the type of pain and route of administration. No strong evidence is available to support benefits of ketamine use.
		Memantine, amantadine, dextromethorphan		Other NMDA agonists were tested in the treatment of neuropathic pain in cancer patients; the results, however, are ambiguous.
	Cannabinoids	Tetrahydrocannabinol + cannabidiol	Each 100 µL dose of spray contains: 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD); doses are adjusted individually	Cannabinoids are to be used only in cancer patients experiencing disease-related symptoms or negative treatment effects such as persistent nausea, vomiting, loss of appetite, and pain, particularly neuropathic pain refractory to other forms of treatment. No sufficient evidence is available to support the efficacy of cannabinoids in the treatment of pain in cancer patients.
	α^2-Adrenergic receptor agonists	Clonidine	Intrathecal single dose 150 µg Infusion 30 µg/h.	Oral: low efficacy. Local topical administration of clonidine efficiently reduces pain associated with herpetic neuralgia. Spinal/epidural clonidine in cancer patients is effective in the treatment of neuropathic pain; however, due to its adverse effects, it should be used only in an inpatient setting (monitoring required) if other treatment methods prove inefficient.
		Tizanidine	2–4 mg tid	Inhibits interneurons at the spinal level to reduce increased skeletal muscle tone.
Drugs used in the treatment of neuropathic pain	Topical drugs	Capsaicin	Capsaicin 8% patch 1 x per 3 months	May be efficient in patients with herpetic neuralgia, persistent post-operative pain (following thoracotomy, mastectomy, or amputation), or chemotherapy-induced polyneuropathy.
		Lidocaine	Lidocaine 5% patch	Topical lidocaine is recommended as the drug of choice in localized peripheral neuropathic pain, e.g. In herpetic neuralgia, persistent post-operative pain in cancer patients.
		Doxepin	Doxepin hydrochloride 5% tid/qid; Do not exceed 10% of total skin area	Used in the treatment of localized neuropathic pain and pruritus. Adverse effects are possible following excessive absorption.
		Clonidine as above	0.1–0.3 mg/d topically	Used in the treatment of localized neuropathic pain and pruritus. Adverse effects are possible following excessive absorption.
	Antidepressants (TCA, SNRI, OTHER)	TCA Amitriptyline	25–100 mg	Most frequently used among all antidepressant drugs Contradiction: micturition disturbances, glaucoma attacks, cholinolytic effects, circulatory failure. Limitations for use in elderly patients.
		Doxepin	25–200 mg	Less cardiotoxic than amitriptyline. May require dose reduction in renal insufficiency. Excessive somnolence may be experienced early in the treatment.
		SNRI Duloxetine	30–120 mg	Better tolerated by patients with cardiac disease burden compared to amitriptyline. Cholinolytic effect.
		Venlafaxine	75–225 mg	Less cardiotoxic than amitriptyline. Cholinolytic effect, serotoninergic effect at doses up to 75 75 mg, serotoninergic and noradrenergic effect at higher doses. Requires cautious, gradual discontinuation.
		OTHER Mirtazapine (NaSSA)	15–30 mg/d	Cases if myelosuppression, usually manifested as granulocytopenia or agranulocytosis, were observed during drug use. Caution should be used in patients with epilepsy or organic brain disorder, hepatic or renal insufficiency, and heart diseases.
		Mianserin (tetracyclic antidepressant)	30–90 mg/d	May cause myelosuppression when used together with certain antiepileptic drugs, analgesics, and anti-inflammatory drugs. Most common adverse effects include excessive sedation and somnolence early in the treatment. Common adverse effects include increased body weight, increased activity of hepatic enzymes, edemas.

Tab. VII. Most common coanalgesics.

CATEGORY	GROUP	DRUG	DOSAGE	COMMENTS
	Antiepileptic drugs	Gabapentin	300–1200 mg tid	Recommended for use in the first line treatment of neuropathic pain in cancer patients.
		Pregabalin	75 mg/d – 300 mg bid	Recommended for use in the first line treatment of neuropathic pain in cancer patients. Note – dose reduction is required when using gabapentin and pregabalin in patients with renal insufficiency.
		Carbamazepine	100–200 mg, up to 1200 mg per day in divided doses	Not recommended in cancer patients due to potential interactions. Carbamazepine increases the risk of leukopenia.
		Oxcarbazepine	300–3000 mg/d	Used in cases of carmabazepine intolerance.
		Valproic acid	300–2000 mg	May cause gastrointestinal complaints, increased body weight, hair loss, edemas, hand tremor, ataxia, as well as thrombocytopenia and liver damage in case of long-term use. No reliable study data are available on the use of valproic acid in cancer patients. The drug is also available as an intravenous formulation
		Lamotrigine	25–100 mg bid	Lamotrigine was found to be effective in painful chemotherapy-induced neuropathy.
	Na+ channel blockers	Lidocaine	3–5 mg/kg i.v. infusion over 30–60 min	Good efficacy in post-amputation pain, phantom pain, and stump pain. May be efficient in multidirectional treatment of chemotherapy-induced pain and other neuropathic pain disorders in cancer patients.
	NMDA antagonists	Ketamine	Oral: 10–25 mg 4–6 times a day; epidural: 30 mg per day; continuous i.v. Infusion: 1–2 µg/kg bw/min	Different doses are used in clinical practice depending on the type of pain and route of administration. No strong evidence is available to support benefits of ketamine use.
		Memantine, amantadine, dextromethorphan		Other NMDA agonists were tested in the treatment of neuropathic pain in cancer patients; the results, however, are ambiguous.
	GABA agonists	Clonazepam (GABA-A receptor agonist)	From 1.5 mg/d up to the maximum dose of 4–8 mg/d	Paradoxical reaction may occur in elderly patients (agitation, aggression). Drug is characterized by long half-life (30–60 h), strong sedation effect, as well as additional relaxation effect on skeletal muscles. Do not use in severe hepatic insufficiency; use in caution with opioid analgesics due to the increased risk of respiratory depression.
		Baklofen (agonista receptora GABA-B)	5–10 mg to 50–60 mg/d	About 10% of patients do not tolerate baclofen due to its adverse effects: dizziness, balance disorders, nausea, vomiting, excessive sedation, and somnolence. Significant dose reduction required in patients with renal insufficiency.
Drugs used in the treatment of bone pain	Osteoclast inhibitors	Bisphosphonates: Zolendronic acid, ibandronate, pamidronate	No optimum analgesic dose of bisphosphonates or denosumab could be determined in a systematic review.	Systematic reviews and meta-analyses provided evidence to confirm the role of bisphosphonates and denosumab in the prevention of bone events in adult patients with advanced cancer including bone involvement (lung cancer, breast cancer, prostate cancer, and myeloma).
	Other mechanisms of action	Denosumab	See above	Studies revealed significant delay in the development of bone pain (functional effect, not related to direct alleviation of bone pain). Denosumab is recommended in patients with renal function disorders.
	Radioactive isotopes	Strontium 89 (Sr89), Samarium 153 (Sm153)	Strontium 89 is available at fixed doses while the dose of samarium 153 is individualized according to patient's weight with the possibility of further dose adjustment. Recommended radioactivity: Sr89 – 150 MBq, Sm153 – 37 MBq/kg	Radioisotopic treatment of bone metastases makes use of the energy of beta radiation from radioisotopes undergoing selective uptake in bone metastases. The therapeutic effect consists in impairing neural transmission and inhibiting the secretion of pain mediators within the metastatic region by the destructive effects of beta radiation. In clinical terms, this is manifested by reduction or, in some cases, resolution of pain, improvement in motor efficiency, and better quality of life. The onset of the analgesic effect is observed 1-2 weeks after administration and lasts up to several months. However, the treatment may be associated with severe adverse effects, such as myelosuppression.
		Hyoscine butylbromide	60–120 mg/d; in exceptional cases, dose may be increased to 150 mg. Administer every 4h or as a continuous s.c. infusion. Oral: 10–100 mg/d	The drug has a peripheral anticholinergic effect associated with the risk of disturbed gastrointestinal propulsion i.e. modification of gastrointestinal absorption and thus the effects of other drugs. Not recommended for use longer than several days due to the possible tachyphylaxia. Drug may case abdominal rebound pain. Hyoscine butylbromide significantly enhances the absorption of digoxin in gastrointestinal tract. Caution should be used upon simultaneous use with corticosteroids due to the possibility of sudden increase in intraocular pressure. This combination is contraindicated in glaucoma patients. Hyoscine butylbromide antagonizes the effects of methoclopramide.

Tab. VII. Most common coanalgesics.

CATEGORY	GROUP	DRUG	DOSAGE	COMMENTS
Drugs used in the treatment of visceral pain	Spasmolytics	Drotaverine	Daily dose 320 mg, administered in divided doses every 6–8 h.	A derivative of papaverine. Relaxes the smooth muscles of the gastrointestinal, urogenital, cardiovascular, and biliary system. Do not use in patients receiving levodopa.
		Mebeverine	Daily dose 400 mg, administered in divided doses every 8–12 h.	A musculotropic spasmolytic exerting a direct relaxation effect on gastrointestinal smooth muscles. It eliminates intestinal spasm while not disturbing proper intestinal motility. Mebeverine may be used in patients with glaucoma and prostatic hyperplasia. It does not cause double vision or mouth dryness.
		Alverine	Daily dose 360 mg, administered in divided doses every 8 h.	As alverine citrate, it is used as a muscle relaxant with strong effect on the smooth muscles of internal organs, particularly the gastrointestinal tract and uterus. Well absorbed from the gastrointestinal tract. May cause hypotonia.

use in this indication include glucocorticosteroids, bisphosphonates, denosumab, and radioisotopes [67, 139].

In patients with bone metastases, activation of inflammatory mediators is accompanied by expression of nerve growth factors (NGF), which leads to significant growth/spread of nerve fibers e.g. within the marrow cavities. This in turn is one of the causes responsible for the development of the neuropathic component of bone pain and provides an indication for the use of antiepileptic drugs for the treatment of this type of pain [121].

Besides adjuvant drugs, treatment of bone pain may include radiotherapy (high efficacy) and surgical treatment of metastases (in selected cases) [25, 103]. When planning the treatment duration, physicians should follow guidelines suggesting that in case of solid tumors bisphosphonate treatment should be continued until significant deterioration in patient's ECOG status and the decision to discontinue treatment should be guided by best clinical judgment. The above conclusions pertain to drugs being used for therapeutic rather than analgesic purposes [67]. A diagram for the treatment of bone pain is presented in Algorithm 5.

