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Department of Phthisiology and Pulmonology

CHRONIC PAIN SYNDROME:

MECHANISMS OF PAIN FORMATION IN INCURABLE PATIENTS, PRINCIPLES OF DIAGNOSIS AND TREATMENT

Handbook
for independent work in preparation
for practical classes for 6th-year students of speciality “Medicine”

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INTRODUCTION

Pain is a multifactorial, unpleasant sensory or emotional process associated with or described in terms of tissue damage (International Association for the Study of Pain (IASP), 1986). This definition emphasises the relationship between the objective (physiological) aspects of pain and its subjective (emotional and psychological) components. The response to pain can vary significantly not only between individuals, but also within the same person, depending on the conditions under which the pain occurs.

From a physiological point of view, pain is a systemic reaction of the body, a biologically important defence mechanism that signals life-threatening danger from the damaging effects of various factors and helps to maintain an integral organism. At the same time, severe and prolonged pain, which often occurs in palliative care patients with cancer or other diseases, forms persistent pathological reactions in the peripheral and central nervous system.

Pain is the most common reason for patients to visit a doctor. About 40 million visits to a doctor are registered in the United States every year for complaints of new-onset pain. Society incurs significant costs in the treatment of pain - in the US, direct and indirect medical costs in connection with various pain syndromes amount to about $4 billion. The pain associated with chronic diseases is not life-threatening, but it significantly affects the overall quality of life of patients. In a 2013 study, the Global Burden of Disease defined this as the "number of years of disability" (NYD) for a wide range of diseases and injuries.

Acute and chronic pain should be considered as the most relevant health problem. About 64 million people suffer from pain from injuries every year, and another 20 million from pain associated with surgical procedures, with many of them experiencing uncontrolled postoperative pain.

A leading and important area of palliative and hospice care aimed at improving the quality of life of terminally ill patients is the provision of adequate pain relief. Pain of varying degrees, from moderate to severe, and even unbearable, occurs in the vast majority of patients in the late stages of cancer and in many non-

cancer diseases, including HIV/AIDS, tuberculosis, cardiovascular, neurological, degenerative and inflammatory processes of bones and joints, etc.

It is possible to prevent or reduce the suffering of patients with incurable diseases through early detection, high-quality diagnosis and adequate treatment, including multidisciplinary therapy for chronic pain syndrome (CPS) and other disorders, as well as through the provision of psychological and social support.

The study guide "Chronic pain syndrome (mechanisms of pain formation in incurable patients, principles of diagnosis and treatment)" is compiled in accordance with the Work Programme for the discipline "Palliative and Hospice Medicine" for 6th year students of medical faculties. The sections of the manual describe the characteristics and components of CPS, classification of pain types, diagnosis and treatment of pain syndrome, its psychological and social aspects, peculiarities of communication between the patient and medical staff, and pain relief in the last hours of a patient's life.

1. General characteristics of chronic pain syndrome

With a prolonged course of severe pain, chronic pain syndrome (CPS) develops, which is inherent in many chronic diseases and almost all common types of malignant tumours, especially in the III-IV clinical stage. CPS is dangerous for the body, causing neurophysiological changes and disruption of the body's homeostasis. Long-term and severe CPS causes complex multicascade pathophysiological and pathopsychological changes in the body, which creates many new adverse clinical and psychological symptoms. CPS causes unspeakable suffering that deforms the patient's psyche up to the development of severe depression and suicidal behaviour, and can completely destroy a person as a person. Chronic pain syndrome syndrome is one of the most severe symptom complexes that disrupts the quality of life of incurable patients.

According to epidemiological studies, between 10% and 55% of people worldwide suffer from chronic bronchitis. According to the results of studies of patients in the terminal stage of the disease, it was found that 35-96% of cancer patients, 63-80% of AIDS patients, 41-77% of cardiovascular patients, 34-77% of COPD patients, and 45-70% of kidney patients have a distinct pain syndrome. Approximately one third of elderly people have pain as one of their main complaints.

Pain management is the most medically treatable aspect of palliative care. It is impossible to relieve a patient of mental, social and spiritual suffering while he or she is suffering physically. Adherence to clinical guidelines for pain management results in an adequate reduction of pain in 70-97% of patients in the late stages of an incurable disease.

Providing adequate pain relief is complicated by limited access to medicines. Medicinal and non-medicinal methods are used to relieve pain, but when the level of pain increases from moderate to severe or extreme pain is observed, opioid. At the same time, according to reports from the United Nations Office for Drug Control, WHO and international organisations, the consumption of opioids for the treatment of CPS is insufficient for medical purposes, resulting in 80% of the world's population having no or insufficient access to treatment for severe pain. The reasons

for this situation include the low priority given to pain relief in healthcare systems, greatly exaggerated fears of addiction, excessive restrictions imposed by national drug control policies, and problems with the procurement, production and distribution of opioids. According to WHO estimates, every year more than 10 million people in countries with no or limited access to controlled medicines have no or limited access to treatment for moderate to severe pain and suffer without adequate treatment, including: 1 million patients with terminal HIV/AIDS; 5,5 million terminal cancer patients; 0,8 million people suffering from trauma; patients with chronic diseases or post-surgical conditions, women in labour, children.

In view of the current trends in the healthcare system and the limited provision of quality pain relief caused by a number of barriers, the issue of ensuring a sufficient amount of opioids and cannabinoids for adequate pain relief and their rational use in accordance with the principles of evidence-based medicine is relevant for many countries, including Ukraine.

Pain is a kind of subjective psychophysiological or mental experience that cannot be quantified by modern research methods in physical units. The sensation of pain and its intensity in a particular person largely depend on his or her psychophysical state (psychological and emotional mood), type of nervous activity, temperament, willpower, moral qualities, motivation, physiological qualities, etc. Pain is largely learned through experiences associated with some kind of injury in the early years of life.

Individual features of pain perception depend on its threshold - the minimum irritation perceived by the patient as unpleasant, and can vary depending on external and internal factors. With a low threshold, a person perceives and feels a small impact in the form of pain, while with a high threshold, only severe irritation causes pain. Pain tolerance is determined by the maximum irritation that a patient can withstand. The interval from the pain threshold to pain tolerance is defined as the tolerance interval.

Based on the simultaneous consideration of threshold and pain tolerance, A. Sangailo (1959) identified 4 types of people:

Type 1 - with a low threshold and low pain tolerance (soon after the sensation of pain, its general intolerance sets in);

Type 2 - with a low pain threshold and a sufficient interval of patience;

Type 3 - with a high threshold but low pain tolerance;

Type 4 - with a high threshold and interval of pain tolerance.

Emotional and behavioural characteristics affect pain tolerance:

a) energetic, mobile, active individuals have a high interval of patience, are capable of self-control, behave adequately in difficult life situations, but at the same time do not tolerate loneliness and prolonged isolation;

b) indecisive, vulnerable, and impressionable individuals tolerate isolation well, but have poor pain tolerance.

The greatest interval of pain tolerance is observed at the age of 10-30 years. At an earlier and later age, the interval of patience decreases. Children have a pronounced emotional component of pain, fear of it. Adolescence is characterised by reduced pain sensitivity and increased adaptive capacity to tolerate pain. Adulthood is characterised by increased pain sensitivity in combination with relatively high adaptation to it. In the elderly and geriatric age, a decrease in pain sensitivity is accompanied by low adaptation to pain. Gender is also important: 70% of people with high pain tolerance are women, and up to 90% of men have a low tolerance interval. In 65-70% of healthy people, pain tolerance is in the average range.

Situational conditions have a significant impact on the manifestation of pain. In the evening, pain sensitivity may increase against the background of reduced tolerance compared to the morning and afternoon. Increased pain sensitivity and decreased patience are observed in stressful conditions (hospitalisation, surgical treatment). In certain situations, pain sensitivity may decrease due to emotional stress. Strong motivation, willpower of the patient, and switching attention to intellectual activity can completely suppress the feeling of pain. The pain can also be relieved by other pain (teeth grinding, clenching of a particular part of the body, etc.). In case of mental disorders (schizophrenia, frontal lobe lesions, alcohol

intoxication), pain sensitivity disorders are possible. Sometimes there is a painless course of severe pathological conditions (myocardial infarction, gastric ulcer). There are observations of individuals with congenital absence of pain sensation. An important role in pain sensitivity is also played by the accumulated experience of pain as a life-threatening phenomenon (pain history - saturation of life with pain syndromes), as well as "painful situations" that lead to the development of pain chronicity with a high frequency.

It is believed that the onset of CPS is associated with initially increased pain sensitivity, which is determined by the peculiarities of a person's mental functions, depending on numerous factors. In the case of CPS, pain becomes a leading cause of long-term psychoemotional disorders. The psychological aspects of pain are very various, depend on many physiological, psychological and social factors, and require careful analysis and an individual approach to pharmacoprophylaxis and therapy of each specific case of pain.

2. Anatomical and physiological components of pain formation

The mechanism of pain formation consists of the interaction of two physiological systems - namely, the pain (nociceptive) and anti-pain (antinociceptive) systems.

The nociceptive neurohumoral system is represented by specific pain receptors (nociceptors), various chemicals, conductive and central pain formations.

Nociceptors are free nerve endings that are elements of sensory neurons that are activated by various stimuli. Free nerve endings that perceive painful stimuli branch out in the epidermis. Below them are touch receptors (Merkel bodies), deeper down are pain plexuses associated with blood vessels, and then pressure receptors (Pacini bodies) and cold receptors (Krause flasks). As a rule, they are closely related to free nerve endings. Pain receptors can be excited by direct exposure to pain mediators. Nociceptors can also be mechanosensitive, thermosensitive, and polymodal. If the intensity of the stimulus exceeds a certain limit, a small sensation can turn into pain. The pulp, cornea, and eardrum contain only free nerve endings. In these tissues, pain occurs faster than other sensations. In internal organs and other parts of the body, they are found where pain can be caused by appropriate stimuli.

The nociceptive system also includes chemicals that are important for the origin of pain. There are several groups of algogens:

- Tissue algogens - compounds that are released into the extracellular space when the membranes of mast cells (histamine), platelets (ATP, serotonin), neutrophils (leukotrienes), macrophages, endothelium (interleukin-1, TNF, endothelin, prostaglandins, nitric oxide) are damaged;

- plasma algogens (bradykinin, kallidin);

- neurokinins - substances released from the peripheral endings of C-nociceptors (substance P, neurokinin A, coccalcigenin);

- excitatory amino acids (L-aspartate, L-glutamate) released by spinal cord neurons under the influence of pain impulses.

The transmission of neurochemical pain excitation after stimulation of peripheral nociceptors to the central structures of the spinal cord and brain is carried

out by afferent nociceptive fibres, which include unmyelinated A-δ fibres and myelinated C-fibres. A-δ fibres transmit early pain, C-fibres transmit late pain (impulses are much slower than A-δ fibres). In the spinal cord, pain is transmitted mainly by spino-thalamic tracts, as well as by afferent fibres of the spino-mesencephalic, spino-reticular, spino-cervico-thalamic tracts and the tract that goes to the nuclei of the dorsal columns. Information about pain coming from the head, face, and oral cavity organs is also transmitted to the central nervous system by sensory fibres of a number of cranial nerves, in particular the trigeminal nerve, and from internal organs - mainly the vagus nerve.

The spinal cord has a special "gate control" mechanism that regulates the flow of impulses from the periphery to the upstream areas responsible for nociceptive perception. The axons of afferent nociceptive fibres terminate in the columns of the posterior horn of the spinal cord, where they come into contact with intermediate neurons of the spinothalamic pathway, which reaches the posterior nuclei of the thalamus and then the somatosensory field of the cerebral cortex. The cells of the other segment of the posterior horn form the substantia gelatinosa (SG), whose short insertion neurons regulate the transmission of pain impulses from peripheral afferent fibres to the optic nucleus. The activity of SG interneurons is subject to modulatory influences. They are activated by descending inhibitory neurons or non-nociceptive afferent impulses (e.g., tactile sensitivity impulses) and inhibited by afferent nociceptive C-fibres. A similar "gate control" system exists in the thalamus (Fig. 1).

The antinociceptive neurohumoral system includes some areas of the central grey matter, the pontine tuberosity, the amygdala, the hippocampus, the cerebellar nuclei, and the reticular formation. The signal for their triggering is a prolonged and persistent increase in the intensity of painful effects (massive mechanical trauma, burn). Damage to the antinociceptive system may be accompanied by the onset of pain. Modern ideas about the mechanisms of pain and analgesia consider at least four endogenous analgesic systems: neural opiate, hormonal opiate, neural non-opiate and hormonal non-opiate.

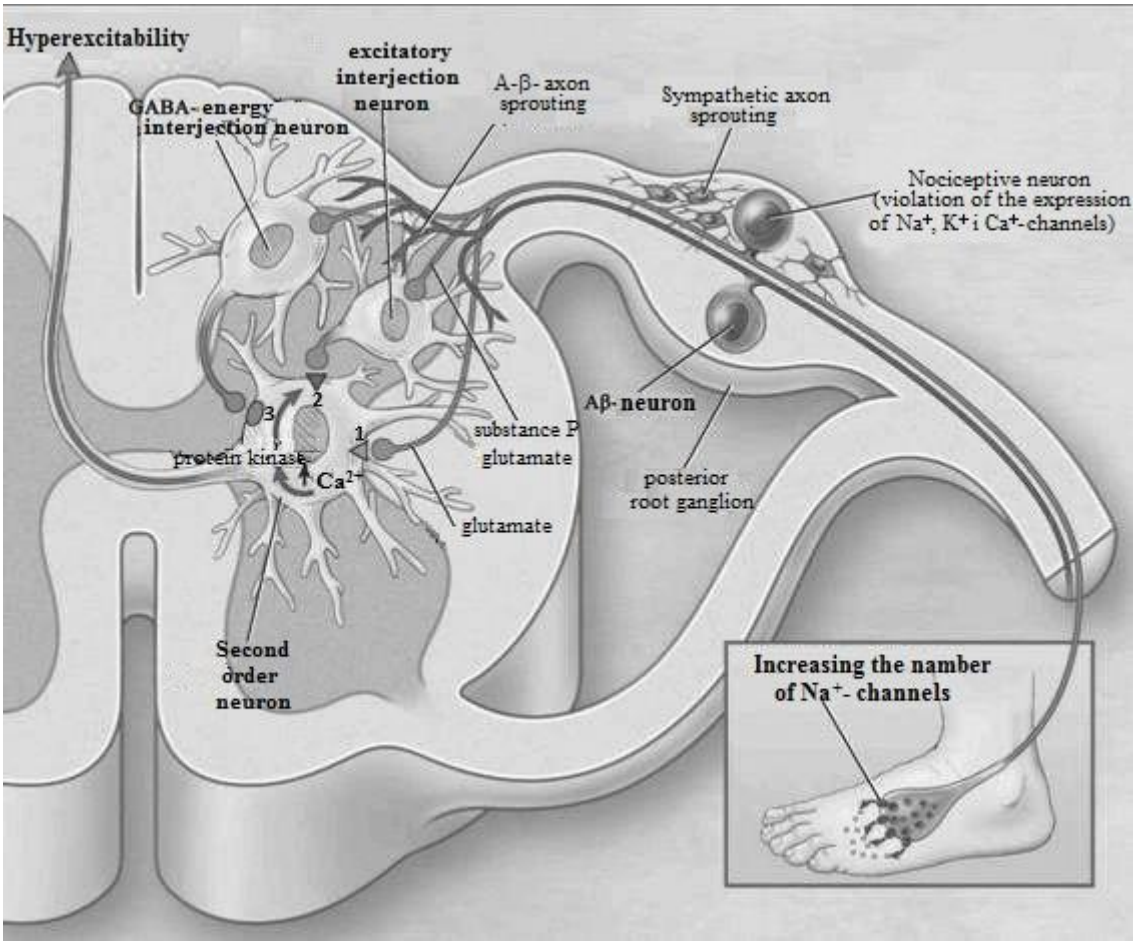


Figure1. Some mechanisms of neuropathic pain syndrome formation.
(accotding to https://doi.org/10.3390/ijms22031448) *

* Illustrative material provided by the author with reference to the original source, some materials have been supplemented and revised.

These systems differ in high-quality and quantitative features of triggering input signals, internal mechanisms and duration of analgesic action.

The central place in the antinociceptive system is occupied by the neuronal opiate system, whose neurons contain endogenous opiates - opioid peptides (endorphin, meth- and leukephalin). The neurons of the prefrontal cortex are encephalic. Hypothalamic neurons contain β–endorphins and dynorphin–α–non-endorphins.

Central grey matter neurons are enkephalin- and dynorphinergic. Morphine-like peptides - endorphins - have a similar effect to narcotic drugs, namely, they have analgesic and sedative effects. Endorphin molecules have a part common to all

morphine derivatives, and it is this part that is required for binding to specific opiate receptors in neurons, which are found in large numbers in the spinal cord, medial nuclei of the thalamus, hypothalamus, limbic structures, frontal cortex and other parts of the central nervous system. The irritation of these areas of the central nervous system, as well as the introduction of endorphins into the body, produces a strong analgesic effect. It has been proven that opioid peptides are modulators (usually inhibitory) of the release of mediators in the neurosecretory structures of the brain and interact with both neurotransmitters and neuropeptides. There is evidence of calcium-dependent release of opioid peptides during depolarisation of presynaptic endings. It has been proven that opioid peptides modulate synaptic transmission in the spinal cord, namely, the transmission of signals associated with pain sensitivity and the release of substances (one of the inhibitory analgesics) from the endings of sensory nerves. Perhaps this mechanism is the basis of the "pain gate" theory. The activity of the opiate analgesic system is subject to circadian fluctuations, but it is insensitive to changes in the function of the endocrine system. The hormonal opiate analgesic system, according to current incomplete understanding, includes 5 levels of the brain: the spinal cord, medulla oblongata, midbrain, hypothalamus and pituitary gland. Functional connections between the neurons of this system are carried out in several ways. Schematically, one of them is as follows: a painful impulse activates the A- and C-fibres of the peripheral nerve, the terminals of which release substance P and possibly other unidentified neurotransmitters to the cells of the fifth layer of the posterior horns of the spinal cord. Branches of these neurons reach the thalamus via the lateral spinothalamic pathway. The enkephalins released at presynaptic opiate receptors inhibit the release of substance P and, therefore, weaken the transmission of pain impulsesThere are two pathways in the brainstem: the first passes through the central grey matter, whose neurons release enkephalins and excite the neurons of the nucleus accumbens by inhibiting the next neuron in the central grey matter; the second bypasses the enkephalinergic neurons of the midbrain and directly activates the neurons of the nucleus accumbens (many of which are serotonergic), which have an inhibitory

effect on the neurons of the spinal cord. Afferent impulses from the spinal cord also reach the hypothalamus and pituitary gland, leading to the release of adrenocorticotropic hormone and β-endorphins. Once they enter the bloodstream, β-endorphins inhibit nociceptive neurons, and when they enter the cerebrospinal fluid of the third ventricle of the brain through the portal vein system, they have a direct inhibitory effect on thalamic neurons and excite inhibitory neurons of the central grey matter.

The hormonal non-opiate analgesic system controls pain with the help of pituitary neurohormones: adrenocorticotropic hormone and vasopressin. There is an assumption that the function of the hormonal non-opiate analgesic system is realised with the participation of other neurohormones (somatostatin, neurotensin, etc.). Neuronal non-opiate analgesia is mediated by the action of monoaminergic (MA) structures of the brainstem. Monoamine-containing neurons are localised in large numbers in brain structures whose function is closely related to nociception and antinociception, and interstructural connections are also made via several MA pathways in the brain. A significant effect on pain sensitivity has also been shown by some drugs whose mechanism of action is associated with changes in the metabolism of monoamines, in particular catecholamines and serotonin.

The presence of interdependent endogenous nociceptive and antinociceptive systems means that analgesic effect can be achieved not only by blocking nociceptive transmission at different levels, but also by activating any link of the endogenous antinociceptive system.

3. Classification of pain

From a biological point of view, physiological and pathological pain are distinguished.

Physiological pain activates protective tissue processes and behavioural reactions in order to eliminate the effect of the algogenic factor and its consequences. This adaptation and protective mechanism performs a signalling function.

Acute physiological pain is a necessary biological adaptive signal of damage that may occur (in the presence of pain experience), is beginning or has already occurred. As a rule, the development of acute pain is associated with well-defined painful irritations of superficial or deep tissues, internal organs, or dysfunction of the smooth muscles of internal organs without tissue damage. The duration of acute pain is limited by the time it takes to repair damaged tissues or the duration of smooth muscle dysfunction. The neurological causes of acute pain can be traumatic, infectious, dysmetabolic, inflammatory and other injuries of the peripheral and central nervous system, meninges, short-term neural or muscle syndromes.

Acute pain can be divided into superficial, deep, visceral and irradiating pain. These types of acute pain differ in subjective sensations, localisation, pathogenesis and causes.

According to the biopsychosocial model, pain is seen as the result of a two-way dynamic interaction of biological neurophysiological processes, psychological, social, religious and other factors. The result of this interaction is the individual nature of pain and the patient's response to pain. Under certain conditions, the strength and duration of pain may exceed its signalling function and not correspond to the degree of injury. Such pain itself turns into a pathogenic factor and becomes pathological.

Pathological pain leads to a decrease in activity and performance, causes psycho-emotional disorders, leads to regional and systemic microcirculatory disorders, secondary immune depression and disruption of visceral systems. In biological terms, pathological pain is dangerous for the body, causing a whole range

of maladaptive reactions. Pathological pain includes causalgia, hyperpathy, primary and secondary hyperalgesia, spontaneous pain attacks, etc.

Pathological pain (pain syndrome) is divided into acute and chronic pain. Acute pathological pain is a new pain that has recently started or has significantly increased, is inextricably linked to the injury and is usually a symptom of a disease.

Chronic pain in clinical practice is a much more urgent condition. Chronic pain often becomes an independent disease, lasts for a long time, and the cause of it can often not be determined. This type of pain is more in line with the concept of a syndrome - a set of symptoms and signs characteristic of a particular condition, not always caused by the same cause. Chronic pain may be independent of the underlying disease or damaging factor and develops according to its own laws. The International Association for the Study of Pain (IASP) defines it as "pain that lasts longer than the normal healing period" - more than 3 months. In practice, this can range from a few weeks to more than six months. Chronic pain can also include recurrent pain conditions (neuralgia, headaches of various origins, etc.). However, the main thing is not the temporal differences, but the neurophysiological, biochemical, psychological and clinical features that differ qualitatively. Acute pain is always a symptom, and chronic pain can become, in fact, an independent disease. It is clear that the therapeutic tactics for the treatment of acute or chronic pain have significant differences. Chronic pain may have a pathological process in the somatic sphere and/or primary or secondary dysfunction of the peripheral or central nervous system; in addition, it may also be caused by psychological factors.

Each type of chronic pain has its own clinical features, determined by the origin and mechanism of its origin, localisation, individual characteristics of the patient's personality, the influence of cognitive and social factors, and the existing "pain experience". The main clinical characteristics of such pain are its duration, monotony, and diffuse nature. The term "chronic pain syndrome" is used to refer to prolonged pain when the disease that caused it has often already been relieved, after acute lumbosacral radiculitis, surgical or therapeutic treatment of the pathological focus. Such pain is often not relieved by analgesics.

Particular attention in practical medicine is paid to the diagnosis and treatment of chronic pain, which accompanies almost all forms of malignant tumours and many incurable somatic diseases. The patient's constant feeling of pain is manifested in specific autonomic, affective and behavioural responses. Fear of the future, reactive depression, insomnia, suicidal attempts and aggressive reactions towards medical staff and relatives develop. Chronic pain forms a central dominant focus in the cerebral cortex, which activates direct neurohumoral mechanisms that increase the severity of its manifestations. To define the concept of "chronic pain", some experts use the term "total (total) pain", which refers to physical stimulus, psychological, social and spiritual factors. In patients with advanced cancer, a comprehensive assessment of the components of total pain plays an important role in choosing approaches to appropriate pathogenetic treatment.

3.1. Types of chronic pain

Chronic pain can be constant or attack-like, depending on the location of the pathological focus, its prevalence or previous treatment. The intensity of pain is divided into mild, moderate, severe/very severe (also referred to as "unbearable" pain).

The International Classification of Diseases (ICD-10) does not systematically list a diagnosis of chronic pain. The IASP has developed a systematic classification of chronic pain that distinguishes between primary and chronic secondary pain syndromes, integrates existing pain diagnoses, provides precise definitions, and describes additional features of the relevant diagnoses in accordance with the WHO model for ICD-11 (fig. 2).

These diagnoses related to pain syndrome were specified in the 11th version of the ICD and released by the WHO in 2018. Taking into account the IASP recommendations, various pathogenetically based types of pain are distinguished by their sources. Each type of pain is caused by a different degree of damage to soft tissues, bones and internal organs in various diseases.

According to the types, there are nociceptive, neuropathic, breakthrough pain and pathopsychological consequences of persistent chronic pain.

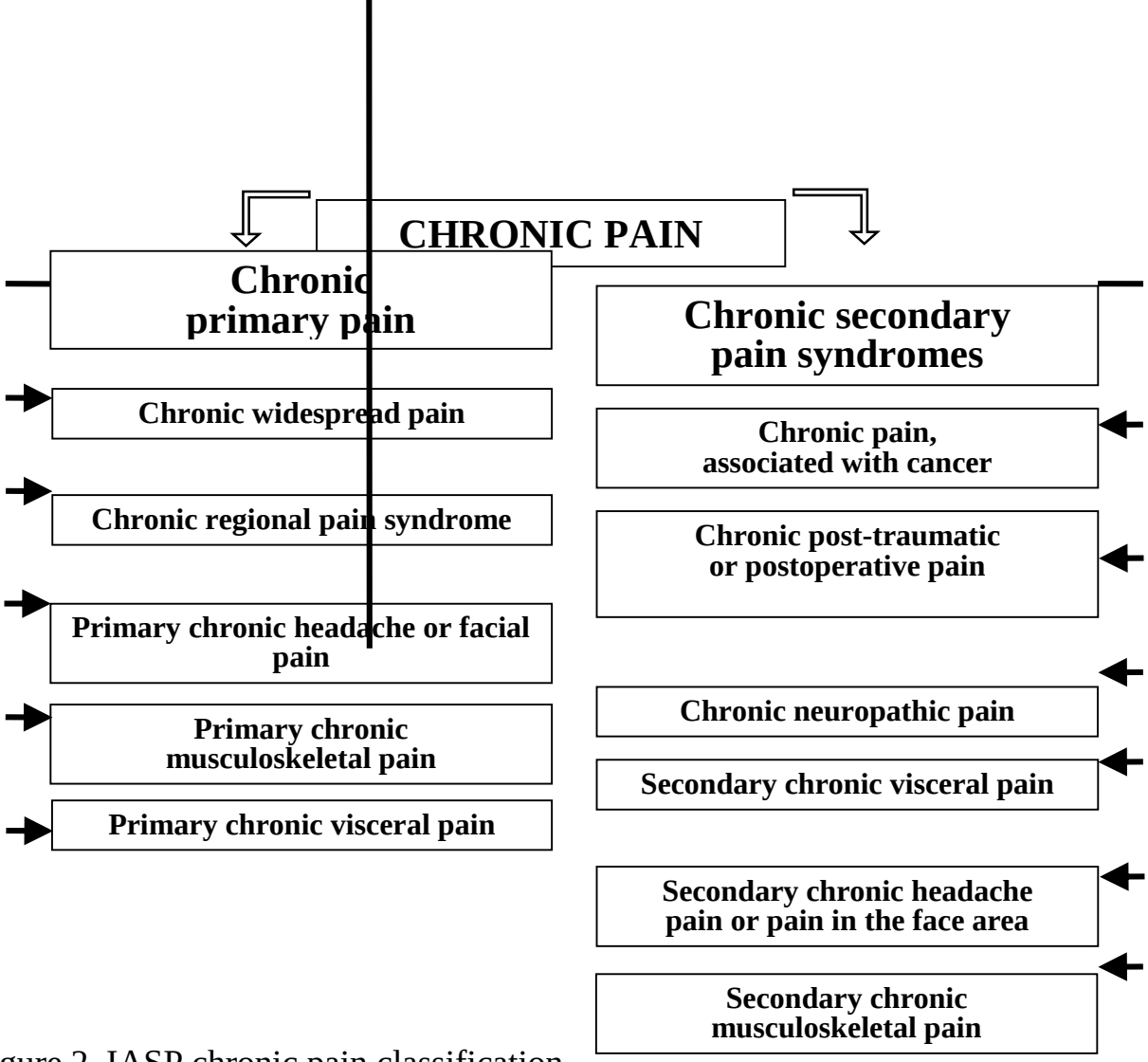


Figure 2. IASP chronic pain classification framework (2018).

(according to https://www.researchgate.net/publication/329950355_Chronic_pain_as_a_symptom_or_a_disease_the_IASP_Classification_of_Chronic_Pain_for_the_International_Classification_of_Diseases_ICD-11)

Nociceptive pain occurs when nociceptors are directly stimulated, and is divided into somatic pain (associated with nociceptor irritation in bone, soft tissue, or muscle spasm) and visceral pain (in carcinomatosis of serous membranes, hydrothorax, ascites, and overstretching of the walls of hollow organs and capsules of parenchymal organs).

Nociceptive somatic pain is divided into superficial and deep pain. Superficial pain is well localised and occurs when the skin is damaged. Deep pain occurs when damaging stimuli affect structures located deeper than the skin and is less clearly localised.

Nociceptive visceral pain is deep, poorly localised, and occurs in internal organs. It occurs when the smooth muscles of the hollow internal organs are strongly stretched or contracted. This type of pain is characterised by numerous autonomic reactions (increased sweating, increased blood pressure, heart rate, etcIt is believed that the interoceptors of internal organs form a separate visceral sensory system. Unlike the five external senses, information from it does not contribute to the formation of our consciousness. Interoceptors of internal organs. Internal organs only send impulses to the corresponding subcortical centres about their functional state, but visceral signals become conscious only when pathology and pain occur. On the other hand, there is a view that the visceral sensory system influences our mood through the subconscious, causing good health or, conversely, unmotivated psychological discomfort.

Neuropathic pain occurs due to complete or incomplete damage to the myelin sheath of peripheral or central conducting pathways, peripheral nerves, roots, trunks or plexuses (compression, tissue dissection, infiltration, ischaemia, metabolic disorders, toxicity).

Neuropathic pain is more often chronic and is caused by damage to the peripheral and/or central nervous system with the development of dysfunction of the nociceptive and antinociceptive systems. The pathophysiological basis of neuropathic pain is neuronal hyperexcitability, which occurs as a result of plastic changes in the structures associated with the conduction and processing of nociceptive signals. Neuropathic pain increases at night and decreases with movement. Other manifestations of sensory neuropathy are also characteristic: numbness, burning, paresthesia. Often there is an increased reaction to painful stimulation (hyperalgesia) or touch (hyperesthesia), as well as the perception of a small irritation as painful (allodynia). Hyperesthesia, hyperalgesia and allodynia are combined under the term "hyperpathy". The treatment of neuropathic pain consists of 3 main components: achieving compensation for metabolic disorders, the use of medications to eliminate pain and paresthesias, and non-drug treatments. This

pathology is often difficult to treat, as it is resistant to many drugs and is accompanied by side effects.

Pain, especially chronic pain, causes untold suffering, deforming the human psyche, and can completely destroy a person as a person.

Neuropathic pain is divided into:

a) central - caused by demyelinating damage in the central nervous system (post-stroke conditions, spinal cord injuries and post-traumatic conditions, multiple sclerosis);

b) peripheral - associated with pathological changes in the peripheral nervous system (peripheral nerve damage in trauma and post-traumatic conditions, radiculopathy, post-herpetic and HIV-associated neuropathy, trigeminal neuralgia, the effect of certain drugs, tumour invasion).

Variants of neuropathic pain are:

- allodynia (occurs under the influence of normal, non-painful stimuli (touch));
- Causalgia is a pathological condition manifested by intense burning pain and accompanied by local vasomotor, trophic and motor disorders. The main triggers of causalgia are nerve damage as a result of trauma, surgery, malignancy, tunnel syndrome, radiotherapy, vascular disorders and infectious lesions;
- paresthesia (abnormal sensitivity to unpleasant stimuli). It can be spontaneous and induced;
- phantom pain - may occur for a long period after amputation of parts of the limbs;
- hyperalgesia (increased pain sensitivity to familiar painful stimuli);
- hypoalgesia (decreased pain sensitivity to usual pain stimuli);
- dysesthesia (unpleasant sensations that may be spontaneous or induced).

Breakthrough pain occurs as sudden acute pain or a significant increase in chronic pain despite appropriate chronic pain management. Breakthrough pain is diagnosed only if two criteria are met simultaneously:

- persistent or prolonged pain (12 hours a day or more), or pain that would be present if the patient did not regularly take analgesics;

- persistent pain (or pain lasting 12 hours a day or more) is controlled satisfactorily.

A prerequisite for the diagnosis of breakthrough pain is to ensure that the treatment of persistent pain is optimal and that there is no increase in pain at the end of the opioid duration or when the opioid is administered in insufficient doses. The key is to differentiate idiopathic breakthrough pain (independent of stimulation) from provoked pain, which is caused by specific known stimuli (diagnostic or therapeutic procedure, predictable situation (movement) or difficult to predict (cough)). We should try to establish the mechanism of breakthrough pain and try to influence it specifically.

Pathological consequences of persistent chronic pain (psychogenic pain, total pain). Psychogenic pain can occur in the absence or in the case of minor tissue damage, and can continue after the elimination of the pathological focus, when the decisive factor is the psychoemotional state. Psychogenic pain is not related to location, its intensity and nature may not correspond to the severity of the disease. Psychological factors have a significant impact on the patient's subjective assessment of pain, overestimation or underestimation of its significance. Pain is inevitably accompanied by emotional processes (fear, anxiety, depression), on the other hand, its individual manifestations directly depend on the state of a person's mental functions, which requires appropriate pharmacological approaches on the part of the doctor. In severe long-term pain, the nociceptive system undergoes plastic changes that determine the formation of chronic pain ("pain disease") and require independent treatment.

Depression and the syndrome that occurs on its background, which is known as "depression-pain", play a special role in the development of chronic pain. Depression often has a latent course, is not recognised by patients themselves, and its only manifestation may be chronic pain. In turn, chronic pain is often a mask of latent depression.

A variety of mechanisms and manifestations, physical, psychological, social and spiritual aspects of suffering in long-term pain syndrome form total pain.

4. Algorithm for diagnosing chronic pain syndrome

The problem of assessing and controlling a set of clinical symptoms that cause the greatest complaints of patients in the terminal period of life is an important and complex clinical task. A fundamental objective difficulty in assessing the presence and severity of a particular clinical symptom in a seriously ill patient in the terminal stage is the inability to apply certain standard diagnostic procedures using instrumental and laboratory methods in most cases. In such cases, it is necessary to rely mainly on the subjective complaints of the patient and his or her relatives, on their own observations and clinical experience of medical staff.

Key principles of diagnosing chronic pain:

1Pain is a subjective, individual characteristic that only the person suffering from it knows about. Pain is what the patient complains about.