Drugs used in the treatment of visceral pain

Visceral pain is experienced by about 30% of cancer patients. It is caused by the pathological process occurring within the visceral, thoracic, abdominal, and pelvic organs. Visceral pain may be of either colic or non-colic character. Symptomatology of non-colic visceral pain differs from that of somatic pain: it is usually diffuse, poorly localized, and caused by different stimuli (Fig. 1).

Colic pain is caused by infiltration and stenosis or complete obstruction of intestinal, ureteric, or bile duct lumen. Examples of visceral pain characterized by rapid-onset, strong intensity and complex physiology (including a neuropathic pain component) include painful, paroxysmal cramps of rectum and urinary bladder (tenesmus) experienced by the patient as painful urge to urinate and defecate. This type of pain often accompanies tumors localized within pelvis minor [164].

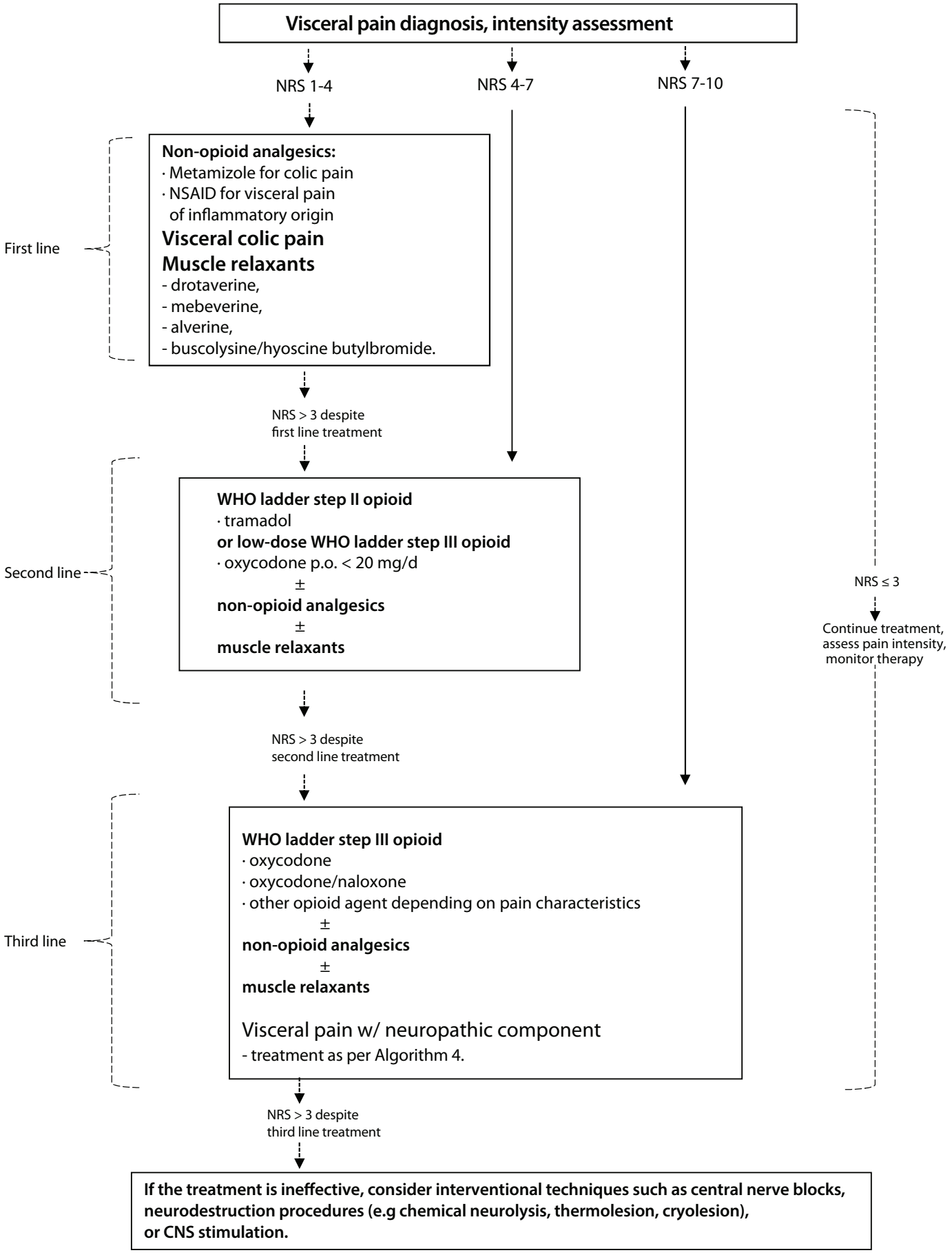
In cases of concomitant colic pains, muscle relaxants such as hyoscine derivatives (usually hyoscine butylbromide which, in contrast to other drugs from the same group, is characterized by only peripheral activity and may be used subcutaneously), atropine and glycopyrrolate are recommended However, it should be highlighted that the use of drugs with peripheral anticholinergic effect is associated with the risk of disturbed gastrointestinal propulsion i.e. modification of gastrointestinal absorption and thus the effects of other drugs. Drugs with lower impact on intestinal peristalsis include drotaverine, mebeverine, and alverine [33, 130]. The treatment of visceral pain in cancer patients is presented in Algorithm 6.

Myorelaxants

Patients with pain caused by skeletal muscle contractures benefit from muscle tone reducing drugs such as baclofen, tizanidine, or benzodiazepines. Methocarbamol is also available. Myorelaxants should be used with caution, starting with low doses due to their sedative effects and significant risk of interactions. Patients with swallowing difficulties may receive subcutaneous midazolam. However, it should be kept in mind that for all the currently available benzodiazepines, myorelaxation is preceded by the sedative effect [97, 198]. Tetrazepam was an exception in this group; however, it is no more in use due to safety reasons as it was associated with the risk of Stevens-Johnson's syndrome, toxic epidermal necrolysis, and erythema multiforme [102]. Medazepam should also not be used in this indication due to its low affinity to peripheral benzodiazepine receptors.

Drugs used to alleviate soft tissue pain

Soft tissue pain is usually due to cancer-related ulceration of skin of mucosal membrane, bedsore ulcerations, or oral mucositis due to chemo- and radiotherapy. Current guidelines recommend systemic opioids, i.e. morphine (at patient-controlled analgesia doses) for the treatment of pain in the course of oral mucositis while suggesting possible analgesic efficacy of gabapentin or transdermal opioids (in patients undergoing conventional or high-dose chemotherapy) and morphine 0.2% mouthwash solution (in patients with head and neck cancer undergoing chemoradiotherapy), as well as methylene blue or doxepin 0.5% mouthwash solution in the treatment of this disorder [81, 87, 153, 157, 169, 186]. The main role in the treatment of ulcer-related pain is played by anticancer treatment, local nursing procedures (including appropriate, specialist dressings and anti-inflammatory treatment) as well as by a holistic approach to the cancer patient [84]. The latter is associated with the fact that patients often suffer from pain, bleeding, effusions, itching, infectious lesions, unpleasant odor, and sense of being ashamed of the changes in their looks and their solitude. The main role in direct pain-targeting therapy is played not only by regular systemic and local treatment (depending on the type of pain), but also by prevention of pain experienced upon dressing



Algorithm 6. Visceral pain treatment algorithm.

changes (besides maintenance of moist environment and appropriate selection of dressings). Some patients may particularly benefit from topical morphine (e.g. morphine gel) [56, 191].

Drugs used in the treatment of adverse effects

Analgesic adjuvants may minimize or prevent adverse effects of analgesic drugs. Treatment of nausea and vomiting usually involves the use of prokinetics (methoclopramide, itopride, prucalopride), antidopaminic agents (haloperidol, thietylperazine), broad-spectrum drugs (olanzapine, levomepromazine), antihistaminics (dimenhydrinate, promethazine), 5-HT3 receptor inhibitors (ondansetron, tropisetron, granisetron, palonosetron).

Following laxatives are used for prevention and treatment of constipation associated with pain treatment (opioids) or developing from other causes: osmotics (lactulose, macrogols), irritants of intestinal nerve plexi (senozides, bisacodyl), or peripherally acting μ-opioid receptor antagonists (PAMORA), particularly oral naloxegol) – the latter group of drugs is used in opioid-induced constipation refractory to traditional laxatives. Gastroprotection with proton pump inhibitors is also considered in patients treated with NSAIDs and steroids.

Concluding highlights:

- Pregabalin or gabapentin are recommended as first line antiepileptic drugs for the treatment of cancer pain including a neuropathic component.
- In patients treated with antiepileptic drugs who are unable to continue oral treatment, intravenous administration of valproic acid or degradable gabapentin formulations for percutaneous endoscopic gastrostomy (PEG) is recommended.
- Amitriptyline or SNRIs (venlafaxine, duloxetine) are recommended as first line antidepressants used as coanalgesic agents in patients with cancer pain.
- Dexamethasone is recommended as first line steroid used as a coanalgesic agent in patients with cancer pain.
- The use of cannabinoids in cancer patients is recommended in patients experiencing neuropathic pain refractory to other treatment as well as chemotherapy-induced nausea and vomiting.

INTERACTIONS OF DRUGS USED IN THE TREATMENT OF PAIN

Analgesics and coanalgesics used in the treatment of pain are characterized by high risk of adverse effects and interactions (Table VIII). Due to the large number of drugs received by cancer patients (>80% patients receives regularly ≥5 drugs), the risk of interactions between individual drugs is high in this population [79, 89, 116, 147]. Following measures are recommended to prevent interactions of analgesic agents used in the treatment of cancer patients:

- Number of drugs and drug doses being reduced only to those absolutely necessary;
- Drugs associated with risk of serious adverse effects being avoided;
- Therapeutic effects and treatment tolerance being assessed regularly;
- Discontinuation being considered for drugs of no significant benefit to patients with short survival prognosis.

TREATMENT OF PAIN IN SPECIAL CASES

Break-through cancer pain, BTCP

Break-through pain is defined as transient increase in pain intensity observed in patients with effective control of baseline pain, usually using opioid analgesics. BTCP is usually characterized by significant intensity (above 5 points in the NRS scale), short duration of the episode (usually ca. 45–60 minutes) and sudden increase in pain intensity (from a few tens of seconds to 240 minutes, usually below 10 minutes). BTCP is observed in a large percentage of cancer patients experiencing pain symptoms (ca. 33–95%, mean61%) and poses a significant challenge in the treatment of chronic pain. Of note is the significant negative impact of BTCP on everyday physical and emotional functioning of patients as well as significant reduction in the quality of life and adverse impact on the costs of the treatment [19, 31, 36].

From the standpoint of etiology, following types of break-through pain may be identified:

1. Spontaneous (idiopathic) pain – occurring without a tangible cause.

2. Incident pain – associated with a specific cause:

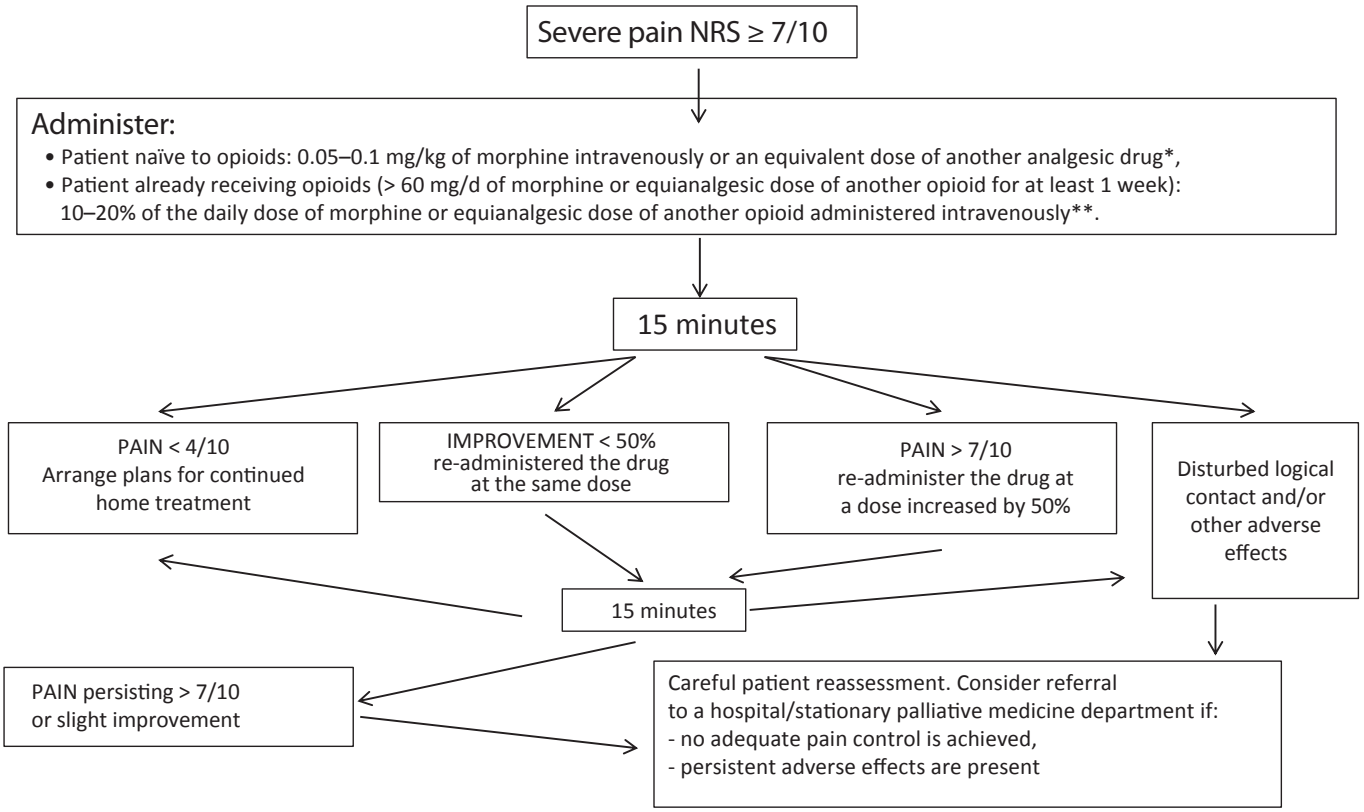
   - Nonvolitional (will-independent) – e.g. associated with intestinal peristalsis, cough.
   - Volitional (will-dependent) – e.g. associated to a change of patient position in bed, ambulation.

3. Procedural pain – caused by nursing procedures (e.g. dressing change), diagnostic procedures (e.g. imaging studies) and therapeutic procedures (e.g. radiotherapy).

In cases of idiopathic and rapid-onset nonvolitional incident pain, fast-acting opioids (intranasal, buccal, and sublingual fentanyl formulations) are recommended so that the pain is alleviated quickly (see chapter: Opioids of the Third Step of the WHO Analgesic Ladder). The choice of the drug should be made on the basis of the characteristics of break-through cancer pain and the properties of the drugs [200, 201].

Oral or subcutaneous opioids may also be used; however, these require longer times until the onset of analgesic effect (20–30 and 10–15 minutes, respectively. Drugs of this type may be more useful in patients with BTCP episodes characterized by slower increase in pain intensity and longer duration (analgesic effects of most common immediate release (IR) oral opioids are usually maintained for about 4–6 hours). In the inpatient setting, very rapid analgesic effect may be achieved by intravenous administration of an analgesic (sometimes a non-opioid analgesic). This route of administration is particularly useful in the treatment of patients with very severe pain [19, 30, 31, 36, 107].

In cases of pain caused by foreseeable activity of patients (incident volitional pain) or nursing, hygienic, diagnostic and therapeutic procedures (procedural pain), pain may be prevented by earlier



* In patients with renal, hepatic, or respiratory insufficiency, the initial dose should be reduced by 25–50% or more depending on the drug and clinical assessment. If intravenous route is inaccessible, drug may be administered subcutaneously.

** Morphine for i.v. administration should be diluted (10 mg in 10 ml) and administer very slowly, monitoring the effects. Discontinue further doses if somnolence, coma, slow or irregular breathing occurs.

Algorithm 7. Morphine dose titration in patients with very strong pain [38, 45].

administration of an analgesic drug (usually an immediate release opioid analgesic) via oral, subcutaneous or intravenous (in the inpatient setting) route. The dose should be adjusted individually; most commonly however, it ranges from ca. 10 to ca. 20% of the daily dose of opioid used in the treatment of baseline pain.

Emergency situations

Severe and extreme pain requiring quick intervention consisting in immediate parenteral (intravenous or subcutaneous) or, less frequently, oral administration of opioid analgesics. Management strategies include administration of fixed or carefully increased (effect-controlled) doses of opioid drugs at constant intervals until pain relief is achieved followed by determination of maintenance dose on the basis of the observed analgesic effect (titration). Such management was shown to be efficient and allowed for pain control being achieved in most patients within 24 hours [32, 63, 111].

On the basis of the aforementioned studies, an algorithm for quick and effective interventions in patients with break-through pain has been developed [38, 45, 114, 174].

Management of opioid overdose and respiratory depression symptoms

In symptoms of opioid analgesic overdose are observed (somnolence progressing to coma, hypotonia, miosis, and respiratory disturbances consisting in shallow and irregular breath with respiratory rate of <8 breaths per minute), intravenous naloxone should be administered immediately starting from a 40 µg dose. Low dose of naloxone restored proper respiratory function while maintaining analgesia. Due to the short duration of the drug's effect (30–60 min), repeated dose or continuous infusion may be required in respiratory depression resulting from administration of a sustained release opioid analgesic. Patients require strict monitoring over a period of 12–24 hours [123, 135, 179].

END-OF-LIFE PAIN

About one half of end-of-life cancer patients (usually patients in their last days/hours of life) experience pain which is frequently accompanied by other symptoms such as weakness, fatigue, lack of appetite, anxiety, somnolence, shortness of breath [71].

Treatment of end-of-life pain in cancer patients [22, 26, 28, 88, 96, 124, 170] consists in:

- Treatment targeting the cause of pain (e.g. Oral care with local symptomatic treatment of pain caused by painful lesions within patient's mouth).
- Consideration of non-pharmacological pain treatment methods appropriate for clinical condition of patients (e.g. delicate massage, oral care, anti-bedsore mattress).
- Ensuring appropriate administration route – patients are often unable to swallow tablets; subcutaneous

Tab. VIII. Selected interactions between drugs used for the treatment of cancer patients [14, 48, 50, 80, 95, 171, 180, 192].