2. A correct assessment of pain is necessary to determine the cause and mechanism.

3. Different types of pain require different treatments.

4. Careful questioning of the patient about his/her pain is essential for diagnosis and effective treatment.

5. It is the physician's duty to determine the nature and cause of the pain and to prescribe effective treatment.

Principles and methods of diagnosis and assessment of chronic pain

An important role in the correct choice of chronic pain treatment tactics is played by the correct assessment and methods of diagnosing the type, causes and intensity of chronic pain with the determination of genesis, which should be based on

1) simple non-invasive methods of assessing pain intensity;

2) assessment of the patient's quality of life;

3) assessment of the patient's individual response to analgesic medications or other symptomatic treatments.

Given the special physical and psychological vulnerability of this patient population, based on general humanitarian and medical ethical considerations, the use of special instrumental and laboratory research methods in this situation is limited.

A complex of diagnostic criteria for the assessment of chronic pain

1) Anamnesis of chronic pain syndrome (its duration, intensity and type of manifestation, location, factors that increase or decrease chronic pain, previously used treatments and their effectiveness) and data from the patient's clinical examination, which provide information on the nature and prevalence of the cancer process or other pain factors, physical, neurological and mental status of the patient. Anamnesis of the disease and pain syndrome is collected, the patient is examined (it is necessary to pay attention to the patient's physical activity; signs of tumour progression; trauma; signs of neuropathy: hypo- or hyperanesthesia, allodynia) and the patient is directly questioned about pain, namely: the nature of pain (Table 1), its localisation and pain radiation (the patient should be asked to show painful places on themselves or on a drawing of the human body, emotional response to pain - fear, anxiety, depression. The OPQRSTU or OLDCART questionnaires are used to assess chronic pain (Table 2).

Table 1.

Recommended questions for chronic pain assessment

Characteristic	Recommended questions
The onset of pain	When did the pain start? How often does the pain occur? How long does the pain last?
Factors that make pain worse or better	What causes pain? What makes it better? What causes more intense pain? When the pain is less: sitting or lying down? Does the pain get worse with movement?
Localisation and radiation of pain	Where does it hurt? Is there radiation of pain? Is the pain felt in one place or in several?
The nature of the pain	How do you feel? Can you compare to the pain you felt once before?
Intensity of pain	How much pain do you have: mild, moderate, severe? How annoying is the pain? Is the pain accompanied by any other symptoms?
Impact of pain	Have you stopped doing them because of the pain? How do you sleep? What do you think is the cause of the pain?

Table 2.

Questionnaires by approach «OPQRSTU» i «OLDCART».

Approach «OPQRSTU»		
Characteristic		**Recommended questions/description**
O	Onset	When did the pain start? Did the pain start immediately or gradually?
P	Provoking/palliating	What causes the pain? What makes the pain less (rest, medicine)? What makes the pain worse?
Q	Quality	Determine if the pain is neuropathic (burning, tingling, numbness, itching, etc.)?
R	Region/radiation	Where did the pain start? Does the pain spread? If so, where is it spreading?
S	Severity	Use verbal description and visual analogue scales to describe the pain
T	Treatment	How do you treat the pain? What was used? Are there any side effects?
U	Understanding	Does the pain cause you distress?

Approach «OLDCART»		
Characteristic		**Recommended questions/description**
O	Onset	Occurrence (when, what is associated with)
L	Location	Localisation (there may be several areas of pain)
D	Duration	Duration (how long, constant, intermittent)
C	Characteristics	Properties (nociceptive, neuropathic)
A	Aggravating factors	Factors that increase pain (movement, sitting, coughing, etc.)
R	Relieving factors	Assessment of chronic pain intensity
T	Treatment	Treatment

2) Assessment of chronic pain intensity.

Diagnosis and assessment are based on the use of simple non-invasive methods to assess pain intensity and pain tolerance.

Pain intensity is classified as mild, moderate, severe/very severe (also known as "unbearable" pain). Assessment of pain intensity based on the patient's subjective feelings is carried out both before treatment and during pain treatment to determine the effectiveness of pain relief.

For this purpose, in palliative medicine, it is most often recommended to use a 5-point scale of verbal assessments of chronic pain intensity, according to which 0 - no pain, 1 point - mild, 2 points - moderate, 3 points - severe, 4 points - severe

pain.It is also proposed to use a visual analogue scale (VAS) of pain intensity from 0 to 10 in the form of a line on which the patient indicates the strength of his or her pain, where "0" means no pain at all, the numbers on the scale reflect an increase in pain, and "10" corresponds to the strongest pain that can be felt. The patient should indicate which of the points on the scale characterises their pain. According to this scale, 1-3 points correspond to mild pain, 4-6 points to moderate pain, 7-9 points to severe pain, and 10 points to unbearable pain.

Various 10-point scales (verbal, facial) for pain assessment can also be used. Such scales are necessary to quantify the initial level and dynamics of chronic pain intensity during treatment and to select the necessary painkillers and the scheme of their use (Fig. 3).

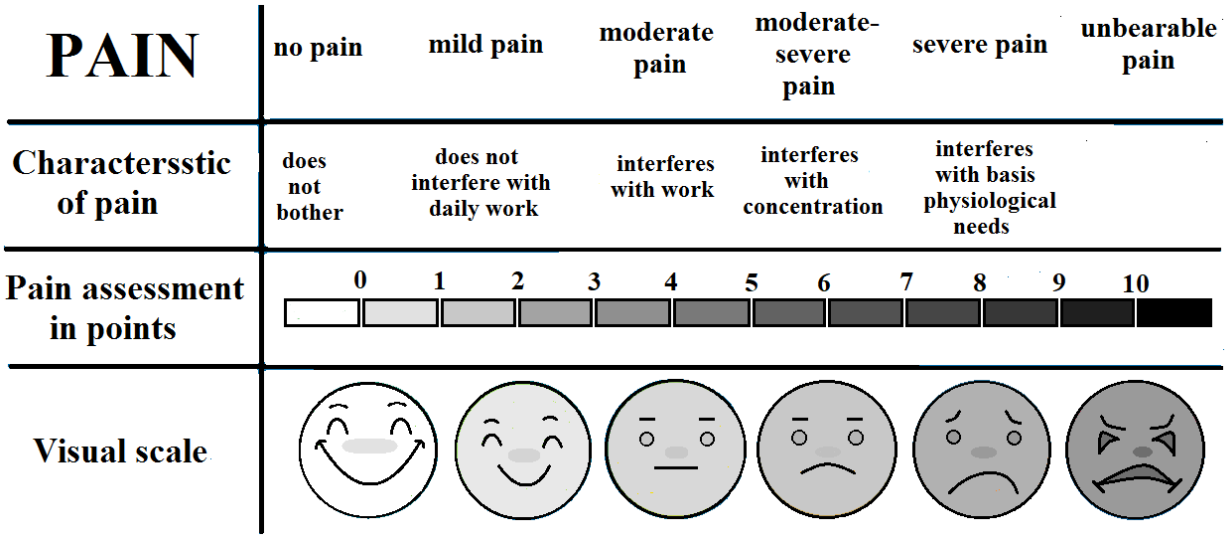


Figure 3. Visual analogue scales for determining pain intensity.

(according to https://www.researchgate.net/figure/Visual-analogue-scale-VAS-for-assessment-of-childrens-pain-perception_fig1_259499877)

For a more detailed assessment of chronic pain and quality of life, a set of criteria recommended by the IASP is used, which includes consideration of a person's social activity, professional activity, spirituality, sexual function, and satisfaction with treatment. It is also necessary to determine the type of pain.

Assessment of the quality of life and general condition of an incurable patient is carried out on a 5-point scale, where: (1) - normal physical activity; (2) - physical activity is somewhat reduced, but the patient can visit the doctor independently; (3)

- physical activity is moderately reduced, bed rest is less than 50% of the day; (4) - physical activity is significantly reduced, bed rest is more than 50% of the day; (5) - minimal physical activity, complete bed rest.

The quality of life and general condition are also assessed using the Karnowski index or the ECOG (Eastern Cooperative Oncology Group) scale (Table 3).

Table 3.

Assessment of the quality of life and general condition of an incurable patient

Karnovsky index	Activity, %	Scale ECOG	Оцінка
The condition is normal, there are no complaints and symptoms of the disease	100	Normal activity	0
Normal activity is preserved, but minor symptoms of the disease are present	90		
Normal activity is possible with additional effort, with moderate symptoms of the disease	80	There are symptoms of the disease, it does not require special care	1
The patient takes care of himself/herself, but is unable to perform normal activities or work	70		
The patient sometimes needs help, but is mostly self-care	60	He is treated on an outpatient basis and is capable of self-care. Spends more than 50% of waking hours actively	2
The patient often needs help and medical care	50		
The patient spends most of his/her time in bed, requires special care and assistance	40	He is only capable of limited self-care, spends 50% of his waking hours in a chair or bed for more than 50% of their waking hours	3
The patient is bedridden, hospitalisation is indicated, although the condition is not urgent	30		
Severe manifestations of the disease require hospitalization and supportive therapy	20	Disabled person, unable to self-care, confined to a chair or bed, needs observation and/or hospitalization	4
Dying patient, rapid progression of the disease	10		

Death	0		

The patient's response to chronic pain therapy, including side effects of medications and other medical procedures, is assessed.

Side effects of analgesics are most often assessed by their nature, severity and frequency. The presence of side effects is determined on a scale where 0 - no side effects; 1 - mild; 2 - moderate; 3 - severe. When assessing the side effects of medicines, it should also be borne in mind that many symptoms similar to the side effects of medicines (poor appetite, nausea, vomiting, constipation, etc.) occur in patients with chronic pain due to the disease itself and are not associated with the administration of analgesics.

Indicators of the patient's physical condition are used to varying degrees depending on the patient's setting (inpatient or home).

Special tests to assess the patient's response to the analgesic effect of medicines and their side effects are rarely performed and only with the patient's consent.

Based on anamnestic, documentary and diagnostic data, the cause, type, intensity of pain syndrome, pain location, concomitant complications and mental disorders are determined. All these criteria are taken into account to develop an individual clinical protocol (clinical route) for the treatment of chronic pain in a patient.

5. Treatment of chronic pain in palliative patients

If the patient himself or his relatives complain of any pain, the medical worker must:

- analyze the history of the disease, the history of pain (conditions of occurrence, factors causing its increase or decrease, duration, character);

- clarify the pain topography, taking into account that the irradiation zones of somatic and visceral pain may overlap;

- specify the mechanism, nature and intensity of pain in commonly defined, accessible terms;

- decide on the use of the necessary analgesics according to the WHO scale, the scheme of their administration, dosage, possible presence of adverse reactions.

Various methods are used in palliative medicine to treat CFS, including: treatment of the underlying disease, pharmacotherapy with analgesics and co-analgesics (adjuvant medicines), neurostimulation; anaesthetic, neurolytic and neurosurgical procedures; physiotherapy; psychotherapy; lifestyle changes; treatment of psychosocial factors that cause or exacerbate pain. The general approach to providing care to a patient with CRPS is based on the «ABCDE» approach:

A (Ask + Acess)	Ask about pain regularly and assess it systematically
B (Believe)	Believe the patient and family members and carers
C (Choose)	Choose methods of pain relief that are appropriate for the patient in the circumstances;
D (Deliver)	Deliver care in a timely, rational and consistent manner
E (Empower)	Empower patients and family members to participate in decision-making

The treatment (control) of chronic pain in palliative care is carried out according to general clinical approaches, including:

1. Etiological therapy: pharmacological, surgical, radiotherapy.

2. Systemic pharmacotherapy: mainly non-invasive (oral, rectal, sublingual, transdermal), as well as parenteral.

3. Local pharmacotherapy with analgesics: epidural, intravenous.

4. Nerve blockade, neurolysis, cryoanalgesia.

5. Electrostimulation analgesia: percutaneous, spinal, cerebral.

6. Destructive neurosurgery.

7. Psychotherapy and psychotherapeutic methods.

8. Auxiliary devices: corsets, prostheses, anti-bedsore devices.

The management of chronic pain is based on 5 basic principles of WHO (1996):

Principle 1 - "Through the mouth". If possible, pain relievers should be administered orally. If the patient is unable to use the medicine in this way, either rectal suppositories or subcutaneous injections should be used.

Principle 2 – "By the hour." To ensure constant pain control, analgesic drugs must be taken taking into account their pharmacokinetic characteristics, for example, morphine - every 4 hours.

Principle 3 – "Ascending". The type of analgesic medicine (basic analgesics, weak or strong opioids) is determined by the degree of pain. If the effect of an analgesic medicine decreases or is absent, the dose should be increased or a more powerful medicine should be used.

Principle 4 – "Individual approach". The dose of the medicine should be determined individually. There is no maximum dose for potent opioid analgesics (under side effect control).

Принцип 5 – "Attention to detail". The treatment of chronic pain must be tailored to the patient's condition, characteristics and needs, individualised.

5.1. Control of chronic pain according to the WHO scheme

The complex of pharmacological measures aimed at controlling chronic pain is based on the conceptual idea that the capabilities of modern clinical medicine, in particular, therapy with highly effective analgesics, can eliminate pain in 80-90% of patients.

Pharmacological pain treatment is based on application:

1. Non-steroidal anti-inflammatory drugs (NSAIDs) and non-narcotic analgesics;

2. Narcotic (opioid) analgesics;

3. Auxiliary (adjuvant) medicinal products (AMPs), whose action is aimed at optimising the effect of analgesics.

At the same time, WHO experts have concluded that severe pain can only be effectively treated with opioid analgesics.

The modern concept of chronic pain pharmacotherapy is based on the recommendations of the WHO and IAPHC (2008) on certain levels (stages) of pain relief, which are the basis of the three stages (the "WHO 3 steps") of chronic pain treatment in palliative oncology, developed and proposed by the WHO.

There are three main levels of pain relief for chronic pain (Fig. 4):

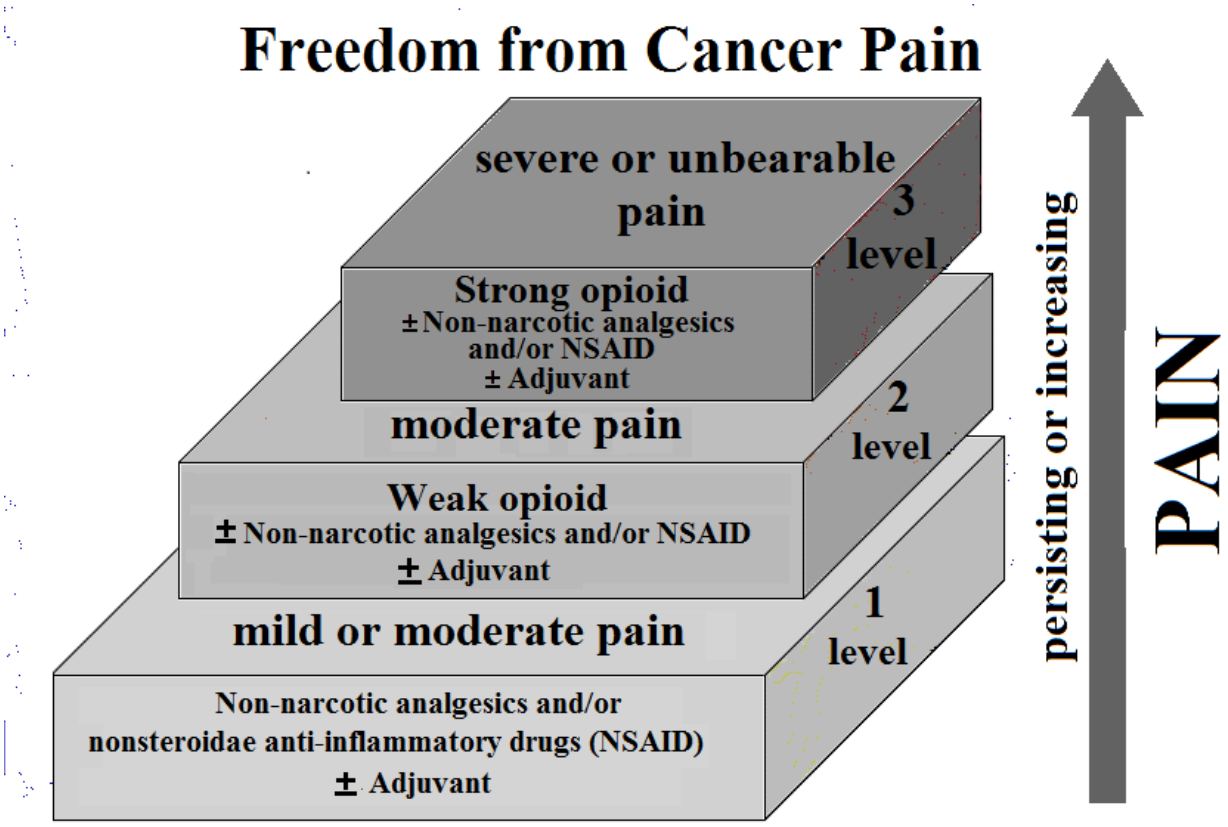


Figure 4. Three-stage pain management regimen for chronic pain, WHO.
(according to Cancer pain relief. WHO. Geneva. 1986.
https://apps.who.int/iris/bitstream/handle/10665/43944/9241561009_eng.pdf)

level 1 - in the presence of mild pain and moderate pain - non-narcotic analgesics and NSAIDs with analgesic effect are prescribed, if necessary, with the

use of additional (adjuvant) medicines aimed at potentiating the effect of analgesics and controlling other symptoms of the disease. Antidepressants (which also have analgesic properties), anticonvulsants, membrane-stabilising drugs, NMDA receptor antagonists, corticosteroids and, in some cases, muscle relaxants are used as adjuvant analgesics. Most palliative patients with this combination of medications receive effective pain relief for a long time - from days to months.

level 2 - in the presence of moderate pain and ineffectiveness of non-narcotic analgesics alone, weak narcotic (opioid) analgesics - codeine, dihydrocodeine, tramadol, or, in low doses, prosidol, morphine sulfate, as well as adjuvant medications - are prescribed in addition to level 1 drugs. The combined use of medications significantly increases the effectiveness of pain relief.

Level 3 - in the presence of severe and unbearable pain (primarily emanating from deep tissues or visceral organs) and ineffectiveness of therapy with drugs of levels 1 and 2, potent opioid analgesics from the morphine group are prescribed, without excluding non-narcotic analgesics and necessary auxiliary (symptomatic) drugs. The doses of opioid analgesics (OA) are selected according to the ascending principle (from the lowest to the highest) until the required pharmacotherapeutic effect is achieved.

Oral administration of medicinal products is the most optimal and is recommended by modern standards of pain relief, especially in palliative care patients; subcutaneous, rectal, transdermal and other methods of administration are used if clinically necessary.

One of the most important principles of analgesic use is to take analgesics "by the hour", regularly, according to the prescribed regimen, and not "on demand" when the pain becomes severe or unbearable. This is the only way to ensure a constant level of medicines sufficient for analgesia and to achieve effective control of the pain syndrome. This is very important when using opioid analgesics, as the development of painful dependence in the treatment of palliative care patients is no longer relevant.

5.2. Control of mild pain with non-narcotic analgesics and non-steroidal anti-inflammatory drugs

The criteria for low-intensity pain are a short pain history, an intensity of 0-40% according to VAS, high effectiveness of non-opioid analgesics (more than 4-6 hours) and a long night's sleep that is not interrupted by pain attacks.

Non-narcotic analgesics and NSAIDs do not affect the development of the main pathological process, the central neurophysiological mechanisms of pain development, but only reduce pain sensations and inflammation by inhibiting the synthesis of algogens.

The pharmacological effects of non-narcotic analgesics (Table 4) are associated with the inhibition of the activity of the cyclooxygenase (COX) enzyme, which produces prostaglandins (PG) from unsaturated fatty acids in the body tissues, which are involved in the processes of inflammation, fever and pain. GH increases the sensitivity of nerve endings to bradykinin, a peptide formed in tissues during inflammation simultaneously with GH and which is a stimulant of pain receptors. Non-narcotic analgesics inhibit the synthesis of PG and thus reduce the sensitivity of nerve endings to bradykinin, reduce tissue swelling in the inflammation site and weaken the mechanical compression of nociceptors in it. The central analgesic effect of non-narcotic analgesics is associated with the penetration of drugs through the blood-brain barrier and blockade of PG synthesis in the hypothalamic centres. In addition to this mechanism, COX-1,2 blockade reduces the transmission of pain impulses at the level of the dorsal root ganglia, as well as the spinal cord and brain. If the intensity of COX inhibition by acetylsalicylic acid is taken as 1, then the activity of butadione will be 5, mefenamic acid - 52, indomethacin - 217. Thus, the peripheral analgesic effect of non-narcotic analgesics is considered to be a consequence of the elimination of hyperalgesia that occurs in inflammatory foci.

All NSAIDs with long-term use have risks of damage to the mucous membrane of the stomach with the development of gastritis or peptic ulcer disease, which can be complicated by bleeding. High doses and long-term use of NSAIDs increase the risk of developing kidney failure, cardiovascular side effects, and coagulopathy.

Table 4.

Distribution of non-narcotic analgesics and NSAIDs by pharmacological effects

Non-narcotic analgesics	Nonsteroidal anti-inflammatory drugs				
	Non-selective COX inhibitors	Selective inhibitors COX-1		Selective COX-2 inhibitors	
		mostly selective	highly selective	mostly selective	highly selective
Paracetamol (Acetaminophen) Analgin (Metamisole sodium)	Acetyl-salicylic acid (high dose), Diclofenac sodium, Indomethacin, Ibuprofen	Acetyl-salicylic acid (high dose), Diclofenac sodium, Indomethacin, Ibuprofen	acetyl-salicylic acid (low dose)	Nimesulide Meloxicam	Celecoxib Parecoxib

Principles of use of non-narcotic analgesics and NSAIDs:

1. When choosing an analgesic, it is necessary to take into account the strength of the analgesic effect of the drug and the severity of the pain syndrome. If there is no effect within 3-4 days, it is necessary to replace the drug with a more effective one.

2. For the treatment of acute and chronic pain, the pharmacokinetic properties of analgesics must be taken into account.

According to the WHO recommendation, for chronic moderate pain, it is advisable to use long-acting analgesics (oxicam, solpaflex (ibuprofen retard), mesulid, diclofenac retard).

3. Carefully determine the dose required for the clinical effect:

a) for long-term course treatment with chronic moderate pain, it is necessary to start with the full daily dose;

б) when the effect is achieved, it is advisable to transfer the patient to a maintenance dose (2/3 - 1/2 of the therapeutic dose).

4. Choose the right route of drug administration.

5. In case of pain syndromes, it is recommended to synchronise the use of drugs with the maximum pain severity during the day, and, if necessary, to use preventive prescription of analgesics.

6. Avoid prescribing potentially toxic drugs

7. The duration of pharmacotherapy should be determined taking into account the nature of the pain syndrome, general condition, and individual drug tolerance:

а) Analgin, butadione, ketorolac, indomethacin are not prescribed for the long term;

б) paracetamol, nimesulide, meloxicam (or other low-toxic drugs) can be used in the long term.

8. Use in combination with other analgesic drugs if necessary. Combination of two drugs from the group of non-opioid analgesics is not recommended as to increased side effects.

The use of non-narcotic analgesics and non-steroidal anti-inflammatory drugs in the treatment of chronic pain is carried out in accordance with their pharmacological properties (Table 5).

Table 5.

Dosage of non-narcotic analgesics and NSAIDs in the treatment of chronic pain

Drug	**Single dose, mg**	**Input interval**	**Maximum daily dose, mg**
Acetylsalicylic acid	500-1000	4 hours	6000
Paracetamol	500-1000	4 hours	6000
Metamizole sodium	500-1000	4 hours	6000
Ibuprofen	200-400	4-6 hours	2400
Diclofenac sodium	50	6-8 hours	150
Indomethacin	25-50	6-8 hours	200
Nimesulide	100	12 hours	200
Celecoxib	100-200	12 hours	400

5.3. Control of pain with centrally acting analgesics (opioids)

Narcotic analgesics are prescribed for chronic pain that cannot be fully controlled by non-narcotic analgesics and NSAIDs.

Opioids (narcotic analgesics) are all substances of natural and synthetic origin that interact with opioid receptors and are similar to morphine in terms of pharmacological properties. Narcotic analgesics from the opioid class are used for pain relief in palliative care:

1. Natural opium alkaloids:

1.1. Morphine: Morphine hydrochloride, Morphine sulphate, Hydrocodone, Combinations of morphine with other drugs.

1.2. Codeine, combinations without psycholeptics.

2. Phenylpiperidine derivatives: Phentaline, Promedol, Trimeperidine.

3. Diphenylpropylamine derivatives: Dextropropoxyphene, combinations without psycholeptics.

4. Oripavine derivatives: Buprenorphine.

5. Morphine derivatives: Butorphanol, Nalbuphine.

6. Other opioids: Tramadol.

The mechanism of analgesic action of narcotic analgesics was elucidated after the discovery of endogenous opioid peptides (enkephalins, endorphins, dynorphins). Endogenous opioids are neurotransmitters of complex systems that inhibit pain sensations. They are able to interact with specific opioid receptors, which also react with narcotic analgesics administered to the body. The analgesic effect of narcotic analgesics is due to their influence on the inter-neuronal transmission of nociceptive impulses at different levels of the central nervous system.

Interacting with opioid receptors, mainly μ, k, δ, located on the presynaptic membrane of thin primary afferents of the spinal cord, morphine reduces the release of mediators of nociceptive signals. The presynaptic effect of morphine is due to the

opening of potassium (μ- and δ–receptors) or blocking of calcium (k-receptors) channels. Both processes lead to a decrease in the movement of calcium ions into the endings of C-fibres, which causes a decrease in the release of mediators. Various mediators are released from the endings of C-fibres, including tachykinins, excitatory amino acids, and some excitatory peptides that interact with numerous receptors. The presynaptic action of morphine, which leads to a decrease in mediator release, is considered to be the most effective component in the mechanism of analgesia.

As a result of opioid receptor disruption of the postsynaptic membrane, it hyperpolarises and inhibits the activity of the posterior horn neurons involved in the conduction of pain impulses. Narcotic analgesics also increase the inhibitory effects of certain structures of the midbrain and medulla oblongata on the activity of spinal cord neuronsMorphine causes changes in the emotional sphere, which can serve as a reason for reducing the emotionally negative feeling of pain. Each type of receptor has several other subtypes. A drug may have both agonist and antagonist properties for the same receptor, which explains the differences in the effects of individual opioids (Table 6).

Table 6.

The effects that occur when opioids interact with different receptor subtypes.

Receptors	Effects
μ (mu)	Analgesia, sedation, euphoria, respiratory depression, dependence, constipation, bradycardia, miosis
δ (delta)	Analgesia, respiratory depression, constipation
κ (kappa)	Analgesia, sedative effect, psychosomimetic effect, dependence formation, constipation, miosis

Morphine, fentanyl, and other drugs belong to the group of opioid receptor agonists, showing the highest affinity for μ receptors. Buprenorphine, butorphanol, nalbuphine, pentazocine belong to the group of partial agonists and agonist-antagonists of opioid receptors.

For the treatment of moderate pain, weak and moderate opioid analgesics are used - tramadol, codeine, dehydrocodeine, or strong opioids in small doses -

prosidol, morphine sulfate. They are often combined with non-narcotic analgesics and/or non-steroidal anti-inflammatory drugs.

Moderate chronic pain is characterised by an intensity of 40-70% of the VAS, usually lasting about 2-3 months, but it can be several days, low effectiveness of drugs (less than 4-6 hours) for the treatment of chronic pain of the 1st degree, and disturbances in night sleep due to pain.

Tramadol is a weak opioid analgesic (0,05-0,1 morphine potential) with a minimal risk of dependence. Tramadol (capsules, tablets) is used in a single dose of 50-100 mg. Tramadol retard 100-200 mg. In elderly patients, the drug may be used in the form of drops. The average duration of action of a single dose of tramadol is 6 hours, and of tramadol retard is 10-12 hours. Long-acting tablets are the best for long-term treatment of chronic pain. The maximum daily dose of tramadol is 400 mg.

Codeine is an opioid of medium analgesic action (0,1 morphine potential). It has a pronounced antitussive effect and causes constipation. It is used mainly in the form of combination medicines to suppress dry cough or as part of complex analgesics. Adults with chronic pain are prescribed 15-60 mg orally every 3-6 hours, with diarrhoea - 30 mg 4 times a day, with cough - 10-20 mg 4 times a day. The maximum daily dose for adults is 120 mg.

Dihydrocodeine is a semi-synthetic opioid analgesic of moderate potency (0,1-0,15 of morphine potential). It has extremely active metabolites (dihydromorphine, dihydromorphine-6-glucuronide) with a significantly greater analgesic effect. Long-acting dihydrocodeine tablets (10-12 hours) are used in a single dose of 60-90 mg twice daily. The maximum daily dose is 240 mg.

Prosidol is a semi-synthetic opioid analgesic of relatively strong action (0,3 morphine potential). It is administered transbuccally in a single dose of 10-20 mg 2-3 times a day. For the treatment of moderate pain, it can be used at a dose of 20-40 mg/day. The average duration of action of a single dose is 4-6 hours. The maximum daily dose is 250 mg. Tolerance develops if used for more than 3 months. The dose and frequency of administration are prescribed by a physician, taking into account

the intensity of pain and the patient's condition. It is prescribed mainly for short-term use when the effect of weak and moderate opioids is insufficient, in breakthrough pain.

If weak and moderate opioids are ineffective in maximum daily doses in combination with non-narcotic analgesics and/or NSAIDs in the treatment of chronic pain, it is necessary to prescribe to strong opioid analgesics.

The criteria for severe chronic pain are intensity of more than 70% of the VAS, insufficient efficacy of tramadol in combination with NSAIDs, short-term effect of a single dose of 20 mg of propidol (less than 4-6 hours), insufficient efficacy of low doses of strong opioids (20 mg/day of morphine sulfate in tablets or capsules), disturbances in night sleep due to pain, and a history of pain, usually more than 3 months, but it can be less than 1 month.

The reference drug ("gold standard") of narcotic analgesics is morphine, which is used in palliative medicine as a powerful painkiller. Its analgesic effect develops while the patient remains conscious. Under the influence of morphine, the subjective assessment of pain and attitude to it changes. At the same time, there is a change in the parameters of the pain reaction: the threshold of pain perception increases, the period of pain tolerance is prolonged, and emotional and behavioural reactions to pain are weakened. Analgesia is accompanied by changes in the mental sphere: self-control decreases, imagination is excited; in some cases, euphoria occurs. Sometimes drowsiness develops.

Morphine (morphine hydrochloride, morphine sulphate) is available in various dosage forms. The drug is mainly prescribed for analgesic effect by mouth (per os) or in rectal and other suppositories, transdermal applications, and injections, and is used in exceptional cases.

When choosing opioid analgesics, the speed of onset and degree of analgesic effect, as well as its duration, play a major role.

Rapid-acting drugs are used to select the analgesic dose, and sustained-release drugs are used after the daily analgesic dose has been selected. In this case, a fast-

acting drug can be prescribed simultaneously with a prolonged-acting drug to quickly relieve breakthrough pain.

Narcotic analgesics (opioids) used in palliative care differ in terms of analgesic potential (activity), speed and duration of action, and dosage (Table 7).

Table 7.

Comparative characteristics of narcotic analgesics

Drug	Analgesic activity*	Duration of action, hours	Start of of action, min	Starting dose, mg	Maximum daily dose, mg
Tramadol	0,05-0,1	4-6	30-60	50	400
Codeine	0,1	4	30-60	30-60	240
Dihydrocodeine	0,1-0,15	4-6	30-60	10	240
Prosidol	0,3	4-6	5-10	10-20	250
Morphine sulfate retard, per os	0,3	10-12	20-30	30	200
Morphine hydrochloride	**1**	4-6	SC, IM 10-15 per os 20-30	5-10	200
Buprenorphine, sublingually	20-30	8-12	30	0,2	2,4
Buprenorphine, parenterally	20-30	6-8	15	0,3	2,4
Fentanyl TTS, transdermally	100	72	18-24 hours	25 μg/h	300 μg/h

*Note: *The analgesic activity of narcotic analgesics is compared with the analgesic effect of Morphine hydrochloride, which is taken as "1".*

Taking into account the effectiveness and safety, promedol in any dosage form is NOT SUITABLE for the treatment of chronic pain syndrome!

The goal of opioid therapy is partial analgesia with preservation or improvement of the most important physiological and mental functions of the patient, taking into account acceptable side effects. When deciding on the prescription of opioids and their long-term use (with the exception of severe and unbearable pain that cannot be controlled by other drugs!) the "principle of the four A's" is applied: Analgesia. Adverse drug effects. Activity. Development of Addiction (Adherence).

At each patient visit, the achievement of therapeutic goals and adverse effects should be assessed (with clear documentation of "4A" in the patient's medical record), on the basis of which a decision on further treatment strategy is made:

- sense of comfort (degree of analgesia);
- the presence of opioid side effects;
- functional state (physical and psychological);
- the presence of abnormal drug-related behaviour.

Rules for prescribing strong opioid analgesics:

1. Initiate treatment with strong opioid analgesics(OA) in opioid-naïve patients with low doses of immediate-release morphine at prescribed doses for treatment of breakthrough pain.

2. If the patient has already taken OA, it is necessary to prescribe a new OA, taking into account the recalculated doses.

3. Most strong OA should be administered orally, as a solution or tablet, or transdermally.

4. In case of chronic pain, OA should be prescribed according to the schedule ("with a watch in the hands"), and not "as needed". It is advisable to prescribe analgesics prophylactically, without waiting for severe manifestations of pain.

5. Starting doses of morphine in opioid-naïve patients are typically 5 to 10 mg every four hours in young and middle-aged adults and 2,5 to 5 mg every four hours in the elderly.

6. It is advisable to prescribe additional doses of medicines, if necessary, for patients with moderate or severe pain for pain relief in breakthrough pain. When oral morphine is used to relieve breakthrough pain, it is necessary to prescribe oral morphine at a dose of one sixth of the daily dose of morphine and this dose should increase with the increase in the daily dose.

For example: initial prescription: 5mg of morphine, daily dose: 5mg*6=30mg, breakthrough dose: 30/6=5mg.

7. After prescribing OA, a thorough individual assessment of pain control, the degree of side effects, and the required total dose of opioids, including doses for

breakthrough pain, should be performed in 24 hours. Check the patient's condition and pain every 3-4 hours.

8. Titrate the dose of morphine to achieve maximum analgesic effect and minimal adverse reactions.

9. In the absence of analgesic effect, the dose should be increased by 30-50% daily.

10. If the first doses cause severe drowsiness, the dose should be reduced by 50% and increased more slowly during titration.

11. After achieving the analgesic effect and controlling adverse reactions, adjust the dose:

- add up the total dose of morphine prescribed for the day
- divide by six to obtain a new dose for regular use and breakthrough pain.

12. If the pain is relieved by a dose of immediate-release opioid every four hours, the prescription can be switched to a slow-release opioid.

13. For the treatment of resistant pain syndromes, it is advisable to use a variety of psychotropic drugs, muscle relaxants, etc.