NON-OPIOID AGENT	INTERACTING DRUG	POTENTIAL INTERACTIONS
NSAID	Glucocorticosteroids	↑ adverse effects of NSAIDs, particularly within the gastrointestinal tract – the risk is lowest for dexamethasone (no mineralcortocoid effect)
NSAID	SSRI/SNRI antidepressants	↑ antiplatelet effect of NSAIDs, ↑ risk of bleeding
NSAID	Antithrombotic agents (vitamin K antagonists, heparin, dabigatran, rivaroxaban, apixaban), sulodexide and platelet aggregation inhibitors	↑ antithrombotic effect, ↑ risk of bleeding
NSAID	Acetylsalicylic acid	↑ adverse effects of NSAIDs, ↑ nephrotoxic effect, ↑ risk of bleeding, ↓ cardioprotective effect of salicylates
NSAID	Bisphosphonates	↑ adverse effects of bisphosphonates, ↑ risk of gastric ulcers, ↑ nephrotoxic effect
NSAID	Cyclosporine	↑ blood cyclosporine levels, ↑ blood NSAID levels, ↑ nephrotoxic effect of cyclosporine
NSAID	Aminoglycosidic antibiotics	↑ nephrotoxic effect of aminoglycosides
NSAID	Fluoroquinolones (particularly ciprofloxacin)	↑ blood fluoroquinolone levels, ↑ risk of seizures
NSAID	Loop diuretics, thiazide diuretics	↓ diuretic effect, ↑ nephrotoxic effect of NSAID
NSAID	Aldosterone antagonists	↓ hypotensive effect ↑ hyperkalemic effect of potassium-sparing diuretics
NSAID	β-Blockers	↓ hypotensive effect of β-blockers
NSAID	ACE inhibitors, angiotensin II receptor blockers	↑ adverse effects of NSAID, particularly renal impairment, ↓ hypotensive effect of ACE inhibitors
Celecoxib, meloxicam	Fluconazole, imatinib, sorafenib	↓ metabolism of celecoxib and meloxicam, ↑ adverse effects of NSAID
Paracetamol	Carbamazepine, phenytoin	↑ metabolism of paracetamol, ↓ analgesic effect, ↑ risk of liver damage
Paracetamol	Warfarin, acenocoumarol	↑ antithrombotic effect of vitamin K antagonists (when used for at least several days)
Opioid	CNS function depressants, e.g. sedatives, sleep inducers	↑ CNS depression
Opioid	Antidepressants (mainly SSRI, SNRI), MAO inhibitors, dextromethorphan	↑ serotonin effect, ↑ risk of serotonin syndrome
Tramadol	Ondansetron	↓ analgesic effect of tramadol
Tramadol	Methoclopramide	↑ risk of adverse/toxic effects of methoclopramide, ↑ risk of serotonin syndrome and neuroleptic malignant syndrome, ↑ risk of seizures
Tramadol	Carbamazepine	↑ CNS depression, ↑ metabolism of tramadol, ↓ analgesic effect, ↓ anticonvulsive effect of carbamazepine, ↑ risk of seizures
Tramadol	Vitamin K antagonists	↑ antithrombotic effect (INR elongation)
Codeine, tramadol	CYP2D6 inhibitors, particularly duloxetine, celecoxib, methoclopramide, methoprolol, propranolol	↓ blood levels of active metabolites of codeine and tramadol, ↓ therapeutic effect
Tramadol, oxycodone, fentanyl, methadone	CYP3A4 inhibitors such as clarithromycin, erythromycin, fluconazole, ytraconazole, voriconazole, amiodarone, metronidazole	↓ metabolism of opioids, ↑ therapeutic effect and adverse effects
Tramadol, oxycodone, fentanyl, methadone	Carbamazepine, phenobarbital and phenytoin	↑ metabolism of opioids, ↓ analgesic effect
Methadone, buprenorphine	Drugs leading to QT elongation, e.g. haloperidol, quetiapine, clarithromycin, escitalopram, hydroxyzine, nilotinib, pazopanib, sorafenib	QT elongation and ↑ risk of torsades de pointes (TdP)
Amitriptyline	CNS depressants, anticholinergics (hydroxyzine, pernazine, promazine, doxepin, mianserin, hyoscine butylbromide) and serotoninergic	QT elongation mat increase the risk of TdP-type ventricular arrhythmias. Amitriptyline metabolism is slowed down (and the effect is enhanced) following administration of CYP2D6 inhibitors.
Duloxetine	Ciprofloxacin (do not use simultaneously), tramadol, methoprolol	Increased risk of complications – anxiety, heart rate disorders. Combinations with other serotoninergic drugs increases the risk of serotonin syndrome.
Phenytoine, carbamazepine, oxcarmazepine	Inducers of a series of cytochrome P450 enzymes, including CYP3A4	Accelerate the metabolism of other drug — substrates of these enzymes, including some opioids, benzodiazepines, amlodipin, lercanidipin, nitrendipin, azole antifungals (fluco-, ytra -, voriconazole), ciprofloxacin, clindamycine, dexamethasone, meloxicam, omeprazole and rabeprazole, as well as "Z" group of sleep inducers (zolpidem, zopiclon, zaleplon)
Tizanidine	Ciprofloxacin	Simultaneous use of rizanidine and ciprofloxacin (a strong CYP1A2 inhibitor) is contraindicated.
Baclofen	Antihypertensive drugs, sleep inducers, other myorelaxants – benzodiazepines!	May enhance the effect of hypotensive drugs, induce sleep and CNS depression.

administration involving a butterfly needle puncture is the most common alternative. A practical solution consists in continuous subcutaneous infusion of drugs using a pump; if this is not feasible, drug is to be administered in divided doses at appropriate intervals (usually every 4 hours). Switching the administration route from oral to subcutaneous should include dosage modification (e.g. 2– to 3-fold reduction in the dose of morphine).

In cancer patients treated in a stationary care setting including the placement of venous ports, drugs may be administered by this route (this is beneficial particularly in patients in agony characterized by significant centralization of circulation when drugs administered via the subcutaneous route are no more efficient due to impaired absorption from the subcutaneous administration site).

- Lack of analgesic effect in patients treated with transdermal opioids (fentanyl, buprenorphine) should lead to the administration route being changed to parenteral.
- Preventive management of procedural pains (e.g. additional dose of an analgesic drug before the pain-causing activity) should be implemented.
- Palliative sedation should be considered in patients with treatment-refractory physical symptoms (including pain) causing significant suffering during the end of life (provided a consent for such sedation has been given by the patient). Palliative sedation consists in controlled use of sedatives to reduce suffering caused by physical symptoms refractory to other methods of treatment by reducing the awareness level in a patient with incurable and advanced disease during the period when death is inevitable and close (hours, days – end-of-life period)
- Pain treatment should be considered a component of comprehensive patient care.

** The article is a modified version of a full version published in BÓL journal: Wordliczek J., Kotlińska-Lemieszek A., Leppert W, et al.: Farmakoterapia bólu u chorych na nowotwory – zalecenia Polskiego Towarzystwa Badania Bólu, Polskiego Towarzystwa Medycyny Paliatywnej, Polskiego Towarzystwa Onkologicznego, Polskiego Towarzystwa Medycyny Rodzinnej, Polskiego Towarzystwa Anestezjologii i Intensywnej Terapii, BÓL, 2017; 18(3): 11–53*

REFERENCES

1. Abrams D.I.: Integrating cannabis into clinical cancer care, Current Oncology, 2016 March; Vol. 23, Supp. 2. S8-S14
2. Ahmedzai S.H., Leppert W., Janecki M., Pakosz A., Lomax M., Duerr H., Hopp M.: Long-term safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe chronic cancer pain, Support Care Cancer, 2015; 23(3): 823-830.
3. Ahmedzai S.H., Nauck F., Bar-Sela G., Bosse B., Leyendecker P., Hopp M.: A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain, Palliat Med, 2012 Jan; 26(1): 50-60.
4. Amato F., Ceniti S., Mameli S., Pisanu G.M., Vellucci R., Palmieri V., Consoletti L., Magaldi D., Notaro P., Marcassa C.: High dosage of a fixed combination oxycodone/naloxone prolonged release: efficacy and tolerability in patients with chronic cancer pain, Support Care Cancer, 2017 May 3; doi: 10.1007/s00520-017-3709-5. [Epub ahead of print].
5. Anderson R., Saiers J.H., Abram S., Schlicht C.: Accuracy in equianalgesic dosing. Conversion dilemmas, J Pain Symptom Manage, 2001; 21: 397-406.
6. Anghelescu D.L., Patel R.M., Mahoney D.P., Trujillo L., Faughnan L.G., Steen B.D., Baker J.N., Pei D.: Methadone prolongs cardiac conduction in young patients with cancer-related pain, J Opioid Manag, 2016; 12: 131-138.
7. Angst M.S., Clark J.D.: Opioid-induced Hyperalgesia. A Qualitative systematic review, Anesthesiology, 2006; 104, 570-587.
8. Banerjee M., Pal S., Bhattacharya B., Ghosh B., Mondal S., Basu J.: A comparative study of efficacy and safety of gabapentin versus amitriptyline as coanalgesics in patients receiving opioid analgesics for neuropathic pain in malignancy, Indian J Pharmacol, 2013; 45(4): 334-338.
9. Bao Y.J., Hou W., Kong X.Y., Yang L., Xia J., Hua B.J., Knaggs R.: Hydromorphone for cancer pain, Cochrane Database Syst Rev, 2016 Oct 11; 10: CD011108.
10. Barnes H., McDonald J., Smallwood N., Manser R.: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness, Cochrane Database Syst Rev, 2016, Mar 31;3:CD011008. doi: 10.1002/14651858.CD011008.pub.2
11. Bauer L.A.: Applied Clinical Pharmacokinetics. Nowy Jork, Mc Graw Hill Medical, 2014.
12. Beaulieu P., Boulanger A., Desroches J., Clark A.J.: Medical cannabis: considerations for the anesthesiologist and pain physician, Can J Anaesth, 2016; 63: 608-624.
13. Bell R.F., Eccleston C., Kalso E.A.: Ketamine as an adjuvant to opioids for cancer pain, Cochrane Database Syst Rev, 2012; 11: Cd003351.
14. Bernard S.A., Bruera E.: Drug interactions in palliative care, J Clin Oncol, 2000; 18(8): 1780-1799.
15. Boström E., Hammarlund-Udenaes M., Simonsson U.S.: Blood-brain barrier transport helps to explain discrepancies in in vivo potency between oxycodone and morphine, Anesthesiology, 2008; 108: 495-505.
16. Brant J.M., Rodgers B.B., Gallagher E., Sundaramurthi T.: Breakthrough Cancer Pain: A Systematic Review of Pharmacologic Management, Clin J Oncol Nurs, 2017, 21, 71-80.
17. Breivik H., Borchgrevink P.C., Allen S.M., Rosseland L.A., Romundstad L., Hals E.K., Kvarstein G., Stubhaug A.: Assessment of pain, Br J Anaesth, 2008, 101, 17-24.
18. Bruera E., Higginson I., von Gunten C.F.: Textbook of Palliative Medicine and Supportive Care. Boca Ratoy, CRC Press, 2015.
19. Caraceni A., Hanks G., Kaasa S. et al.: Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC, Lancet Oncol, 2012; 13: 58-68.
20. Carlson C.L.: Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review, J Pain Res, 2016 Jul 22; 9: 515-534.
21. Carmona-Bayonas A., Jiménez Fonseca P., Virizuela Echaburu J.: Tapentadol for Cancer Pain Management: A Narrative Review, Pain Pract, 2017 Jan 13; doi: 10.1111/papr.12556.
22. Cherny N.I., Radbruch L.: European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care, Palliat Med, 2009; 23(7): 581-593.
23. Chien C.W., Bagraith K.S., Khan A., Deen M., Strong J.: Comparative responsiveness of verbal and numerical rating scales to measure pain intensity in patients with chronic pain, J Pain, 2013; 14, 1653-1662.
24. Chizh B.A., Headley P.M.: NMDA antagonists and neuropathic pain-multiple drug targets and multiple uses, Curr Pharm Des, 2005; 11: 2977.
25. Chow R., Hoskin P., Hollenberg D., Lam M., Dennis K., Lutz S., Lam H., Mesci A., DeAngelis C., Chan S., Chow E.: Efficacy of single fraction conventional radiation therapy for painful uncomplicated bone metastases: a systematic review and meta-analysis, Ann Palliat Med, 2017, 6, 125-142.
26. Cook D., Rocker G.: Dying with dignity in the intensive care unit, N Engl J Med, 2014; 370, 2506-2514.
27. Corli O., Floriani I., Roberto A., Montanari M., Galli F., Greco M.T., Caraceni A., Kaasa S., Dragani T.A., Azzarello G., Luzzani M., Cavanna L., Bandieri E., Gamucci T., Lipari G., Di Gregorio R., Valenti D., Reale C., Pavesi L., Iorno V., Crispino C., Pacchioni M., Apolone G.; CERP Study of Pain Group (List of collaborators); CERP Study of Pain Group: Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV ‚real life' trial on the variability of response to opioids, Ann Oncol, 2016; 27, 1107-1115.

28. Costantini M. et al.: End-of-life care: pathways and evidence, Curr Opin Support Palliat Care, 2014; 8, 399-404.
29. Daeninck P., Gagnon B., Gallagher R., Henderson J.D., Shir Y., Zimmermann C., Lapointe B.: Canadian recommendations for the management of breakthrough cancer pain, Curr Oncol, 2016; 23(2): 96-108.
30. Davies A., Buchanan A., Zeppetella G., Porta-Sales J., Likar R., Weismayr W., Slama O., Korhonen T., Filbet M., Poulain P., Mystakidou K., Ardavanis A., O'Brien T., Wilkinson P., Caraceni A., Zucco F., Zuurmond W., Andersen S., Damkier A., Vejlgaard T., Nauck F., Radbruch L., Sjolund K.F., Stenberg M.: Breakthrough cancer pain: an observational study of 1000 European oncology patients, J Pain Symptom Manage, 2013 Nov; 46(5): 619-628.
31. Davies A.N. et al.: The management of cancer-related breakthrough pain: recommendations of a task. group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland, Eur J Pain, 2009, 13, 331-338.
32. Davis M.P., Weissman D.E., Arnold R.M.: Opioid dose titration for severe cancer pain: a systematic evidence-based review, J Palliat Med, 2004 Jun; 7(3): 462-468.
33. Davis M.P.: Drug Management of Visceral Pain: Concepts from Basic Research, Pain Research and Treatment, 2012; article ID 265605, 18 pages doi:10.1155/2012/265605.
34. Davis M.P.: Cannabinoids for Symptom Management and Cancer Therapy: The Evidence, J Natl Compr Canc Netw, 2016; 14, 915-922.
35. De Stoutz N.D., Bruera E., Suarez-Almazor M.: Opioid rotation for toxicity reduction in terminal cancer patients, J Pain Symptom Manage, 1995; 10: 378-384.
36. Deandrea S., Corli O., Consonni D. et al.: Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature, J Pain Symptom Manage, 2014; 47: 57-76.
37. Deer T.R., Leong M.S., Gordin V.: Treatment of chronic pain by medical approaches. New York, Springer, 2015.
38. DeSandre P.L., May K.: Palliative care in emergency department, w: Cherny N.I., Fallon M.T., Kaasa S., Portenoy R.K., Currow D.C. (eds.): Oxford Textbook of Palliative Medicine. Oxford, Oxford University Press, 2015: 118-119.
39. Dou Z., Jiang Z., Zhong J.: Efficacy and safety of pregabalin in patients with neuropathic cancer pain undergoing morphine therapy, Asia Pac J Clin Oncol, 2017; 13: 57-64.
40. Douglas C., Murtagh F.E., Chambers E.J., Howse M., Ellershaw J.: Symptom management for the adult patient dying with advanced chronic kidney disease: a review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group, Palliat Med, 2009 Mar; 23(2): 103-110.
41. Doverty M. et al.: Hyperalgesic responses in methadone maintenance patients, Pain, 2001; 90: 91-96.
42. Drug Safety Information. https://www.fda.gov/Drugs/DrugSafety/ ucm111313.htm.
43. Eisenach J.C., DuPen S., Dubois M. et al.: Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group, Pain, 1995; 61: 391.
44. Elsner F., Radbruch L, Loick G., Gaertner J., Sabatowski R.: Intravenous versus subcutaneous morphine titration in patients with persisting exacerbation of cancer pain, J Palliat Med, 2005 Aug; 8(4): 743-750.
45. Emanuel L.L., Quest T. (eds.): The EPEC Project. The Education in Palliative and End-of-life Care for Emergency Medicine (EPEC™-EM) Curriculum. Chicago, Northwestern University, 2008.
46. FDA Public Health Advisory. Risk of burns during MRI scans from transdermal drug patches with metallic backings. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrug Safety Information forPatientsandProviders/DrugSafetyInformationforHeathcare Professionals /PublicHealthAdvisories/ucm111313.htm (Accessed on January 03, 2012
47. Felleiter P., Gustorff B., Lierz P. et al.: Use of the World Health Organization guidelines on cancer pain relief before referral to a specialized pain service, Schmerz, 2005; 19: 265e271.
48. Feng X.Q., Zhu L.L., Zhou Q.: Opioid analgesics-related pharmacokinetic drug interactions: from the perspectives of evidence based on randomized controlled trials and clinical risk management, Journal of Pain Research, 2017; 10: 1225-1239.
49. Finnerup N.B., Attal N., Haroutounian S., McNicol E., Baron R., Dworkin R.H., Gilron I., Haanpää M., Hansson P., Jensen T.S., Kamerman P.R., Lund K., Moore A., Raja S.N., Rice A.S., Rowbotham M., Sena E., Siddall P., Smith B.H., Wallace M.: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis, Lancet Neurol, 2015; 14, 162-173.
50. Gaertner J., Ruberg K., Schlesiger G. et al.: Drug interactions in palliative care – it's more than cytochrome P450, Palliat Med, 2012; 26: 813-825.
51. Gaertner J., Stamer U.M., Remi C., Voltz R., Bausewein C., Sabatowski R., Wirz S., Müller-Mundt G., Simon S.T., Pralong A., Nauck F., Follmann M., Radbruch L., Meißner W.: Metamizole/dipyrone for the relief of cancer pain: A systematic review and evidence-based recommendations for clinical practice, Palliat Med, 2017; 31: 26-34.
52. Garcia de Paredes M.L., del Moral Gonzalez F., Martinez del Prado P. et al.: First evidence of oncologic neuropathic pain prevalence after screening 8615 cancer patients. Results of the on study, Ann Oncol, 2011; 22: 924-930.
53. Gasche Y., Daali Y., Fathi M. et al.: Codeine intoxication associated with ultrarapid CYP2D6 metabolism, N Engl J Med, 2004; 351: 2827-2831.
54. George R., Jeba J., Ramkumar G., Chacko A.G., Tharyan P.: Interventions for the treatment of metastatic extradural spinal cord compression in adults, Cochrane Database Syst Rev, 2015; (9): Cd006716.
55. Graczyk M., Krajnik M.: Opioidofobia lekarzy i chorych jako przeszkoda w skutecznym leczeniu bólu u chorego na nowotwór, w: Malec-Milewska M., Krajnik M., Wordliczek J. (red.): Chory na nowotwór – kompendium leczenia bólu. Warszawa, Medical Education, 2013: 291-303.
56. Grassi L., Riba M.: Psychopharmacology in Oncology and Palliative Care. Nowy Jork, Springer, 2014.
57. Greco M.T., Roberto A., Corli O. et al.: Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer, J Clin Oncol, 2014; 32: 4149e4154.
58. Guan J., Tanaka S., Kawakami K.: Anticonvulsants or Antidepressants in Combination Pharmacotherapy for Treatment of Neuropathic Pain in Cancer Patients: A Systematic Review and Meta-analysis, Clin J Pain, 2016; 32, 719-725.
59. Hadley G., Derry S., Moore R.A., Wiffen P.J.: Transdermal fentanyl for cancer pain, Cochrane Database Syst Rev, 2013 Oct 5; (10): CD010270.
60. Hara S.: Opioids for metastatic bone pain, Oncology, 2008; 74 Suppl 1: 52-54.
61. Hardy J., Quinn S., Fazekas B., Plummer J., Eckermann S., Agar M. et al.: Double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain, J Clin Oncol, 2012; 30(29): 3611-3617.
62. Harris J.T., Suresh Kumar K., Rajagopal M.R.: Intravenous morphine for rapid control of severe cancer pain, Palliat Med, 2003 Apr; 17(3): 248-256.
63. Haywood A., Good P., Khan S. et al.: Corticosteroids for the management of cancer-related pain in adults, Cochrane Database Syst Rev, 2015; CD010756.
64. Heintze K., Fuchs W.: Codeine Ultra-rapid Metabolizers: Age Appears to be a Key Factor in Adverse Effects of Codeine, Drug Res (Stuttgart), 2015; 65: 640-645.
65. Heiskanen T., Mätzke S., Haakana S., Gergov M., Vuori E., Kalso E.: Transdermal fentanyl in cachectic cancer patients, Pain, 2009; 144: 218-222.
66. Hendriks L.E., Hermans B.C., van den Beuken-van Everdingen M.H. et al.: Effect of Bisphosphonates, Denosumab, and Radioisotopes on Bone Pain and Quality of Life in Patients with Non-Small Cell Lung Cancer and Bone Metastases: A Systematic Review, J Thorac Oncol, 2016; 11: 155.
67. Hill K.P.: Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA, 2015; 313, 2474-2483.
68. Hjermstad M.J., Fayers P.M., Haugen D.F., Caraceni A., Hanks G.W., Loge J.H., Fainsinger R., Aass N., Kaasa S.; European Palliative Care Research Collaborative (EPCRC).: Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review, J Pain Symptom Manage, 2011; 41: 1073-1093.
69. Hjermstad M.J., Gibbins J., Haugen D.F., Caraceni A., Loge J.H., Kaasa S.; EPCRC, European Palliative Care Research Collaborative: Pain assessment tools in palliative care: an urgent need for consensus, Palliat Med, 2008; 22: 895-903.
70. Hui D., dos Santos R., Chisholm G.B., Bruera E.: Symptom Expression in the Last Seven Days of Life Among Cancer Patients Admitted to Acute Palliative Care Units, J Pain Symptom Manage, 2015 Oct; 50(4): 488-494.
71. Jackson K., Ashby M., Howell D., Petersen J., Brumley D., Good P. et al.: The effectiveness and adverse effects profile of 'burst' ketamine in refractory cancer pain: the VCOG PM 1–00 study, J Palliat Care, 2010; 26(3): 176-183.
72. Johnson J.R., Burnell-Nugent M., Lossignol D., Ganae-Motan E.D., Potts R., Fallon M.T.: Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of thc:cbd extract and thc extract in patients with intractable cancer-related pain, J Pain Symptom Manage, 2010; 39: 167-179.
73. Jongen J.L., Huijsman M.L., Jessurun J. et al.: The evidence for pharmacologic treatment of neuropathic cancer pain: beneficial and adverse effects, J Pain

Symptom Manage, 2013; 46: 581.