The DIRE clinical rating score is used to predict the long-term use of opioid analgesia for chronic non-cancer pain. It consists of four factors that are assessed individually and then added together to create a DIRE score: diagnosis, refractoriness, risk, and effectiveness.

The risk factor is divided into four subcategories, in which each is scored separately; the scores are then added together to produce a score. The subcategories of risk are psychological health, chemical health, trustworthiness and social support. Each factor is scored on a scale of 1 to 3, with 1 representing the least compelling or least favourable case for opioid prescribing and 3 representing the most compelling or favourable case for opioid prescribing. The total score is used to determine whether a patient is a suitable candidate for opioid analgesia. Scores can range from 7 as the lowest score (patient receives all 1s) to 21 as the highest score (patient receives all 3s). Scores between 14-21 indicate a more successful opioid prescribing process in terms of patient adherence and treatment effectiveness. For each factor,

the patient's score ranking from 1 to 3 is based on the explanation in the right-hand column (Table 8).

Table 8.

DIRE score for predicting long-term opioid analgesia

Score	Factor	Explanation
1	**Diagnosis (D)**	Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, non-specific back pain
2		Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain
3		Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.
1	**Intractability (I)**	Few therapies have been tried and the patient takes a passive role in his/her pain management process.
2		Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers prevent (insurance, transportation, medical illness).
3		Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.
Risk (R). It is calculated by the sum of points. R = Total of P+C+R+S below		
1	**Psychological (P)**	Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues.
2		Personality or mental health interferes moderately. Example: depression or anxiety disorder.
3		Good communication with clinic. No significant personality dysfunction or mental illness.
1	**Chemical Health (CH)**	Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse.
2		Chemical coper (uses medications to cope with stress) or history of chemical dependence (CD) in remission.
3		No CD history. Not drug-focused or chemically reliant.
1	**Reliability (R)**	History of numerous problems: medication misuse, missed appointments, rarely follows through.
2		Occasional difficulties with compliance, but generally reliable.
3		Highly reliable patient with meds, appointments & treatment.
1	**Social Support (SS)**	Life in chaos. Little family support and few close relationships. Loss of most normal life roles.
2		Reduction in some relationships and life roles.
3		Supportive family/close relationships. Involved in work or school and no social isolation.
1	**EFFICACY SCORE (ES)**	Poor function or minimal pain relief despite moderate to high doses
2		Moderate benefit with function improved in a number of ways (or insufficient info – hasn't tried opioid yet or very low doses or too short of a trial).
3		Good improvement in pain and function and quality of life with stable doses over time.

Total score = D + I + R + E Score 7–13: Not a suitable candidate for long-term opioid analgesia Score 14–21: May be a good candidate for long-term opioid analgesia

A prerequisite for the diagnosis of breakthrough pain is to ensure that the treatment of persistent pain is optimal and is not due to increased pain at the end of the opioid's duration of action or to an insufficient dose. The key is to differentiate between idiopathic breakthrough pain (independent of stimulation) and provoked pain, which is caused by specific known stimuli (diagnostic or therapeutic procedure, predictable situation (movement) or difficult to predict (cough)). We should try to establish the mechanism of breakthrough pain and try to influence it specifically.

Drug therapy for breakthrough pain is based on the prescription of "rescue doses" of a drug administered as needed to eliminate breakthrough pain or prevent its occurrence. Usually, a drug with immediate release and the fastest possible onset of action is prescribed.

Breakthroughs of mild pain (grade 1) in the setting of non-opioid analgesic therapy are controlled with adjuvant and symptomatic medications.

Moderate pain breakthroughs (grade 2) in the setting of prolonged opioid therapy (tramadol, dihydrocodeine) are controlled by additional tramadol (up to 400 mg/day), NSAIDs and non-narcotic analgesics, adjuvant and symptomatic medications.

Severe pain breakthroughs (grade 3) in the setting of therapy with prolonged-release strong opioids (fentanyl TTS, long-acting morphine sulfate orally) are controlled by Prosidol 10 to 20-40 mg buccally or under the tongue or by morphine (or omnipotent) 5-10 mg IV, IM, or SC.

The amount of the rescue dose is usually in the range of 1/10-1/6 (or 10-20%) of the daily dose of the opioid prescribed systematically, taking into account the equivalence of the doses (however, it should be remembered that rescue doses of opioids should be titrated individually). If pain occurs between doses of morphine

when taking it regularly (on an hourly basis), short-acting morphine should be prescribed at a dose of 50-100% of the single dose that is administered regularly every 4 hours (1/6 of the daily dose).

In case of predictable provoked pain, an analgesic should be prescribed prophylactically, e.g., morphine orally in the form of an immediate-release preparation 30-60 minutes before the stimulus that causes pain. In idiopathic pain, the drug should be administered as soon as the pain occurs. Parenteral opioid administration may be the optimal method of treatment of breakthrough pain (in some patients, in particular in hospital). In case of persistent pain that occurs as a result of a short-term effect of a dose of the main analgesic in combination with adjuvants, the dose of the main drug should be increased.

Switching from one opioid to another should be used in the case of intolerable and treatment-resistant side effects or the development of opioid tolerance. In case of incomplete cross-tolerance between opioids, the initial dose of the opioid should be reduced to a lower value, which is calculated on the basis of the table of equivalence of analgesic effect. Consultation with a specialist in palliative care or pain medicine is recommended when changing opioids. Recalculation of equipotential doses of narcotic analgesics is performed using conversion tables (Table 7).

To safely switch from one narcotic analgesic to another (opioid rotation), the equipotential dose of the new drug selected should be reduced by 50% at the first dose, and then, in the absence of adverse effects, gradually increased to the required dose.

Narcotic analgesics have significant side effects (Table 9).

All varieties of opioid drugs are contraindicated, individual drugs have their own contraindications for significant respiratory failure, increased intracranial pressure.

Measures in case of side effects of opioids:

- daytime drowsiness - usually occurs at the beginning of opioid treatment or after a significant increase in dose and disappears after a few days. If the drowsiness

persists or increases, you should try to reduce the dose of the opioid to a dose at which the pain does not yet begin to return; then you should find out other possible causes of drowsiness (the effect of other medications, dehydration, renal failure, hypercalcaemia) and, if they are identified, take appropriate treatment measures. Persistent drowsiness may be an indication to change the medicine to another opioid;

Table 9.

Possible side effects of narcotic analgesics

Respiratory system	- depression of the respiratory center (in large doses - paralysis); - depression of the cough reflex; - bronchoconstriction.
Central nervous system (CNS)	- sedation, euphoria (possible dysphoria); - nausea, vomiting; - miosis
Cardiovascular system	- bradycardia, arterial hypotension, vasodilatation.
Urinary system	- increasing the tone of the smooth muscles of the ureters, bladder, sphincter of the urethra; - reduction and difficulty in urination.
Gastrointestinal tract (GIT)	- increasing the tone of the gastrointestinal sphincters; - inhibition of intestinal peristalsis; - constipation.
Skin	- itching, sweating.
Muscular system	- increasing the tone of the trunk muscles and spinal reflexes.
Nociceptive system	- hyperalgesia (after high doses).
Immune system	- immunosuppression, inhibition of the cell link of immunity.
Common manifestations	- promoting the development of hypothermia, reducing the underlying metabolism.
Psycho-somatic disorders	- drug dependence, abstinence, tolerance.

- nausea and vomiting - may occur in the first few days of opioid use and usually resolve on their own. It is necessary to warn the patient about the possibility of early-onset nausea and vomiting, and to agree with him/her on actions to be taken in case of their occurrence: provide the patient with antiemetics for short-term regular use or «on request». Other causes of nausea should be ruled out, and if it persists for a long time, it is possible to replace it with another opioid;

- constipation is the most common adverse effect, and the patient should be informed about it. Laxatives should be prescribed to all patients who have started taking strong opioids;

- reduction in respiratory rate and depth (respiratory depression) is the most threatening side effect. It is necessary to warn the patient about the possibility of its occurrence and provide the patient with access to oxygen therapy. In cases of mild and moderate respiratory depression, respiratory stimulants (analeptic) of direct (caffeine-sodium benzoate, ethimizole) and mixed (cordiamine, camphor, sulfocamphocaine) action can be used, which directly excite the respiratory centre and therefore reduce the effect of drugs that suppress its activity in mild poisoning.

The toxic effect of morphine develops at a dose of more than 120 mg. **In case of an overdose of opioids** when used for therapeutic purposes, stunning, loss of consciousness, respiratory depression with a decrease in respiratory rate to 8-10/min (Cheyne-Stokes), cyanosis of the mucous membranes, pallor of the skin develop, manifestations of morphine coma are observed - lowering of blood pressure, bradycardia, hypothermia, anuria, miosis (with severe hypoxia, pupils dilate), pupils react poorly to light, blood circulation is disturbed, tendon reflexes (elbow, knee, Achilles tendon) increase. Death can occur from paralysis of the respiratory centre.

In case of an opioid overdose, the patient should be referred to a hospital (if at home), the next dose of opioid should be cancelled, adequate hydration should be provided to increase diuresis, airway patency and access to oxygen therapy. In the case of respiratory depression, the morphine antagonist naloxone should be administered intravenously. In the case of an immediate threat to life (unconscious patient, with single respiratory movements, or not breathing), treatment begins with a dose of 0.4 mg. In other situations, lower doses are used (to prevent pain relapse and acute withdrawal symptoms): 0,02-0,1 mg IV every ≈2 minutes until effective breathing is restored. Oxygen therapy is mandatory.

Regardless of the route and time of administration of morphine, it is necessary to wash the stomach with a 0,05% solution of potassium permanganate (oxidises morphine into an inactive form - oxymorphine). Adsorbent drugs, saline laxatives, and forced diuresis are also used. Atropine sulfate is repeatedly administered to reduce the tone of the parasympathetic nervous system.

If death does not occur within the first 6-12 hours, the prognosis is considered favourable (during this time, most of the administered drug is inactivated).

5.4. Adjuvant (auxiliary) drugs and methods of treatment

In palliative medicine, they are used to eliminate or relieve symptoms other than severe pain, causing the greatest suffering to patients and characteristic of the terminal period of oncological and other incurable diseases. The prescription of adjuvant therapy with coanalgestics is also necessary at all stages of anesthesia in the treatment of chronic pain. The goal of the use of adjuvant drugs is to enhance, modulate the action of real, classical analgesics, and influence on the mental functions and symptoms affected by chronic pain in incurable patients associated with stress syndrome and the influence of the pathological process on the functioning of vital organs and systems of the patient.

Adjuvant therapy also includes medicines for the correction of cardiovascular, renal, and liver dysfunctions, haematological disorders and immunocorrection, treatment of infectious complications, and dyspeptic disorders, treatment of ulcerative skin and mucous membranes, haemorrhagic syndrome, reduction of osteoporosis and hypercalcaemia, correction of cachexia and general metabolic disorders, symptomatic treatment of edema, lymphedema and serous effusions, etc.

Co-analgesics do not have an independent powerful analgesic effect similar to opioids or non-narcotic analgesics and NSAIDs, but they contribute to the analgesic effect of the latter and allow for more rational therapy of pain syndrome. Adjuvant therapy drugs include:

1. Coanalgesics with neuro- and psychotropic effects:

- antidepressants (Amitriptyline, Imipramine);
- tranquilizers (Diazepam, Phenazepam) and antipsychotics (Aminazine);
- anticonvulsants (Carbamazepine, Clonazepam, Finlepsin);
- sedatives and hypnotics (barbiturates, benzodiazepines, herbal sedatives).

2. Antihistamines (Diphenhydramine, Suprastin, Tavegil).

3. Bisphosphonates for the treatment of bone pain and prevention of bone resorption (Ibandronate, Zolendranate, Clodronate, Pamidronate, Mebifon).

4. Antiemetics and drugs that eliminate nausea.

5. Systemic glucocorticoids (Hydrocortisone, Dexamethasone).

The main indications for the use of coanalgetic adjuvants:

- relief of pain syndrome that is resistant to opioid therapy, in particular neuropathic pain;

- reducing the total dose of opioids in order to reduce their side effects.

When choosing additional analgesia drugs, you should follow the principles:

1. The choice of a drug for a particular type of pain is based on the clinical picture. It is advisable to use a pain assessment questionnaire that allows you to distinguish between burning, scorching, stabbing pain (responds well to antidepressants) and pulsating pain with intermittent intensification (more effective anticonvulsants).

2. The dose should be gradually increased (every 5-7 days) to the therapeutic blood concentration. In this case, continuous monitoring and discontinuation of the dose increase is performed in the following situations

- when the analgesic effect is achieved;

- in case of adverse events;

- when the concentration reaches a toxic level.

5.4.1. Antidepressants

There is a direct and inverse relationship between chronic pain and depression. Prolonged pain induces depression, which in turn contributes to increased pain. Therefore, antidepressants are used in the complex treatment of pain. The mechanism of the analgesic effect of these drugs is associated with the inhibition of the reuptake of monoamines (serotonin and norepinephrine) in the corresponding synapses of the brain, which results in the enhancement of segmental and supraspinal mechanisms of pain impulse control. Antidepressant drugs appear to modify the sensory perception of pain by inhibiting the action of the serotonergic and

noradrenergic systems on the transmission of pain stimuli from the posterior horns of the spinal cord to the brain stem.

Antidepressants are effective in the treatment of chronic pain in post-herpetic neuralgia, diabetic and other neuropathies, spinal pain, fibromyalgia, migraine, arthritis, tension headache, after a stroke, and in malignant tumours. The analgesic effect is manifested at a dose approximately 2 times lower than that used in psychiatric practice (Table 10). In combination therapy of pain syndrome, a daily dose of 50-75 mg in three doses is considered sufficient. The antidepressant effect usually develops 2-3 weeks after the start of therapy, and 4-5 days are sufficient to achieve analgesia.

Table 10.

Dosing of antidepressants in the treatment of chronic pain

Drug	Amitriptyline	Imisin	Paroxetine	Nefazadone	Venlafaxine
Single dose, mg	25	25	10	100	37,5-75
Daily dose (max), mg	100	100	20	200	150

5.4.2. Tranquilizers

They play an auxiliary role in the treatment of pain syndromes of various genesis, as they increase the threshold of pain sensitivity, reduce the need for analgesics, increasing their effect. With chronic pain contribute to the elimination of mental disorders involved in the formation of pain or its consequence.

Need to use in the complex treatment of nociceptive and neuropathic pain - with neuralgia, headaches, injuries, pseudostenocardial pain. In case of pain syndrome and simultaneous increase of muscle tone in patients with degenerative changes of musculo-ligamentous apparatus, arthrosis, post-traumatic reflex spasms, etc., traquilizers are used, which have the ability to relax muscles, usually simultaneously with analgesics (Table 11). For various pains that occur against the background of severe forms of depression, it is advisable to use antidepressants independently or simultaneously with tranquilizers.

A rather strong synergistic analgesic effect is inherent in hydroxyzine (100 mg of the drug is equivalent to 8 mg of morphine). Reducing pain tolerance largely

depends on the severity of unpleasant sensations, especially depression and anxiety. In such cases, anti-anxiety medications (benzodiazepine derivatives) are used, which have a muscle relaxant effect. In case of short-term anxiety caused by acute pain, midazolam (7,5 mg) and lorazepam (0,5-1 mg) are indicated. In case of prolonged anxiety, lorazepam is prescribed 2-3 times a day or bromazepam (1,5-3 mg). In case of increased irritability, medazepam (5-10 mg), chlorazepate (95 mg) or chlordiazepoxide (25 mg) are most effective. As a rule, tranquillisers are well tolerated and do not cause dangerous complications. The most serious complication is mental and physical dependence in case of long-term prescription.

Table 11.

Dosage of tranquilizers in the treatment of chronic pain

Drug	Diazepam	Medazepam	Tetrazepam	Phenazepam
Single dose, mg	5	5-10	50	0,5-1,0
Daily dose (max), mg	15	30	150	3,0 (4,0)
Drug	Bromazepam	Lorazepam	Hydroxyzine	Chlordiazepoxide
Single dose, mg	1,5-3,0	0,5-1,0	50	10
Daily dose (max), mg	12 (15)	3,0	100 (150)	30

5.4.3. Neuroleptics

The antipsychotic effect of neuroleptics is mainly due to the blockade of dopaminergic systems in the brain, and the neuroleptic (sedative) effect is mainly due to α-adrenoceptor, m-choline and H1-histamine blocking action.

The antipsychotic effect is manifested by the elimination of symptoms of psychosis (delirium, agitation), and the neuroleptic (sedative) effect is manifested by the suppression of reactions to external stimuli, the weakening of psychomotor arousal and affective tension, and the suppression of fear. Neuroleptics potentiate the effect of narcotic and non-narcotic analgesics, reduce skeletal and smooth muscle tone, and have antihistamine effects.

Haloperidol, triptazine, etaperazine, sulpiride have mainly antipsychotic effects, while droperidol, aminazine, and tizercine (levomepromazine) have more sedative effects. Tizercine in a dose of 20 mg is comparable in analgesic effect to 10 mg of morphine. The division of neuroleptics into antipsychotic and sedatives is

conditional, since with an increase in dose, all neuroleptics have a depressant effect on mental and motor activity (Table 12).

Table 12.

Dosing of neuroleptics in the treatment of chronic pain

Drug	Aminazine	Droperidol	Tizertsin
Single dose, mg	25-50	2,5-5,0	25
Daily dose (max), mg	150	10 (20)	50 (100)

At the same time, neuroleptics are characterised by the phenomenon of the "antipsychotic threshold", below which the antipsychotic effect is not realised and only nonspecific effects are manifested - hypnotic, sedative, anti-anxiety.

5.4.4. Anticonvulsants

Antiepileptic and antispastic drugs are anticonvulsants, which used in palliative medicine.

Sodium channel blockers (membrane stabilising agents).