74. Juba K.M., Khadem T.N., Hutchinson D.J., Brown J.E.: Methadone and Corrected QT Prolongation in Pain and Palliative Care Patients: A Case-Control Study, J Palliat Med, 2017; 20: 722 -728.
75. Kane C.M., Mulvey M.R., Wright S., Craigs C., Wright J.M., Bennett M.I.: Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis, Palliat Med, 2017 Jun: 269216317711826. doi: 10.1177/0269216317711826. [Epub ahead of print].
76. Kim H.J., Kim Y.S., Park S.H.: Opioid rotation versus combination for cancer patients with chronic uncontrolled pain: a randomized study, BMC Palliat Care, 2015; 14: 41.
77. King S., Forbes K., Hanks G.W., Ferro C.J., Chambers E.J.: A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project, Palliat Med, 2011; 25(5): 525-552.
78. Kotlinska-Lemieszek A., Paulsen O., Kaasa S., Klepstad P.: Polypharmacy in patients with advanced cancer and pain: a European cross-sectional study of 2282 patients, J Pain Symptom Manage, 2014 Dec; 48(6): 1145-1159.
79. Kotlinska-Lemieszek A., Klepstad P., Haugen D.F.: Clinically significant drug-drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review, Drug Des Devel Ther, 2015; 9: 5255-5267.
80. Krajnik M., Zylicz Z., Finlay I., Luczak J., van Sorge A.A. Potential uses of topical opioids in palliative care-report of 6 cases, Pain, 1999; 80(1-2): 121-125.
81. Krantz M.J., Martin J., Stimmel B., Mehta D., Haigney M.C.: QTc interval screening in methadone treatment. Ann Intern Med, 2009; 150: 387-395.
82. Kress H.G., Koch E.D., Kosturski H., Steup A., Karcher K., Lange B., Dogan C., Etropolski M.S., Eerdekens M.: Tapentadol prolonged release for managing moderate to severe, chronic malignant tumor-related pain, Pain Physician, 2014; 17(4): 329-343.
83. Kubota K., Kobayashi W., Sakaki H., Nakagawa H., Kon T., Mimura M., Ito R., Furudate K., Kimura H.: Professional oral health care reduces oral mucositis pain in patients treated by superselective intra-arterial chemotherapy concurrent with radiotherapy for oral cancer, Support Care Cancer, 2015; 23(11): 3323-3329.
84. Kuip E.J., Zandvliet M.L., Koolen S.L., Mathijssen R.H., van der Rijt C.C.: A review of factors explaining variability in fentanyl pharmacokinetics; focus on implications for cancer patients, Br J Clin Pharmacol, 2017; 83: 294-313.
85. Kumar A., Maitra S., Khanna P., Baidya D.K.: Clonidine for management of chronic pain: A brief review of the current evidences, Saudi Journal of Anaesthesia, 2014; 8: 92-96.
86. Lalla R.V., Bowen J., Barasch A., Elting L., Epstein J., Keefe D.M., McGuire D.B., Migliorati C., Nicolatou-Galitis O., Peterson D.E., Raber-Durlacher J.E., Sonis S.T., Elad S. and The Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO), Cancer, 2014; 120: 1453-1461.
87. Leadership Alliance for the Care of Dying People, One Chance to Get It Right: Improving People's Experience of Care in the Last Few Days and Hours of Life. London, LACDP, 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/ 323188/ One_chance_to_get_it_right.pdf.
88. LeBlanc T.W., McNeil M.J., Kamal A.H., Currow D.C., Abernethy A.P.: Polypharmacy in patients with advanced cancer and the role of medication discontinuation, Lancet Oncol, 2015 Jul; 16(7): e333-341.
89. Leppert W., Kowalski G.: Long-term administration of high doses of transdermal buprenorphine in cancer patients with severe neuropathic pain, Onco Targets Ther, 2015; 8: 3621-3627.
90. Leppert W., Majkowicz M.: The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain, Int J Clin Pract, 2010; 64: 1681-1687.
91. Leppert W., Zajaczkowska R., Wordliczek J., Dobrogowski J., Woron J., Krzakowski M.: Pathophysiology and clinical characteristics of pain in most common locations in cancer patients, J Physiol Pharmacol, 2016; 67: 787-799.
92. Leppert W.: Tramadol as an analgesic for mild to moderate cancer pain, Pharmacol Rep, 2009; 61: 978-992.
93. Leppert W.: Dihydrocodeine as an analgesic for the treatment of moderate to severe chronic pain, Curr Drug Metab, 2010; 11: 494-506.
94. Lexicomp® Drug Interactions. Dostępne pod adresem URL: http://www.uptodate.com/drug-interact.
95. Lindqvist O., Lundquist G., Dickman A., Bükki J., Lunder U., Hagelin C.L., Rasmussen B.H., Sauter S., Tishelman C., Fürst C.J.; OPCARE9: Four essential drugs needed for quality care of the dying: a Delphi-study based international expert consensus opinion, J Palliat Med, 2013 Jan;16(1): 38-43.
96. Lussier D., Huskey A.G., Portenoy R.K.: Adjuvant analgesics in cancer pain management, Oncologist, 2004; 9: 571-591.
97. Lyons P.J., Rivosecchi R.M., Nery J.P., Kane-Gill S.L.: Fentanyl-induced hyperalgesia in acute pain management, J Pain Palliat Care Pharmacother, 2015; 29(4): 378-384.
98. Ma H., Liu Y., Huang L., Zeng X.T., Jin S.H., Yue G.J., Tian X., Zhou J.G.: The Adverse Events of Oxycodone in Cancer-Related Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, Medicine (Baltimore), 2016 Apr; 95(15): e3341. doi: 10.1097/MD.0000000000003341.
99. Maida V., Daeninck P.J.: A user's guide to cannabinoid therapies in oncology, Curr Oncol, 2016; 23: 398-406.
100. Malik O.S., Kaye A.D., Urman R.D.: Perioperative Hyperalgesia and Associated Clinical Factors, Curr Pain Headache Rep, 2017 Jan; 21(1): 4.
101. Martín-Merino E., de Abajo F.J., Gil M.: Risk of toxic epidermal necrolysis and Stevens-Johnson syndrome associated with benzodiazepines: a population-based cohort study, Eur J Clin Pharmacol, 2015; 71: 759-766.
102. McDonald R., Ding K., Brundage M., Meyer R.M., Nabid A., Chabot P., Coulombe G., Ahmed S., Kuk J., Dar A.R., Mahmud A., Fairchild A., Wilson C.F., Wu J.S.Y., Dennis K., DeAngelis C., Wong R.K.S., Zhu L., Chan S., Chow E.: Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial, JAMA Oncol, 2017 Jul 1; 3(7): 953-959.
103. McLean S., Twomey F.: Methods of Rotation from another Strong Opioid to Methadone for the Management of Cancer Pain: A Systematic Review of the Available Evidence, Pain Symptom Manage, 2015; 50: 248-259.
104. Mercadante S., Arcuri E., Tirelli W., Casuccio A.: Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a, controlled, double-blind, crossover, double-dose study, J Pain Symptom Manag, 2000; 20(4): 246-252.
105. Mercadante S., Bruera E.: Opioid switching in cancer pain: From the beginning to nowadays. Crit Rev Oncol Hematol, 2016; 99: 241-248.
106. Mercadante S., Marchetti P., Cuomo A., Caraceni A., Mediati R.D., Mammucari M., Natoli S., Lazzari M., Dauri M., Airoldi M., Azzarello G., Bandera M., Blasi L., Cartenì G., Chiurazzi B., Costanzo B.V., Degiovanni D., Fusco F., Guardamagna V., Iaffaioli V., Liguori S., Lorusso V., Mameli S., Mattioli R., Mazzei T., Melotti R.M., Menardo V., Miotti D., Moroso S., De Santis S., Orsetti R., Papa A., Ricci S., Sabato A.F., Scelzi E., Sofia M., Tonini G., Aielli F., Valle A.; IOPS MS study group: Breakthrough Cancer Pain: Preliminary Data of The Italian Oncologic Pain Multisetting Multicentric Survey (IOPS-MS), Adv Ther, 2017; 34: 120-135.
107. Mercadante S., Portenoy R.K.: Breakthrough cancer pain: twenty-five years of study, Pain, 2016; 157(12): 2657-2663.
108. Mercadante S., Portenoy R.K.: Opioid poorly-responsive cancer pain. Part 3. Clinical strategies to improve opioid responsiveness, J Pain Symptom Manage, 2001; 21: 338.
109. Mercadante S., Velucci R., Cuomo A., Adile C., Cortegiani A., Valle A., Villari P., Casuccio A.: Long-term efficacy and tolerability of intranasal fentanyl in the treatment of breakthrough cancer pain, Support Care Cancer, 2015; 23: 1349-1354.
110. Mercadante S., Villari P., Ferrera P., Casuccio A., Fulfaro F.: Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion, Cancer, 2002; 95: 203-208.
111. Mercadante S., Villari P., Ferrera P., Porzio G., Aielli F., Verna L., Casuccio A.: Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine, J Pain Symptom Manage, 2006; 32: 175-179.
112. Mercadante S.: Opioid rotation for cancer pain: rationale and clinical aspects, Cancer, 1999; 86: 1856-1866.
113. Mercadante S.: Intravenous morphine for management of cancer pain, Lancet Oncol, 2010; 11: 484-489.
114. Mercadante S.L., Berchovich M., Casuccio A. et al.: A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients, Am J Hosp Palliat Care, 2007; 24: 13.
115. Miranda V., Fede A., Nobuo M., Ayres V., Giglio A., Miranda M. et al.: Adverse drug reactions and drug interactions as causes of hospital admission in oncology, J Pain Symptom Manage, 2011; 42: 342-353.
116. Moksnes K., Dale O., Rosland J.H., Paulsen O., Klepstad P., Kaasa S.: How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial, Eur J Cancer, 2011; 47: 2463-2470.
117. Moore N., Darwish M., Amores X., Schneid H.: A review of the pharmacokinetic

profile of transmucosal fentanyl formulations, Curr Med Res Opin, 2012; 28: 1781-1790.