The anticonvulsant effect of carbamazepine (finlepsin) is due to sodium ducts blockade, which helps to reduce the impulse that forms a painful paroxysm. It has a moderate antidepressant and normothymic effect. Carbamazepine is effective in the treatment of typical trigeminal neuralgia, laryngopharyngeal neuralgia, paroxysmal pain in multiple sclerosis, and diabetic neuropathy. The single dose for adults is 0,2-0,3 g, and the daily dose is 0,6-1,2 g (Table 13).

Gabapentin has similar properties and is effective in the treatment of neuropathic pain. The initial daily dose is 900 mg (300 mg 3 times); if necessary, the dose is gradually increased to a maximum of 3600 mg per day. In the first 3 days, the dose can also be gradually increased to 900 mg per day.

Lamotrigine inhibits the release of excitatory amino acids into the synaptic cleft. It has analgesic properties in the treatment of various types of migraine, trigeminal neuralgia and other neuropathic pain syndromes. The dosage of the drug depends on the specific nosology.

Table 13.

Dosing of sodium channel blockers in the treatment of chronic pain

Drug	Carbamazepine	Gabapentin	Lamotrigine
Single dose, mg	200-300	300	50-100
Daily dose (max), mg	600 (1200)	900 (3600)	100 (400)

Myorelaxants

They reduce skeletal muscle tone. Depending on the mechanism of action, they are divided into antispastic and antispasmodic. Antispastic drugs are prescribed for neurological diseases accompanied by spastic syndrome. Spasmolytic drugs are used for pathology of the musculoskeletal system with acute and chronic pain (Table 14).

Midocalm (tolperizone hydrochloride) is a centrally acting antispastic agent. In "overstimulated" neurons, it prevents the emergence and conduction of an action potential. It also increases peripheral blood flow, which does not depend on the muscle relaxant effect, which allows the drug to be prescribed for obliterating angiopathies. It is administered intravenously, intramuscularly, orally (Table 14). In the pharmacotherapy of pain syndromes, it is effectively combined with NSAIDs, sedatives, antiepileptics, and antihypertensives.

Sirdalud (tizanidine) is a centrally acting muscle relaxant. It has an antispastic effect in chronic spastic conditions of spinal and cerebral origin. It eliminates acute painful muscle spasms and clonic convulsions. The mechanism of action is associated with a decrease in the release of excitatory amino acids from interneurons, which selectively inhibits the polysynaptic mechanisms of the spinal cord responsible for muscle hypertonicity.

Baclofen is used - an agonist of GABA receptors with antispastic action, for the treatment of spastic muscle pain in multiple sclerosis and other spinal disorders of central genesis. Causes a decrease in the release of excitatory amino acids, suppressing synaptic activity at the spinal level, which causes a decrease in muscle tone.

Table 14.

Dosage of muscle relaxants in the treatment of chronic pain

Drug	Mydocalm	Tizanidine	Baclofen
Single dose, mg	IV 100 mg, IV - 100, orally – 50 (150)	2 (4)	5 (10)

Daily dose (max), mg	IV 100 mg, IV - 200, orally – 150 (450))	6 (12)	30 (60)

Blockers of calcium duct

Calcium ions are involved in the processes of regulation of pain sensitivity at various stages of the transmission of nociceptive signals. An increase in the irritability of spinal cord neurons as a result of the activation of the neurotransmitter system of excitatory amino acids depends on the enhanced entry of calcium ions into the cells. When opioid κ-receptors are stimulated by endogenous ligands or opioid analgesics, membrane calcium ducts are blocked and the movement of calcium ions at the end of primary afferents in the spinal cord is reduced and, accordingly, the release of mediators is inhibited. A similar result is found when potassium ducks are opened upon excitation of μ- and δ-receptors. L-type calcium channel blockers verapamil, nimodipine (Table 15) exhibit analgesic properties. In the clinic, these substances have proven to be effective in the treatment of neuropathic pain.

Table 15.

Dosage of calcium channel blockers in the treatment of chronic pain

Drug	Verapamil	Nimodipine	Pregabalin
Single dose, mg	40	30	75 (150)
Daily dose (max), mg	120	90	300 (600)

Antidepressants and anticonvulsants are the first-line treatment for neuropathic pain, in which other painkillers, in particular morphine, are less effective. In the case of nociceptive pain, psychotropic drugs play an auxiliary role by potentiating the effect of other painkillers or increasing the ability to tolerate pain by reducing negative feelings.

5.4.5. Medicines for the treatment of bones

Metastases of primary tumors from various organs often occur in the bone tissue, and in incurable patients with non-oncological diseases, especially in the elderly and senile, osteoporosis is noted. These lesions are often accompanied by bone pain. To reduce pain, in addition to opioids, non-narcotic analgesics and NSAIDs, add drugs that affect bone tissue - bisphosphonates, Calcitonin.

Bisphosphonates - are a generic name for a group of medications that reduce progressive bone loss. Drugs of this group are used for the treatment of a significant number of diseases: osteoporosis and tumors, metastases in bone tissue, hypercalcemia along with deforming osteodystrophy or due to malignant tumors, myeloma disease, hyperparathyroidism, pathology in the formation of bone tissue, Paget's disease.

The process of bone tissue is maintained by the balance between osteoblasts, which form bones, and osteoclasts, which destroy them. Bisphosphonates inhibit bone destruction by osteoclasts. The number of osteoclasts is constantly regulated by their self-destruction through apoptosis, which is facilitated by bisphosphonates. The mechanism of action is based on the structural analogy of bisphosphonates with pyrophosphate. The bisphosphonate group mimics the structure of pyrophosphate, thereby inhibiting the activation of enzymes that utilise pyrophosphate. The specificity of the drugs is based on two phosphonates that work together to coordinate calcium ions. Bisphosphonate molecules bind to calcium and accumulate in high concentrations only in bones. When bisphosphonates enter the bone tissue, they are destroyed by osteoclast cells.

The main pharmacological effect of bisphosphonates is the creation of obstacles to the natural destruction of bone tissue in some diseases. Bisphosphonates are able to provide an analgesic effect, thereby significantly improving the condition of patients. They are used for metastases of malignant tumors in bones and myeloma, hypercalcemia caused by malignant tumors, Paget's disease (deforming osteitis). In the treatment of oncology, they can cope with the consequences of the appearance of cancer cells, preventing their growth.

Ibandronate (bondronate), clodronate, pamidronate (Aredia), zoledronate (Zometa), mebifon (Table 16) are used in the treatment of chronic pain.

Calcitonin inhibits the natural process of bone resorption caused by osteoblasts, reduces the amount of calcium and phosphates in the blood, is an antagonist of parathyroid hormone, stimulates the function of osteoblasts and the formation of bone tissue, and has an analgesic effect. It is used for pain due to bone

metastases or osteoporosis, phantom and neuralgic pains. It is used in infusions. Calcium and vitamin D preparations are prescribed at the same time.

For bone pain associated with tumor metastases, Paget's disease, neurodystrophic diseases, a daily dose of 200 IU intramuscularly or subcutaneously daily, once, for 2-4 weeks, an additional dose of 200 IU every other day for 6 weeks is possible.

Table 16.

Dosage of bisphosphonates in the treatment of chronic pain

Drug	**Dose, mg**	**Feature of application**	**Frequency of application**	**Duration of treatment**
Pamidronate	90	Intravenous in 250 ml of 0,9% pH NaCl, 5% glucose solution in 1,5-2 hours	1 time per month	1-5 courses The interval is 1 month
Mebiphone	300	Intravenous in 200 ml of 0,9% NaCl solution in 30-40 minutes	1 course - 5 days, course dose – 1,5 g	1-6 courses The interval is 3 weeks
Ibandronate	6	Intravenous in 100 ml of 0,9% NaCl solution, 5% glucose solution in 20-30 minutes	1 time in 3-4 weeks	3-4 courses. The interval is 1 month
Clodronate	1500	In one dose in the morning		6 months
Zoledronate	4	Intravenous in 100 ml of 0,9% NaCl solution, 5% glucose solution in 20-30 minutes	1 time per month	2-3 courses. The interval is 1 month

5.4.6. Blockers of histamine H_1-receptors (antihistamines)

Histamine has a very important role in peripheral nociceptive mechanisms in inflammatory and allergic reactions, in particular, it is associated with irritation of sensitive skin receptors that participate in the formation of itching, burning and pain sensations. The importance of histamine neurons of the central nervous system in the processes of pain perception and control is unclear. The pain-relieving property of antihistamine substances has been proven, the question of the predominant localization of their action has not been resolved. Blockers of histamine H1 receptors are effective enough for pain of moderate intensity in oncological practice, for

incurable non-neoplastic diseases, for diseases accompanied by neuropathic pain (Table 17). Analgesic activity is characteristic of all drugs of this group.

Table 17.

Dosing of histamine H1 receptor blockers in the treatment of chronic pain

Drug	Dimedrol	Suprastin	Tavegil	Promethazine
Single dose, mg	50	25	1	12,5-25
Daily dose (max), mg	100-150 (200)	75-100 (150)	2 (4)	75-100 (150)
Duration of treatment	Depends on the achieved effect and tolerability of the drug. Need periodic control			

5.4.7. Glucocorticosteroids

The use of glucocorticosteroids (GC) in palliative therapy for incurable diseases is based on their positive effect on the body's defenses, antitoxic effect, improvement of cardiovascular system function. In many cases, GCs are effective in the treatment of severe neuropathic pain, in incurable non-neoplastic diseases, in which pain is associated with chronic inflammatory processes. These drugs are prescribed for bone pain, pain when stretching the capsule of internal organs, intestinal obstruction, headache with brain metastases. GCs are effective for nausea or incessant vomiting due to chemotherapy. Doses and dosing regime are determined individually, depending on the disease, its characteristics and severity, the effectiveness of the treatment, the severity of the pain syndrome (Table 18).

Table 18

Dexamethasone dosage in the treatment of chronic pain syndrome

Dexamethazone	**Palliative treatment of oncological diseases**		**Exacerbation of rheumatoid arthritis, severe form**	
	Initial dose	Long-term use	Initial dose	Long-term use
	8-16 mg/day	4-12 mg/day	12-16 mg/day	6-12 mg/day

5.4.8. Local anesthetics

They cause a limited blockade of pain sensitivity, prevent the occurrence and arrival of pain impulses in the central nervous system. They have membrane-stabilizing activity, cause blockade of sodium channels of the excitatory membranes of neurons, which makes it impossible to conduct an impulse. First, unmyelinated B- and C-fibers are blocked, then myelinated A-δ-fibers. There is a gradual disappearance of pain, temperature, tactile, proprioceptive and motor sensitivity. To

stop the neuropathic component in chronic pain, lidocaine TTS (patch) is used in a dose of 700 mg, 1-3 patches once a day. It is not recommended to use for more than 12 hours.

5.4.9. Antiemetics and anti-nausea drugs

Causes of nausea and vomiting when using opioids:

- the beginning of therapy, when a temporary feeling of nausea may occur;
- atony and paresis of the gastrointestinal tract (GIT).

Metoclopramide (Cerukal) is a first-line antiemetic that helps reduce nausea and stimulates peristalsis of the gastrointestinal tract. Single dose: 20 mg; daily – 60 mg (for all methods of administration). Frequency of reception - 1-3 times/day. When used simultaneously with morphine, it accelerates its absorption when taken orally and enhances the sedative effect. If the effect is insufficient, the action of metoclopramide can be enhanced by prescribing dexamethasone.

Haloperidol is an effective neuroleptic with a powerful central antiemetic effect, which is taken at 0,3-0,5 mg 2-3 times a day (1,5-3 mg/day). Haloperidol together with a narcotic analgesic, tranquilizer, or hypnotic can increase the depressant effect of these drugs on consciousness.

The most powerful of modern antiemetics are ondansetron drugs (latran, zofran), which block serotonin 5HT3 receptors responsible for the vomiting reflex. The need for these drugs rarely arises, they are used according to special schemes, mainly for the treatment of nausea and vomiting associated with the toxic effect of chemotherapy.

In case of uncontrollable and profuse vomiting, drugs that inhibit gastrointestinal secretion are additionally prescribed - buscopan 60-120 mg/day.

Most antiemetics can cause extrapyramidal disturbances, especially in young patients, who need correction with akineton or cyclodol. The duration of prescribing

antiemetics on the background of opioid therapy usually does not exceed 2 weeks. During this period, in most cases, tolerance to the emetic effect of opioids develops.

5.4.10. Physical methods of chronic pain treatment

The complexity and diversity of pathogenetic mechanisms of chronic pain require not only medication. In some cases, the use of physical therapy can bring significant relief to the patient, often breaking the existing cycle of pain - muscle tension - circulatory disorders - pain.

Heat therapy is particularly effective in treating muscle spasms, myofascial pain, and general musculoskeletal discomfort associated with immobility and weakness. Heating relieves pain both as a competitive stimulus and through a direct effect on tissues. The sensation of heat weakens nociceptive transmission in the dorsal horns of the spinal cord and can cause an inhibitory effect at the level of the brainstem. The local effect includes muscle relaxation, increased blood flow and tissue flexibility. Heat treatment of surface fabrics is carried out with the help of water or electric heaters, special lamps. Warming of deep tissues is achieved by ultrasound, short-wave diathermy, and microwaves. Heat treatment can cause tissue damage and is contraindicated:

- in areas of metal or synthetic prostheses, areas with bone cement;
- in areas of reduced sensitivity, paralyzed or ischemic areas;
- in infected areas;
- directly above the tumor area.

Cryotherapy reduces the local inflammatory response and reduces the release of inflammatory mediators due to the effect of cold. It is indicated for spastic muscle pain. It is carried out by local exposure to an ice bubble or irrigation with a cooling agent (chlorethyl). It is contraindicated in areas with sensory disorders and insufficient blood supply.

Mechanical therapies (touch, massage) - can relieve pain in muscle spasms, myofascial syndromes or general musculoskeletal discomfort associated with immobility and weakness. Consciously touching the patient with the hand has a

calming and warming effect and has no side effects. It is used in treatment with vibration therapy to eliminate muscle pain, tension, pain after nerve damage and amputations. Massage promotes the production of endorphins, general and muscle relaxation. Massage should prepare the patient for their own physical activity, not replace it.

Exercise, both active and passive, can improve pain control and reduce overall musculoskeletal discomfort. Physical activity stimulates the production of endorphins, induces positive emotions and improves mood. With adequately dosed loads, the patient's physical form improves, and the negative manifestations of the disease progression are suppressed.

Manual therapy is used to treat back pain of non-cancerous origin. It is contraindicated in patients with cancer in the presence or likelihood of metastatic spinal lesions.

Orthopaedic devices and appliances (prostheses, splints, etc.) can relieve or prevent pain by stabilising or immobilising painful areas. Walking devices play an important role in the prevention of movement-related pain. Immobilisation, such as wheelchair use and bed rest, is necessary for patients suffering from severe pain in the setting of optimal analgesic therapy and the use of the physical support devices described above.

5.5. Modified WHO analgesic ladder for the treatment of chronic non-oncological pain

The WHO three-stage pain management system for the treatment of chronic pain in cancer has been extended to treat chronic pain in incurable non-cancer diseases. However, the prolonged use of opioids for the treatment of chronic non-cancer pain ("CNCP"), especially in high-income countries, has led to problems associated with inappropriate prescribing, lack of knowledge about side effects of long-term use, opioid abuse, and addiction. Significant advances in basic knowledge about pain and its treatment have led to updated recommendations for the treatment

of CNCP, while the WHO three-step ladder of pain relief in cancer remains unchanged.

The US Centers for Disease Control and Prevention (DCP) in 2016 and the American Society of Interventional Pain Physicians (ASIPP) in 2018 supplemented the WHO recommendations and proposed non-opioid pharmacological and non-drug treatments (NSAIDs, muscle relaxants, integrative medicine, minimally invasive methods) for the treatment of chronic pain. Integrative medicine, as a holistic model that combines acupuncture, massage, yoga, relaxation, spinal manipulation, aims to combine complementary and alternative therapies based on evidence and is used to relieve chronic pain at all stages of pain management to reduce or even stop the use of analgesics for all types of pain. In practical recommendations for the treatment of chronic pain, interventional methods are proposed at the third level. Minimally invasive therapies (nerve block, spinal cord stimulation, epidural and subarachnoid spinal injection of local anaesthetics, surgery and disc decompression) are used when non-opioids and weak opioids, together with adjuvant and integrative therapies, are no longer able to manage pain, but before strong opioids are prescribed.

When the above methods of pain relief are ineffective, patients with chronic pain should be prescribed strong opioids as a "last resort", at the fourth level. The adapted WHO 4-step analgesic ladder is shown in Fig. 5.

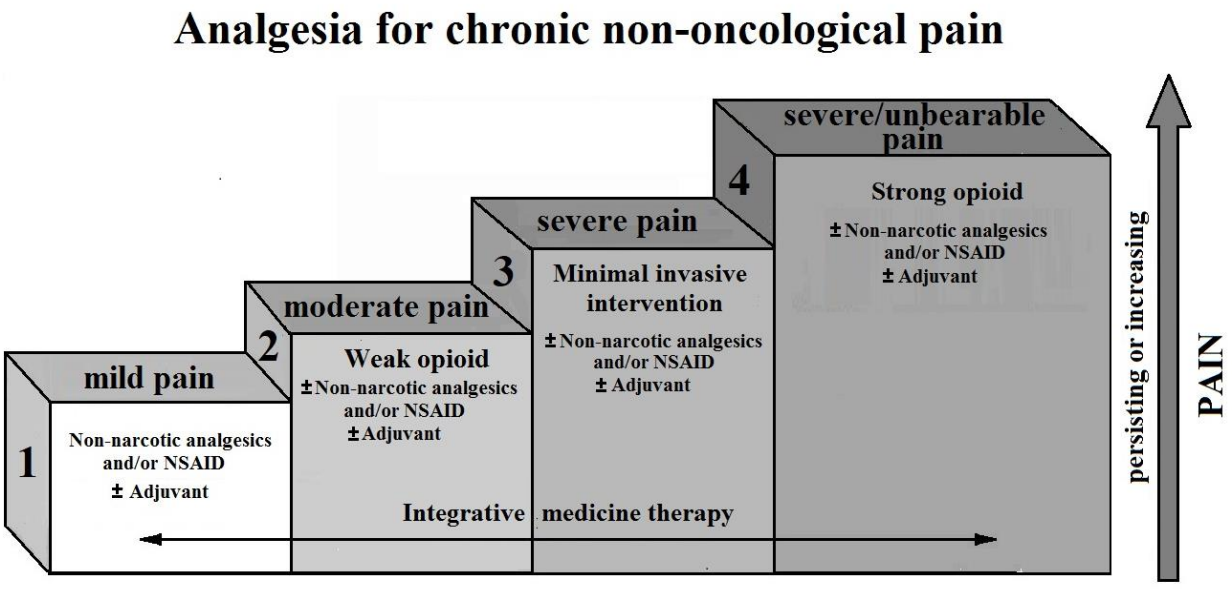
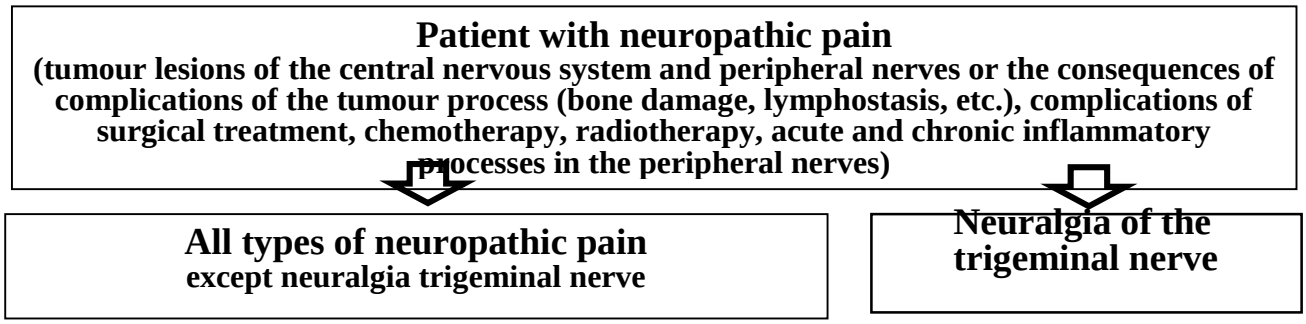


Figure 5. Modified WHO analgesic ladder
with chronic non-oncological pain.

(according to The Modified WHO Analgesic Ladder: Is It Appropriate for Chronic Non-Cancer Pain? / J. Yang, B.A. Bauer, D.L. Wahner-Roedler, T.Y. Chon, L. Xiao // J Pain Res. 2020; 13: 411–417. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7038776/)

6. General approaches to the treatment of neuropathic and nociceptive pain

At the beginning of treatment, ff the patient has a neuropathic component of the pain syndrome associated with nerve damage, anticonvulsant drugs are used in combination with adjuvants (antidepressants, tranquilizers, and local anesthetics). In case of ineffectiveness of pain treatment, another anticonvulsant drug with a different mechanism of action is added (Fig. 6). Narcotic analgesics of weak and moderate action (level 2) are used in case of urgent need.



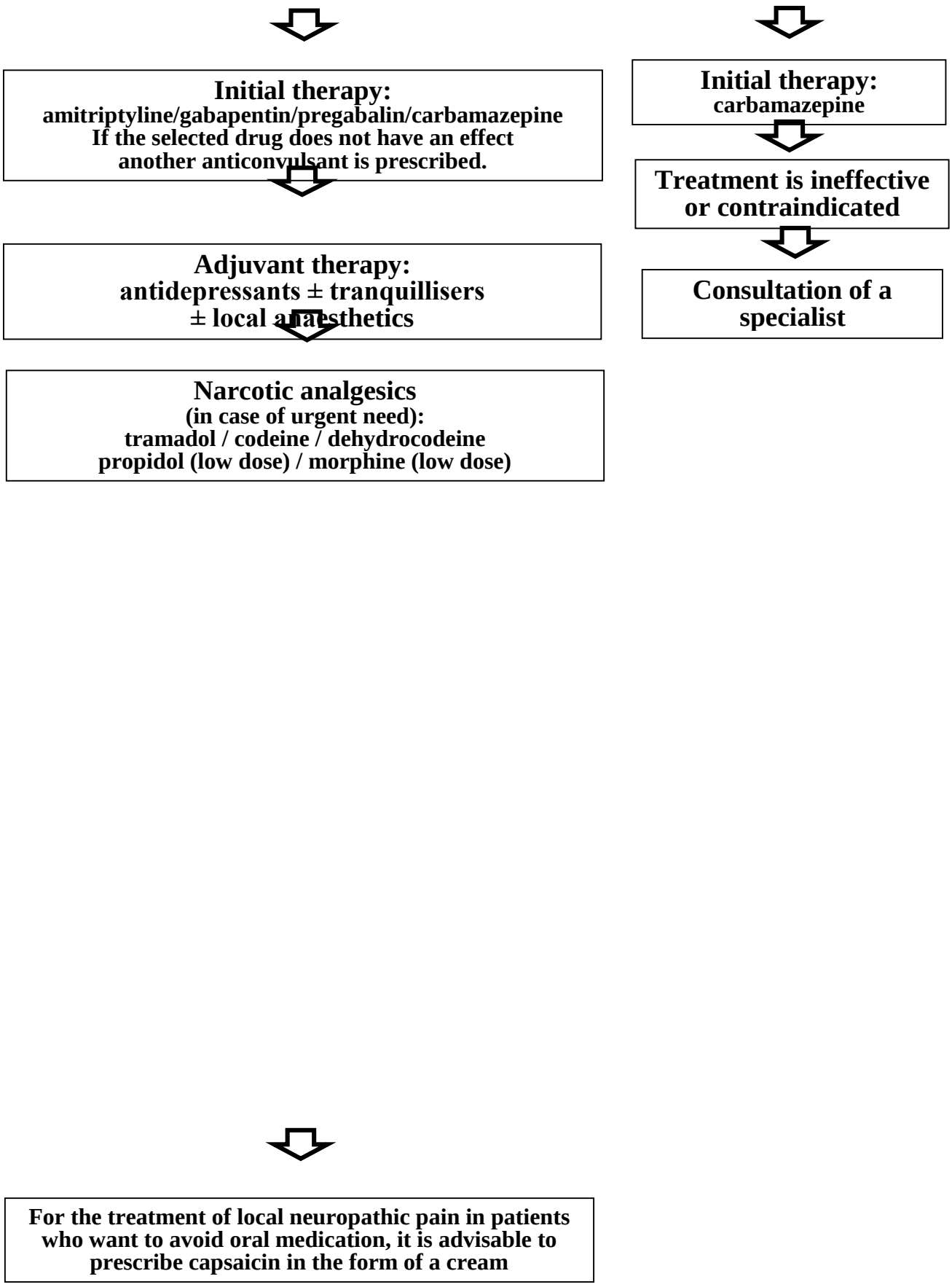


Figure 6. Algorithm for treatment of neuropathic pain.

(according to Neuropathic pain – pharmacological management. NICE clinical guideline 173 (2013)

https://www.nice.org.uk/guidance/cg173/evidence/full-guideline-pdf-4840898221)

An exception is the treatment of trigeminal neuralgia, which is carried out with carbamazepine. In the case of ineffective treatment or the presence of contraindications, a consultation of the relevant specialist is carried out.

Nociceptive pain (somatic or visceral), which develops during oncological processes and many incurable non-oncological diseases, is treated according to the algorithm of the WHO "3-step" system with the use of non-narcotic analgesics, non-steroidal anti-inflammatory drugs, opioids, adjuvant drugs (Fig. 7).

For the most part, in many oncological processes and non-oncological incurable diseases, pain has a mixed mechanism and, as a rule, a significant inflammatory component, which requires not only pain relief, but also the appointment of anti-inflammatory, pathogenetic and symptomatic agents.

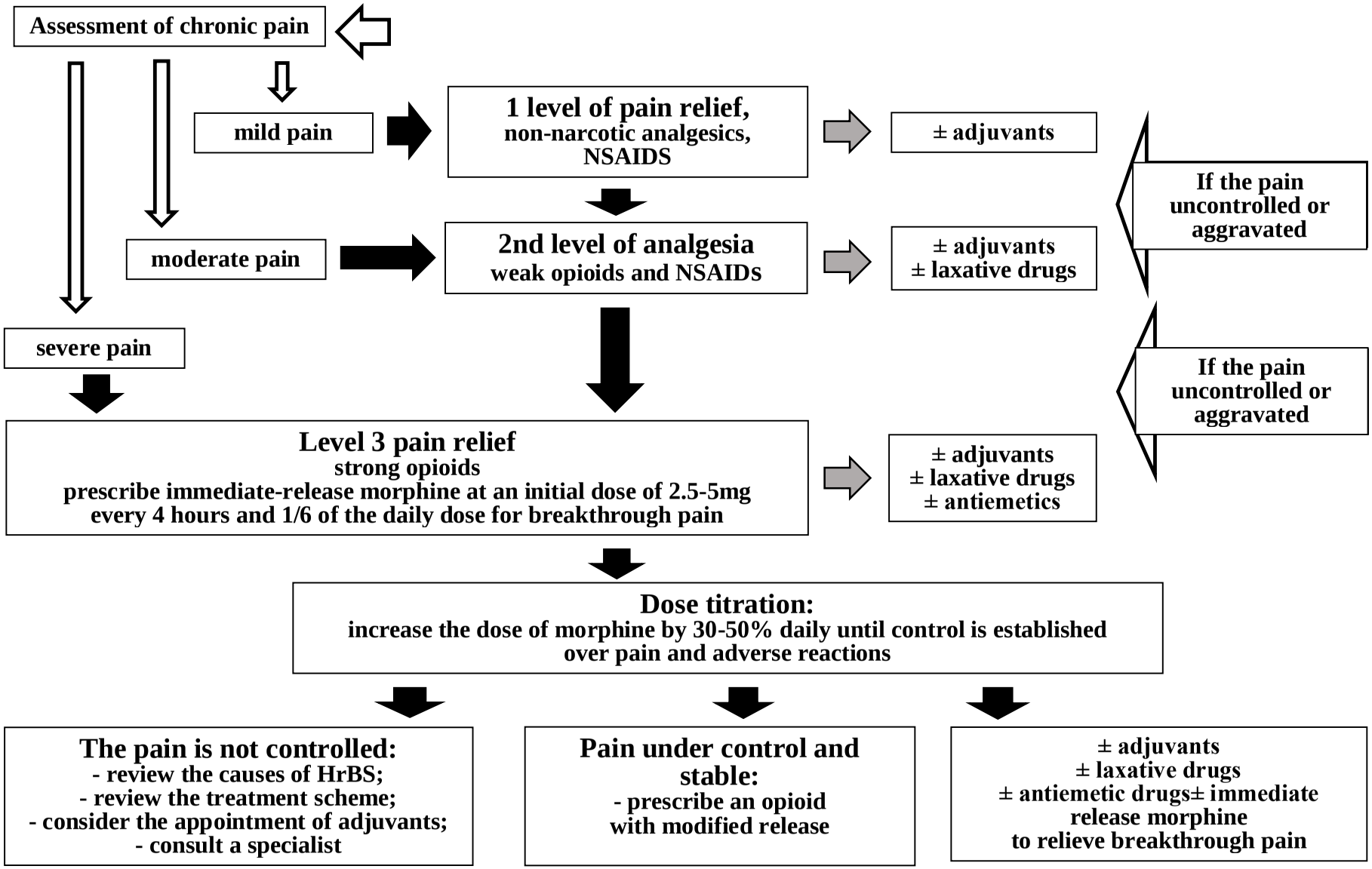


Figure 7. Algorithm for the treatment of nociceptive pain in oncological processes and incurable non-oncological diseases (according by PAIN & SYMPTOM CONTROL GUIDELINES, Greater Manchester & Cheshire Cancer Network, Reviced Final June 2015 https://docplayer.net/22647289-Pain-symptom-control-guidelines-palliative-care-greater-manchester-strategic-clinical-network.html)

7. Psychological and social aspects of chronic pain management

In the process of progression of an incurable disease, a patient's attitude towards themselves and relationships with others change. These changes are negative and affect the progression or regression of the pain syndrome. WHO experts have defined the term "total pain" to describe the chronic pain that accompanies a seriously ill patient (Fig. 8).

Psychotherapy. Patients suffering from intense chronic pain and feel various emotional experiences, anxiety, and depression can be stabilised by conventional psychotherapy, as well as with the use of antidepressants and anxiolytics. Psychotherapy helps patients to adapt to the problems caused by the disease and contribute to positive results in pain control.

Hypnosis is a useful method of treating chronic pain syndrome in the terminal stages. It is advisable to use techniques based on the stimulation of the hallucinatory sensation of anaesthesia, which includes direct blocking of pain in the mind, or the reduction of pain by self-hypnosis, which increases the body's defences against pain impulses of a particular intensity level, sensory substitution or pain shifting.

Cognitive behavioural treatment is a combination of behavioural therapy and cognitive psychology, where the main factor determining the patient's behaviour is thinking. The aim is to help patients identify and change thoughts, beliefs and behaviours that may be exacerbating pain, depression or anxiety and to teach them skills to relieve pain. When successful, patients are able to overcome pain attacks, anxiety, depression and social discomfort.

There is an algorithm for the route of a patient with chronic pain syndrome and the doctor's actions (Fig. 9) to determine the causes, type and intensity of pain, the stages of treatment, specialist consultations and hospitalisation.

The treatment of chronic pain is carried out in cooperation between primary and specialised medical care. Primary responsibility for diagnosis and treatment

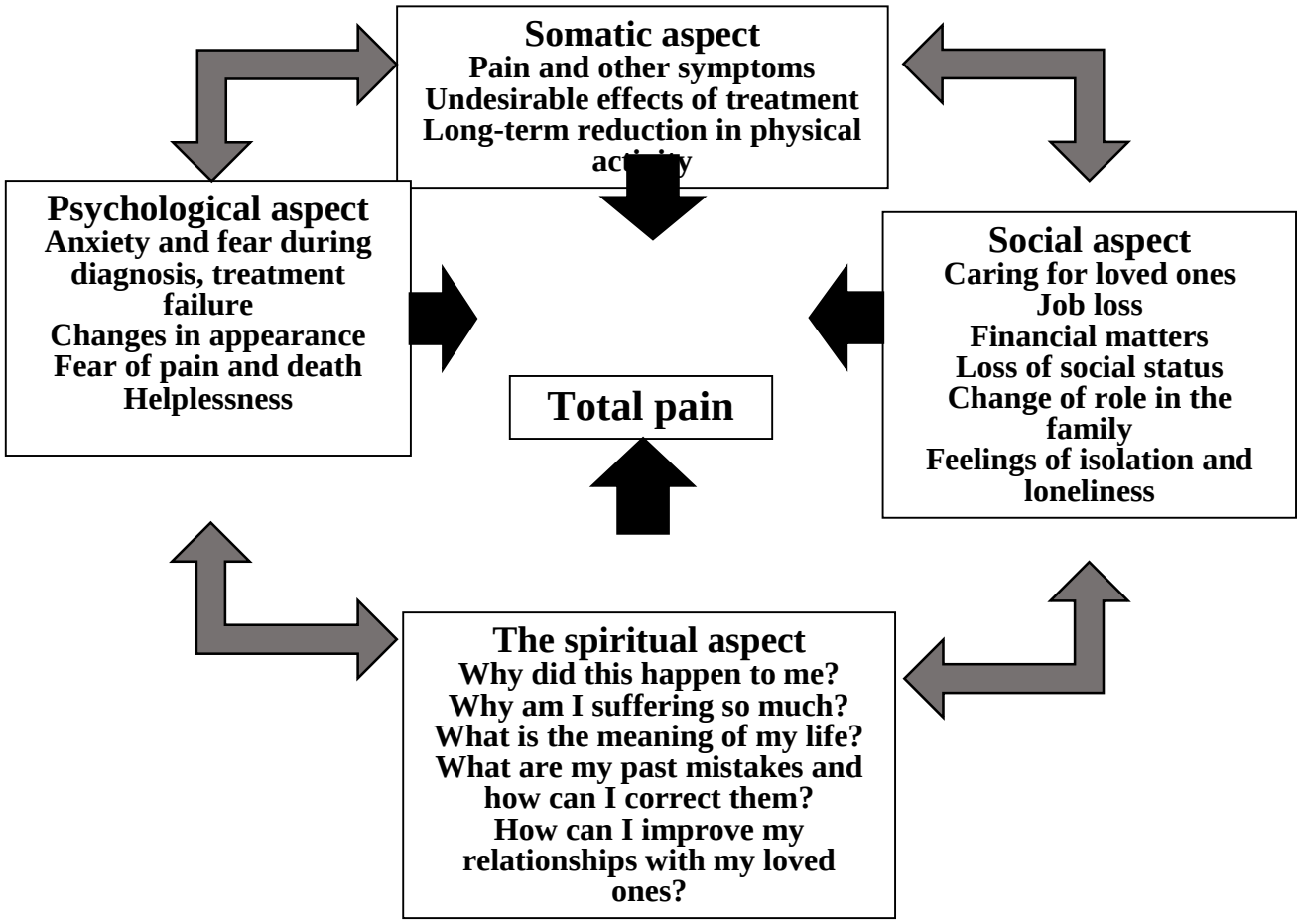


Figure 8. Aspects of chronic pain development

(after J. Binnebezel. The phenomenon of total pain in palliative and hospice care.https://er.ucu.edu.ua/bitstream/handle/1/1680/Binnebezel_Fenomen%20totalnoho%20boliu.pdf?sequence=1&isAllowed=y)

The primary responsibility for the diagnosis and treatment of patients with chronic pain lies with primary care (family doctor, family doctor). Consultations with specialists in other doctors of medicine are carried out on an as-needed basis. Specialised medical care provides treatment for patients with many diseases and problematic conditions, and is carried out in cooperation between different specialists. The lead specialist is a specialist who treats the main disease and coordinates with other specialists to provide advice. Pain treatment clinics should be set up in hospitals, where specialists of at least two specialties are responsible for therapy. Inpatients with chronic pain should be managed by a multidisciplinary team, including an anaesthetist specialising in pain management, a psychiatrist, psychologist, neurologist, orthopaedist and social worker.