118. Morita T., Takigawa C., Onishi H., Tajima T., Tani K., Matsubara T. et al.: Opioid rotation from morphine to fentanyl in delirious cancer patients: an open-label trial, J Pain Symptom Manage, 2005; 30: 96-103.
119. Murtagh F.E., Chai M.O., Donohoe P., Edmonds P.M., Higginson I.J.: The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice, J Pain Palliat Care Pharmacother, 2007; 21(2): 5-16.
120. Nakamura N., Takahashi O., Zenda S., Kawamori J., Ogita M., Onozawa M., Arahira S., Toshima M., Motegi A., Hirano Y.: Neuropathic Pain Features in Patients with Bone Metastases, Clin Oncol (R Coll Radiol), 2016; 28: 204-208.
121. NCCN Clinical practice Guideline in oncology, Adult Cancer Pain. Version 2, 2017; http: nccn.org (on line May 2017).
122. NHS Medicines Q&As. What naloxone dose should be used in adults to urgently reverse the effects of opioids or opiates? Dostępne pod adresem URL: www.evidence.nhs.uk.
123. NICE guideline [NG31]. Care of dying adults in the last days of life Published date: December 2015. Dostępne pod adresem URL: https://www.nice.org.uk/guidance/ng31.
124. NICE. Palliative Care for adults: strong opioids for pain relief. Clinical guideline [CG140]. Dostępne pod adresem URL: https://www.nice.org.uk/guidance/cg140.
125. Nicholas M.K., Asghari A., Blyth F.M.: What do the numbers mean? Normative data in chronic pain measures, Pain, 2008; 134: 158-173.
126. Nielsen S., Sabioni P., Trigo J.M., Ware M.A., Betz-Stablein B.D., Murnion B., Lintzeris N., Khor K.E., Farrell M., Smith A., Le Foll B.: Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis, Neuropsychopharmacology, 2017 Apr 5. doi: 10.1038/npp. 2017.51. [Epub ahead of print].
127. Nishihara M., Arai Y.C., Yamamoto Y., Nishida K., Arakawa M., Ushida T. et al.: Combinations of low-dose antidepressants and low-dose pregabalin as useful adjuvants to opioids for intractable, painful bone metastases, Pain Physician, 2013; 16(5): E547-52.
128. Núñez Olarte J.M.: Oxycodone and the challenge of neuropathic cancer pain: a review, Oncology, 2008; 74 Suppl 1: 83-90.
129. Olesen A.E., Farmer A.D., Olesen S.S., Aziz Q., Drewes A.M.: Management of chronic visceral pain, Pain Manag, 2016; 6: 469-486.
130. Olesen A.E., Kristensen K., Staahl C., Kell S., Wong G.Y., Arendt-Nielsen L., Drewes A.M.: A population pharmacokinetic and pharmacodynamic study of a peripheral κ-opioid receptor agonist CR665 and oxycodone, Clin Pharmacokinet, 2013 Feb; 52(2): 125-137.
131. Opioids in Palliative Care: Safe and Effective Prescribing of Strong Opioids for Pain in Palliative Care of Adults. NICE Clinical Guidelines, No. 140; National Collaborating Centre for Cancer (UK). Dostępne pod adresem: https://www.ncbi.nlm.nih.gov/books/NBK115251/
132. Paice J.A., Portenoy R., Lacchetti C., Campbell T., Cheville A., Citron M., Constine L.S., Cooper A., Glare P., Keefe F., Koyyalagunta L., Levy M., Miaskowski C., Otis-Green S., Sloan P., Bruera E.: Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline, J Clin Oncol, 2016; 34: 3325-3345.
133. Paisley P., Serpell M.: The role of topiceuticals in cancer pain, Curr Opin Support Palliat Care, 2017; 11: 93-98.
134. Pan Birmingham NHS Cancer Network. Guidelines for the use of naloxone in palliative care in adult patients 2012.
135. Paulsen O., Aass N., Kaasa S., Dale O.: Do corticosteroids provide analgesic effects in cancer patients? A systematic literature review, J Pain Symptom Manage, 2013; 46: 96-105.
136. Paulsen O., Klepstad P., Rosland J.H. et al.: Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial, J Clin Oncol, 2014; 32: 3221.
137. Pigni A., Brunelli C., Caraceni A.: The role of hydromorphone in cancer pain treatment: a systematic review, Palliat Med, 2011; 25: 471-477.
138. Porta-Sales J., Garzón-Rodríguez C., Llorens-Torromé S., Brunelli C., Pigni A., Caraceni A.: Evidence on the analgesic role of bisphosphonates and denosumab in the treatment of pain due to bone metastases: A systematic review within the European Association for Palliative Care guidelines project, Palliat Med., 2017; 31: 5-25.
139. Portenoy R.K., Ganae-Motan E.D., Allende S. et al.: Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded dose trial, J Pain, 2012; 13: 438-449.
140. Portenoy R.K.: Adjuvant analgesics in pain management, w: Hanks G., Cherny N.I., Christakis N., Fallon M., Kaasa S., Portenoy R.K. (eds).: Textbook of Palliative Medicine, 4th, Oxford, Oxford University Press, 2010: 361.
141. Prommer E.: Review article: dexmedetomidine: does it have potential in palliative medicine?, Am J Hosp Palliat Care, 2011; 28: 276.
142. Prommer E.E.: Ketamine for pain: an update of uses in palliative care, J Palliat Med, 2012; 15(4): 474-483.
143. Raptis E., Vadalouca A., Stavropoulou E., Argyra E., Melemeni A., Siafaka I.: Pregabalin Vs Opioids for the Treatment of Neuropathic Cancer Pain: A Prospective, Head-to-Head, Open-Label Study, Pain Pract, 2014; 14(1): 32-42.
144. Reddy A., Schuler U.S., de la Cruz M., Yennurajalingam S., Wu J., Liu D., Bruera E.: Overall Survival among Cancer Patients Undergoing Opioid Rotation to Methadone Compared to Other Opioids, J Palliat Med, 2016 Dec 20. doi: 10.1089/jpm.2016.0316. [Epub ahead of print].
145. Reddy S., Hui D., El Osta B., de la Cruz M., Walker P., Palmer J.L., Bruera E.: The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study, J Palliat Med, 2010; 13: 33-38.
146. Riechelmann R.P., Zimmermann C., Chin S.N., Wang L., O'Carroll A., Zarinehbaf S. et al.: Potential drug interactions in cancer patients receiving supportive care exclusively, J Pain Symptom Manage, 2008; 35: 535-543.
147. Riley J., Branford R., Droney J., Gretton S., Sato H., Kennett A., Oyebode C., Thick M., Wells A., Williams J., Welsh K., Ross J.: Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial, J Pain Symptom Manage, 2015; 49: 161-172.
148. Ripamonti C., Groff L., Brunelli C., Polastri D., Stavrakis A., De Conno F.: Switching from Morphine to Oral Methadone in treating Cancer Pain: What Is the Equianalgesic Dose Ratio?, J Clin Oncol, 1998; 16: 3216-3221.
149. Ripamonti C.I., Santini D., Maranzano E., Berti M., Roila F.: Management of cancer pain: ESMO Clinical Practice Guidelines, Ann Oncol, 2012, 23, (Suppl 7): 139-154.
150. Roeckel L.A., Le Coz G.M., Gavériaux-Ruff C., Simonin F.: Opioid-induced hyperalgesia: Cellular and molecular mechanisms, Neuroscience, 2016 Dec 3; 338: 160-182. doi: 10.1016/j.neuroscience.2016.06.029.
151. Rogríguez D., Urrutia G., Escobar Y., Moya J., Murillo M.: Efficacy and Safety of Oral or Nasal Fentanyl for Treatment of Breakthrough Pain in Cancer Patients: A Systematic Review, J Pain Palliat Care Pharmacother, 2015; 29: 228-246.
152. Roldan C.J., Nouri K., Chai T., Huh B.: Methylene Blue for the Treatment of Intractable Pain Associated with Oral Mucositis, Pain Pract, 2017 Feb 22. doi: 10.1111/papr.12566.
153. Rosario M., Francesco R., Sergio F., Niccolò G.L., Alba F., Maurizio N., Sergio A., Stefania G., Filippo A.: Effectiveness of tapentadol prolonged release for the management of painful mucositis in head and neck cancers during intensity modulated radiation therapy, Support Care Cancer, 2016 Oct; 24(10): 4451-4455.
154. Salas S., Frasca M., Planchet-Barraud B., Burucoa B., Pascal M., Lapiana J.M. et al.: Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in palliative care, J Palliat Med, 2012; 15(3): 287-293.
155. Sanford M., Silverman M.D.: Opioid Induced Hyperalgesia: Clinical Implications for the Pain Practitioner, Pain Physician, 2009; 12: 679-684.
156. Sarvizadeh M., Hemati S., Meidani M., Ashouri M., Roayaei M., Shahsanai A.: Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer, Adv Biomed Res, 2015 Feb 11; 4: 44.
157. Schmidt-Hansen M., Bennett M.I., Arnold S., Bromham N., Hilgart J.S.: Oxycodone for cancer-related pain, Cochrane Database Syst Rev, 2015 Feb 27; (2): CD003870. doi: 10.1002/14651858.CD003870.pub5.
158. Schmidt-Hansen M., Bromham N., Taubert M., Arnold S., Hilgart J.S.: Buprenorphine for treating cancer pain. Cochrane Database Syst Rev, 2015 Mar 31; (3): CD009596. doi: 10.1002/14651858.CD009596.pub4.
159. Schmidt-Hansen M., Taubert M., Bromham N., Hilgart J.S., Arnold S.: The effectiveness of buprenorphine for treating cancer pain: an abridged Cochrane review, BMJ Support Palliat Care, 2016; 6: 292-306.
160. Schneider S., Ait-M-Bark Z., Schummer C., Lemmer P., Yegles M., Appenzeller B., Wennig R.: Determination of fentanyl in sweat and hair of a patient using transdermal patches, J Anal Toxicol, 2008; 32: 260-264.
161. Schröder W., Tzschentke T.M., Terlinden R., De Vry J., Jahnel U., Christoph T., Tallarida R.J.: Synergistic Interaction between the Two Mechanisms of Action of Tapentadol in Analgesia, J Pharmacol Exp Ther, 2011 Apr; 337(1): 312-320.
162. Schumacher K.L., Plano Clark V.L., West C.M. et al.: Pain medication

management processes used by oncology outpatients and family caregivers part II: home and lifestyle contexts, J Pain Symptom Manage, 2014; 48: 784-796.