Hospitalization of the patient (institution/department, where the patient is sent)
No
Write a prescription on opioid analgesics
Yes

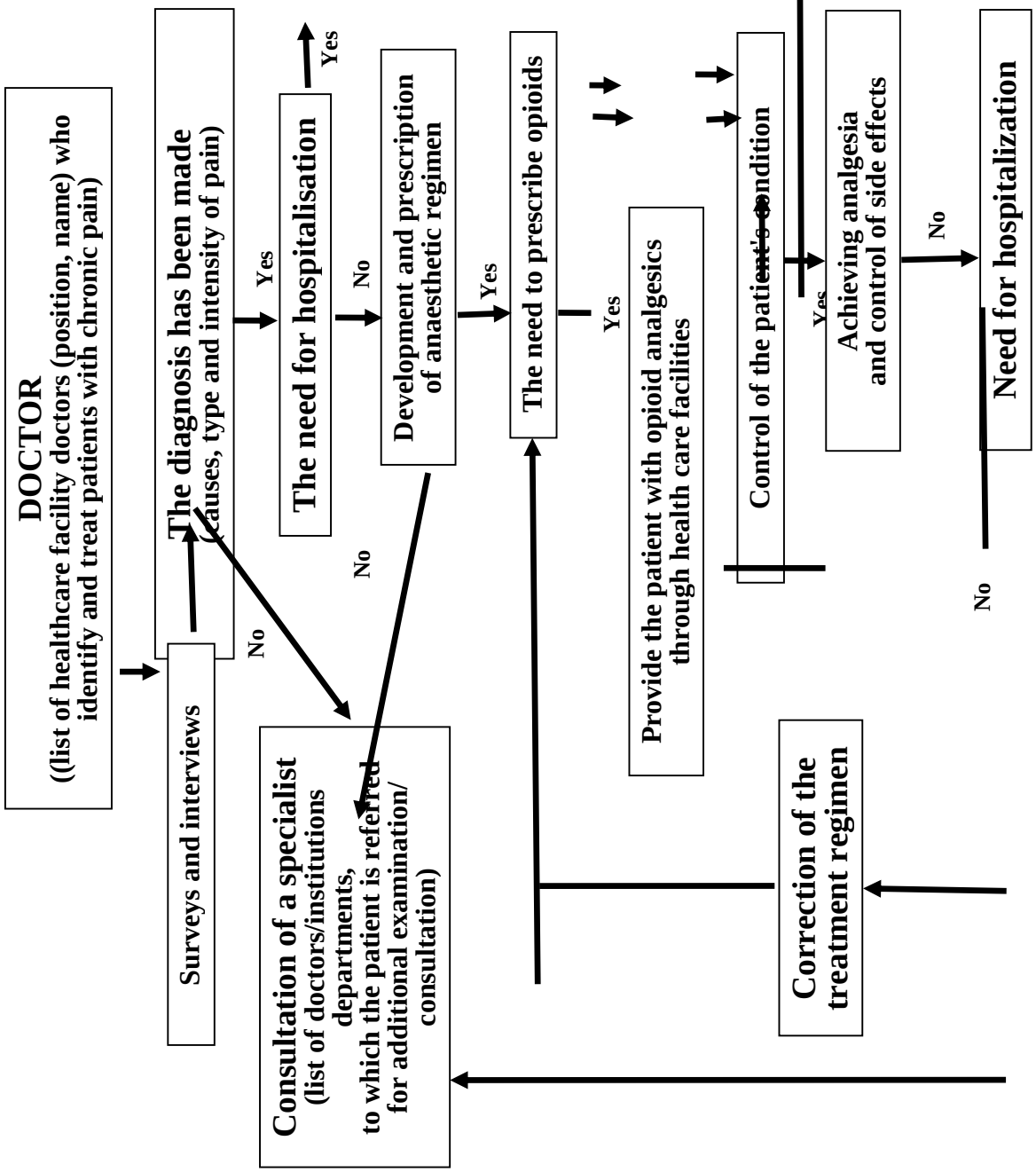


Figure 9. The clinical pathway of a patient with chronic pain and the actions of a doctor (according to the Development of a local protocol of palliative care in the treatment of chronic pain syndrome (methodological recommendations) (38.16/79.16) https://www.dec.gov.ua/wp-content/uploads/2019/11/rec_polial.pdf)

8. Communication between patients and carers and healthcare professionals

For palliative care patients, good communication, planning and trust are fundamental to conscious pain management. In order to achieve maximum pain relief with minimal side effects, pain should be assessed and its manifestations should be discussed at the beginning of the patient's illness (before achievements the palliative stage), if possible. If necessary, patients should be informed that most types of pain can be relieved with medicines without

persistent side effects. Communication is enhanced when information is provided in an accessible way and patients feel confident and trusted when they are listened to.

Caregivers can play an active role in pain assessment and management, but managing pain for the caregiver requires good communication with the clinician. Clinicians need to be aware of the burdens that caregivers have to fulfil.

Doctors and nursing staff should get to know the patient and his or her family so that they can express their fears, wishes and concerns with confidence. Patient input plays an important role in getting the best treatment possible. Clinicians should encourage patients to report the intensity, quality, location and nature of their pain.

Doctors at all levels need to communicate with each other, with nurses and support staff, with patients and their families, and with carers. As the community takes an increasingly central role in care, general practitioners and community nursing staff need to be fully involved.

When communicating with a palliative care patient, you need to take this into account:

- Good communication with patients and carers is possible when it is at their level of understanding, is not condescending, and uses specific medical terms, and when healthcare staff know the patient and carers well and listen actively;
- Poor communication between patients and professionals can lead to an incomplete clinical assessment, and patients may not report all manifestations of pain;
- pain, its assessment and treatment should be discussed at an early stage of the disease;
- Patients are more likely to discuss their pain if certain strategies are used, such as "pain diaries" and the opportunity to communicate with other patients.

Palliative care services should support patients to communicate effectively with others and professionals. Health care professionals should be trained to address the specific challenges of communicating with patients with terminal illness, carers and other professionals.

9. Features of pain relief in the last hours of life

Pain in patients with end-stage disease should be controlled, even when confusion or profound cognitive impairment is noted. To diagnose pain in such patients, the Checklist of Nonverbal Pain Indicators (CNPI) (Table 19) and the Pain Assessment in Advanced Dementia Scale (PAINAD) (Table 20) are used, which allows for an assessment of the pain syndrome based on the patient's reactions.

Table 19.

Non-verbal indicators of pain (Checklist of Nonverbal Pain Indicators)

Indicators	With movement	At rest
Vocal reactions: non-verbal (sighs, gasps, moans, grunts, cries)		
Grimaces (wincing, furrowed brows, squinting eyes, clenching teeth, tight lips, pained expression)		
Fixation (squeeze or hold onto the sheet, blanket, compress and fix the affected area of the body)		
Excitement, anxiety (constant or periodic changes in body position, swaying, periodic or constant arm movements, inability to lie still)		
Rubbing the affected area		
Vocal reactions: verbal (moaning, screaming, words expressing discomfort or pain, cries of protest)		
Subtotal score		
Total score		
Calculating the points: 0 - the indicator is absent, 1 - the indicator was noted even during short periods of activity or at rest. The scores are summed up in the columns "with movement", "at rest" and total. There are no clear quantitative indicators to assess the severity of pain; the presence of any of these indicators may indicate pain and requires further examination, treatment and monitoring by a doctor		

It is not recommended to reduce the dose of opioids in the presence of hypotension or confusion (if they are not the result of an excessive dose of opioids).

If an opioid analgesic is stopped, its dose should be reduced gradually, by no more than 5 mg per day, to avoid withdrawal symptoms and pain breakthrough. Opioids should be maintained at an effective dose even in the absence of consciousness.

It is recommended to assess the severity and dynamics of other severe symptoms (pressure ulcers, vomiting, edema, constipation, urinary retention, episodes of agitation) that increase the patient's suffering.

Table 20.

Pain rating on the scale Pain Assessment in Advanced Dementia Scale.

Behavior	0	1	2	Score
Breathing Independent of vocalization	Normal	- Occasional labored breathing - Short period of hyperventilation	- Noisy labored breathing - Long period of hyperventilation - Cheyne-Stokes respirations	
Negative vocalization	None	- Occasional moan or groan - Low-level speech with a negative or disapproving quality	- Repeated troubled calling out - Loud moaning or groaning - Crying	
Facial expression	Smiling or inexpressive	- Sad - Frightened - Frown	- Facial grimacing	
Body language	Relaxed	- Tense - Distressed pacing - Fidgeting	- Rigid - Fists clenched - Knees pulled up - Pulling or pushing away - Striking out	
Consolability	No need to console	- Distracted or reassured by voice or touch	- Unable to console, distract, or reassure	
Total Score				
The patient should be observed for five minutes before the scores are assessed and recorded. The total score is from 0 to 10 points. Interpretation: 1-3 - mild pain; 4-6 - moderate pain; 7-10 - severe pain				

In case of refractory pain syndrome, it is advisable to consider the use of medication sedation with neuroleptics, benzodiazepines, barbiturates and propofol. The possibility of medication sedation is discussed with the patient and/or his/her legal representative and considered at a meeting of the medical commission.

CONCLUSIONS

The problem of managing chronic pain in incurable patients with cancer and non-cancer diseases is a leading one in the provision of palliative and hospice care.

The management of chronic pain is a multidimensional problem with the definition of the necessary balance between providing adequate pain relief to a level that ensures a quality of life that is acceptable for terminally ill patients, while preventing and eliminating side effects, overdose and preventing the development of addiction to drugs, especially narcotic opioids. Such management should be

carried out by a multidisciplinary team of specialists of different profiles, using all possible approaches and means of its correction, depending on the types and degrees of pain.

Modern approaches to the treatment of chronic pain in Ukraine are indicated in the regulatory documents of the medical care standardisation system:

- Order of the Ministry of Health of Ukraine № 311 of 25.04.2012 "Unified Clinical Protocol for Palliative Care in Chronic Pain Syndrome";

- Order of the Ministry of Health of Ukraine № 311 dated 25.04.2012 "Pain Control. Adapted evidence-based clinical guideline";

- Order of the Ministry of Health of Ukraine № 1308 of 04.06.2020 "On Improving the Organisation of Palliative Care in Ukraine".

TEST TASKS

for independent preparation

1. Nociceptive visceral pain is characterized by:
A. It occurs as a result of damage to the nervous system at the peripheral level.
B. Occurs as a result of tissue damage or exposure to a painful agent. This pain is well-localized, can be intermittent or constant.
C. Occurs when organs with sympathetic innervation are damaged. This pain is poorly localized, diffuse.
D. Occurs as a result of damage to the nervous system at the central level.
E. Occurs in the absence of activation of nociceptors and visible organic damage, including the nervous system.

2. Nociceptive somatic pain is characterized by:
A. It occurs when organs with sympathetic innervation are damaged. This pain is poorly localized, diffuse.
B. Occurs as a result of tissue damage or exposure to a painful agent. This pain is well-localized, can be intermittent or constant.
C. Occurs as a result of damage to the nervous system at the peripheral level.
D. Occurs as a result of damage to the nervous system at the central level.
E. Occurs in the absence of activation of nociceptors and visible organic damage, including the nervous system.

3. What is NOT part of the antinociceptive system?
A. Nicotinergic system.
B. Opioidergic system.
C. Serotoninergic system.
D. Noradrenergic system.
E. System of endogenous cannabinoids.

4. Which substance belongs to blood plasma algolens (stimulators of irritation that cause pain in minimal concentrations)?
A. Neurokinin
B. L-glutamate.
C. Cocalcigenin.
D. Serotonin.
E. Bradykinin.

5. Which substance belongs to neurokinins - algolens (stimulators of irritation, which in minimal concentrations cause a pain sensation), which are released from the peripheral endings of C-nociceptors?
A. Serotonin.
B. L-glutamate.
C. Kalidin.
D. Cocalcigenin.
E. Endothelins.

6. What methods of diagnostic testing can be used to assess the intensity of chronic pain?
A. Visual-analog and verbal rating scales.
B. The Glasgow Scale.
C. The APACHE Scale.
D. The SOFA Scale.
E. Karnowski index.

7. The intensity of pain is assessed as "moderate" on the numerological rating scale:
A. From 0 to 2 points.
B. From 0 to 6 points.
C. From 2 to 5 points.
D. From 4 до 7 points.
E. From 4 до 9 points.

8. What is the principle of "upward" drug therapy for chronic pain syndrome?

A. Analgesics should be prescribed regularly according to the regimen, in accordance with the duration of the drug effect, without waiting for the development of pain.
B. The selection of drugs for pain relief is carried out from non-opioid analgesics for mild pain, weak opioids for moderate pain and strong opioid analgesics for severe pain.
C. The need for "individualized" selection of the most effective analgesic in the right dose with the least side effects.
D. All injectable forms of analgesics should be excluded as much as possible.
E. Taking into account the patient's characteristics and monitoring his/her condition.

9. General principles of treatment of chronic pain syndrome according to WHO recommendations:
A. "by mouth, individual approach".
B. "by the hour, by mouth".
C. "ascending, individualized approach".
D. "by the hour, ascending, individual approach".
E. "by the hour, by mouth, ascending, individualized, with attention to detail".

10. Which drugs are non-steroidal anti-inflammatory drugs from the group of selective COX-2 inhibitors?
A. Codeine, Tramadol.
B. Diclofenac sodium, Indomethacin.
C. Nimesulide, Meloxicam.
D. Diazepam, Phenazepam, Aminazin.
E. Hydrocortisone, Dexamethasone.

11. What drugs belong to weak opioids?
A. Codeine, Tramadol.
B. Morphine, Fentanyl.
C. Diazepam, Aminazine.
D. Diclofenac sodium, Indomethacin.
E. Dimedrom, Tavegil.

12. Which method of morphine administration is preferred in the treatment of chronic pain syndrome in palliative patients?
A. Intravenously.
B. Subcutaneously.
C. Intramuscularly.
D. Inside.
E. Rectally.

13. When a standard dose of morphine hydrochloride is taken orally, the analgesic effect occurs after:
A. 5-10 minutes.
B. 15-20 minutes.
C. 20-30 minutes.
D. 30-60 minutes.
E. More than 1 hour.

14. When a standard dose of morphine hydrochloride is taken orally, the analgesic effect continues:

A. 1-2 hours.
B. 2-3 hours.
C. 4-6 hours.
D. 6-8 hours.
E. Up to 12 hours.

15. When a standard dose of morphine hydrochloride is administered taken, the analgesic effect occurs in:
A. Almost instantly.
B. 5-10 minutes.
C. 15-20 minutes.
D. 20-30 minutes.
E. 30-60 minutes.

16. What drugs should be prescribed according to the WHO pain management ladder in case of grade 3 - severe pain, according to the visual analog scale - more than 70%?
A. Paracetomol + adjuvant therapy.
B. Weak opioids + paracetomol or NSAIDs.
C. Strong opioids in low doses.
D. Weak opioids + paracetomol + adjuvant therapy.
E. Strong opioids + paracetomol or nonsteroidal anti-inflammatory drugs (NSAIDs) + adjuvant therapy.

17. What is the main side effect of opioid drugs?
A. Dyspepsia, nausea, vomiting, constipation.
B. Cough supression.
C. Bradycardia, decrease of blood pressure.
D. Respiratory depression.
E. Dizziness, sedation or excitement, hallucinations, delirium.

18. What drugs belong to tranquilizers?
A. Dimedrom, Suprastin, Tavegil.
B. Morphine, Fentanyl, Hydromorphone.
C. Amitriptyline, Imipramine.
D. Barbital, Phenobarbital.
E. Diazepam, Phenazepam, Aminazine.

19. What drugs belong to antidepressants?
A. Diazepam, Phenazepam,
B. Morphine, Fentanyl, Hydromorphone.
C. Imisin, Paroxetine, Nefazadone.
D. Barbital, Phenobarbital.
E. Dimedrom, Suprastin, Tavegil.

20. Which of the following are the most common symptoms and disorders of vital activity in palliative care patients?
A. Decompensated dysfunction of vital organs and systems that occur in the last months, weeks or days of palliative care patients' lives.
B. Acute pain syndrome, which sometimes requires the use of narcotic analgesics to control.
C. Compensated dysfunction of vital organs and systems that develop and manifest themselves over a long period of time.

D. Mental and psycho-emotional disorders in psychiatric patients, including depressive states or affects, alcoholic delirium, etc.
E. Post-traumatic complications, consequences of strokes and heart attacks that do not significantly limit the motor activity and ability of patients to self-care

Answers to control test questions

Questions	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Answers	C	B	A	E	D	A	D	B	E	C	A	D	C	C	A	E	D	E	C	A

RECOMMENDED LITERATURE

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