163. Sikandar S., Dickenson A.H.: Visceral pain: the ins and outs, the ups and downs, Curr Opin Support Palliat Care, 2012; 6: 17-26.

164. Sima L., Fang W.X., Wu X.M., Li F.: Efficacy of oxycodone/paracetamol for patients with bone-cancer pain: a multicenter, randomized, double-blinded, placebo-controlled trial, J Clin Pharm Ther, 2012; 37: 27-31.

165. Smith E.M., Pang H., Cirrincione C. et al.: Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA, 2013; 309(13): 1359-1367.

166. Solassol I., Caumette L., Bressolle F., Garcia F., Thézenas S., Astre C., Culine S., Coulouma R., Pinguet F.: Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients, Oncol Rep, 2005; 14: 1029-1036.

167. Soto E., Stewart D.R., Mannes A.J., Ruppert S.L., Baker K., Zlott D. et al.: Oral ketamine in the palliative care setting: a review of the literature and case report of a patient with neurofibromatosis type 1 and glomus tumor-associated complex regional pain syndrome, Am J Hosp Palliat Care, 2012; 29(4): 308-317.

168. Starmer H.M., Yang W., Gourin C.G., Kumar R., Jones B., McNutt T., Cheng S., Quon H.: One-Year Swallowing Outcomes in Patients Treated with Prophylactic Gabapentin During Radiation-Based Treatment for Oropharyngeal Cancer, Dysphagia, 2017 Jun; 32(3): 437-442.

169. Stocker R., Close H.: Assessing the uptake of the Liverpool Care Pathway for dying patients: a systematic review, BMJ Support Palliat Care, 2013 Dec; 3(4): 399-404.

170. Stockley's Drug Interactions. Dostępne pod adresem URL: https://www.medicinescomplete.com/mc/stockley.

171. Straube C., Derry S., Jackson K.C., Wiffen P.J., Bell R.F., Strassels S., Straube S.: Codeine, alone and with paracetamol (acetaminophen), for cancer pain, Cochrane Database Syst Rev, 2014 Sep 19; (9): CD006601. doi: 10.1002/14651858.CD006601.pub4.

172. Suno M, Endo Y, Nishie H i wsp: Refractory cachexia is associated with increased plasma concentrations of fentanyl in cancer patients. Therapeutics and Clinical Risk Management 2015:11 751–757.

173. Swarm R.A. et al.: NCCN Clinical Practice Guidelines in Oncology, Adult Cancer Pain, Version 2, 2017.

174. Szczudlik A., Dobrogowski J., Wordliczek J. et al.: Diagnosis and management of neuropathic pain: Review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society – Part two, Polish Journal of Neurology and Neurosurgery, 2014; 48: 323-435.

175. Szczudlik A., Dobrogowski J., Wordliczek J. et al.: Diagnosis and management of neuropathic pain: Review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society – Part one, Neurol Neurochir Pol, 2014; 48: 262-271.

176. Tateo S.: State of the evidence: Cannabinoids and cancer pain-A systematic review, J Am Assoc Nurse Pract, 2017; 29: 94-103.

177. The International Narcotics Control Board (INCB). 2004 Annual Report, Press Release No. 6. Use of essential narcotic drugs to treat pain is inadequate, especially in developing countries. March 3 2004. Dostępne pod adresem URL: www.incb.org.

178. Twycross R., Wilcock A., Howard P.: Palliative Care Formulary (PCF5), 5th Edition. Palliativedrugs.com Ltd, Nottingham, 2014.

179. US Food and Drug Administration. Professional Drug Information. Dostępne pod adresem URL: http://www.drugs.com.

180. Ueberall M.A., Lorenzl S., Lux E.A., Voltz R., Perelman M.: Efficacy, safety, and tolerability of fentanyl pectin nasal spray in patients with breakthrough cancer pain, J Pain Res, 2016; 9: 571-585.

181. van den Beuken-van Everdingen M.H., de Graeff A., Jongen J.L., Dijkstra D., Mostovaya I., Vissers K.C.; national guideline working group "Diagnosis treatment of cancer pain": Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review, Pain Pract, 2017; 17: 409-419.

182. van den Beuken-van Everdingen M.H., Hochstenbach L.M.J., Joosten E.A.J. et al.: Update on prevalence of pain in patients with cancer: systematic review and meta-analysis, J Pain Symptom Manage, 2016; 50: 1070-1090.

183. Vayne-Bossert P., Escher M., de Vautibault C.G., Dulguerov P., Allal A., Desmeules J., Herrmann F.R., Pautex S.: Effect of topical morphine (mouthwash) on oral pain due to chemotherapy - and/or radiotherapy - induced mucositis: a randomized double-blinded study, J Palliat Med, 2010; 13(2): 125-128.

184. Vissers K.C.P., Besse K., Hans G., Devulder J., Morlion B.: Opioid Rotation in the Management of Chronic Pain: Where Is the Evidence?, Pain Pract, 2010; 10: 85-93.

185. Vokurka S., Skardova J., Karas M., Kostkova J., Steinerova K., Koza V., Bystricka E.: Oropharyngeal mucositis pain treatment with transdermal buprenorphine in patients after allogeneic stem cell transplantation, J Pain Symptom Manage, 2010; 39(6): e4-6.

186. Wall and Melzack's textbook of pain. McMahon S. et al. (eds.):, 6th ed. Philadelphia, Elsevier Saunders, 2013.

187. Whiting P.F., Wolff R.F., Deshpande S., Di Nisio M., Duffy S., Hernandez A.V., Keurentjes J.C., Lang S., Misso K., Ryder S., Schmidlkofer S., Westwood M., Kleijnen J.: Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA, 2015; 313(24): 2456-2473.

188. Wiffen P.J., Derry S., Moore R.A.: Tramadol with or without paracetamol (acetaminophen) for cancer pain, Cochrane Database Syst Rev, 2017 May 16; 5: CD012508. doi:10.1002/14651858.CD012508.pub2.

189. Wiffen P.J., Wee B., Moore R.A.: Oral morphine for cancer pain, Cochrane Database Syst Rev, 2016; 4: CD003868.

190. Woo K.Y., Abbott L.K., Librach L.: Evidence-based approach to manage persistent wound-related pain, Cur Opin Support Palliat Care, 2013; 7 (1): 86-94.

191. Woosley R.L., Heise C.W., Romero K.A, www.crediblemeds.org, Azcert, QT drugs List, on line 2017.

192. Wordliczek J., Zajaczkowska R.: Pain mechanisms in cancer patients, w: Hanna M. et al. (eds.): Cancer Pain. Nowy Jork, Springer, 2013: 47-70.

193. World Health Organization. Cancer Pain Relief. Geneva, 1986.

194. World Health Organization. Cancer Pain Relief. Geneva, 1996.

195. Wrzosek A., Woron J., Dobrogowski J., Jakowicka-Wordliczek J., Wordliczek J.: Topical clonidine for neuropathic pain, Cochrane Database of Systematic Reviews, 2015; Issue 8: 1-34.

196. Yennurajalingam S., Frisbee-Hume S., Palmer J.L. et al.: Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer, J Clin Oncol, 2013; 31: 3076.

197. Yomiya K., Matsuo N., Tomiyasu S., Yoshimoto T., Tamaki T., Suzuki T., Matoba M.: Baclofen as an adjuvant analgesic for cancer pain, Am J Hosp Palliat Care, 2009; 26: 112-118.

198. Zecca E., Brunelli C., Bracchi P. et al.: Comparison of the Tolerability Profile of Controlled-Release Oral Morphine and Oxycodone for Cancer Pain Treatment. An Open-Label Randomized Controlled Trial, J Pain Symptom Manage, 2016; 52: 783-794.

199. Zeppetella G., Davies A., Eijgelshoven I., Jansen J.P.: A network meta–analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes, J Pain Symptom Manage, 2014; 47: 772-785.

200. Zeppetella G., Davies A.N.: Opioids for the management of breakthrough pain in cancer patients, Cochrane Database Syst Rev, 2013 Oct 21; (10): CD004311.

201. Zheng S., He L., Yang X., Li X., Yang Z.: Evaluation of intrathecal drug delivery system for intractable pain in advanced malignancies: A prospective cohort study, Medicine (Baltimore), 2017 Mar; 96(11): e6354.

Word count: 14200 Page count: 30 Tables: 8 Figures: 2 Algorithm: 7 References: 201

DOI: 10.5604/01.3001.0012.2904 Table of content: https://ppch.pl/issue/11208

Copyright: Copyright © 2018 Fundacja Polski Przegląd Chirurgiczny. Published by Index Copernicus Sp. z o. o. All rights reserved.

Competing interests: The authors declare that they have no competing interests.

The content of the journal „Polish Journal of Surgery" is circulated on the basis of the Open Access which means free and limitless access to scientific data.

This material is available under the Creative Commons - Attribution 4.0 GB. The full terms of this license are available on: http://creativecommons.org/licenses/by-nc-sa/4.0/legalcode

Corresponding author: dr n. med. Renata Zajączkowska: Klinika Intensywnej Terapii Interdyscyplinarnej 31-501 Kraków, ul. Kopernika 50, e-mail: renia356@ poczta.onet.pl

Cite this article as: Wordliczek J., Kotlińska-Lemieszek A., Leppert W, i wsp.: Pharmacotherapy of pain in cancer patients – recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons; Pol Przegl Chir 2018: 90 (4): 55-84