

PRACTICAL ASPECTS OF PAIN RELIEF IN PALLIATIVE MEDICINE

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ABSTRACT

Background. Treatment of chronic pain in adults and children is regulated by the national standard of Ukraine, which recommends adherence to the choice of painkillers in accordance with the WHO three-step protocol. But the treatment standard does not detail the use of painkillers according to nosological units.

Aim. To determine the need for different types of analgesia in palliative patients depending on the main palliative diagnosis.

Materials and Methods. System analysis, aggregation and bibliosemantic methods were used. The list of palliative diagnoses was determined when studying the need and forecasting the need for palliative and hospice care according to the methodology of the Ukrainian Center for Social Data (2019), improved by us in 2021–2024.

Results and Conclusions. The conducted research made it possible to determine the predominant types of pain, their possible intensity and corresponding groups of pharmaceutical drugs with an analgesic effect in the units from the list of palliative diseases proposed by us. Neuropathic pain is mainly present in diabetes (diabetic polyneuropathy) and phenylketonuria. Predominantly nociceptive pain is present in cardiovascular diseases of palliative stages, tuberculosis, rheumatoid arthritis, cystic fibrosis and chronic hepatitis in children. Predominantly mixed (nociceptive and neuropathic types of pain at the same time) characteristic of HIV/AIDS, epilepsy, dementia, multiple sclerosis, fibrosis and cirrhosis of the liver, chronic obstructive pulmonary disease, palliative stage kidney disease in adults, cerebral palsy, inflammatory diseases of the central nervous system and mucopolysaccharidoses in children. We proposed to clarify the national standard for treatment of chronic pain in adults and children, and to define the necessary non-steroidal anti-inflammatory drugs, non-narcotic analgesics, weak and strong opioids, anticonvulsants, antidepressants, and other adjuvants with an analgesic effect. The perspective of further studies is to detail the dosage of drugs with an analgesic effect and to calculate the need at the national level for reimbursement under the "Affordable Medicines" program.

Keywords: *neuropathic pain, nociceptive pain, analgesics, opioids, reimbursement.*

INTRODUCTION

The Ministry of Health of Ukraine includes malignant stage 3–4 neoplasms, HIV/AIDS, congenital malformations, cardiovascular, respiratory, neurological, atrophic-degenerative diseases, and post-traumatic conditions that cannot be cured by modern available drugs in the list of palliative

diseases [1]. The need for Palliative and Hospice Care (PHC) is growing: 1.5 million Ukrainians need it immediately before the end of life, and about 600,000 in the last year of life. Unfortunately, the list of palliative diseases according to such a number of patients is not detailed by the Ministry of Health of Ukraine. In 2023, only 130,000 people received palliative care in Ukraine (11.5–46.2% of the need). In the world, the need for PHC is 20 million at the end of life. Some 6% of these are children. 80% of such patients live in low- and middle-income countries. Coverage of palliative care in the world also does not exceed 50% of the need [2–4].

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The medical component of palliative care is elimination of life-threatening symptoms (carrying the risk of premature death even with an incurable disease) by carrying out pathogenetic therapy, palliative surgical interventions, as well as symptomatic therapy, to relieve pain, first of all. Timely and sufficient analgesia significantly improves the quality of life of patients and is one of the main needs of palliative patients [2; 5].

Among the 289 disabling diseases that were responsible for the global burden of disease in the world during 1990–2010, a significant part belonged to palliative diseases and were accompanied by chronic pain [6]. Among these diseases, the first place was occupied by psychoneurological disabling disorders: dementia, demyelinating diseases, strokes in adults; severe and profound mental retardation and other diseases of children (congenital malformations, inflammatory diseases of the central nervous system, severe perinatal conditions, cerebral palsy). Chronic pain is also accompanied by damage to the musculoskeletal system and joints [7], frequent periodic pain of significant force – tension headache and migraine. About 3% of the world's population has a disability due to injuries that are accompanied by chronic pain. At the same time, the number of such patients is even greater in terms of the number of Years Lived with Disability (YLD): according to [7], the number of victims of injuries was more than 6%, that is, it was twice as large. The results of studying the number of Years of Life Lost (YLL) [8] are also important for our research. Correlations between YLD and YLL indicators are usually not established: some diseases predict long-term disability and a palliative state, others require palliative treatment and care during the last year of life [9]. For example, neurological disorders were responsible for almost 43 million cases of YLD during the period, but they accounted for only about 9 million YLL. Another example of the absence of correlative relationships is the following: in the older age group in studies [7; 8] most cases of YLD were associated with Alzheimer's and Parkinson's diseases, while YLL was associated with cancer.

Considerable attention of the medical community and the society during the period of research of YLD and YLL indicators (1990–2010) was focused on HIV/AIDS, which was called the "plague of the 20th century". In the last stages of development, the disease is palliative and associated with intense pain in the case of neuroAIDS. Today, there are 39 million people living with HIV/

AIDS in the world, with an annual increase in the number of infected people by 1–1.5 million people and annual AIDS deaths in the range of 600–700 thousand [10; 11]. Without the use of AntiRetroviral Therapy (ART), it takes 7–12 years from HIV infection to the development of AIDS. Drug use shortens the period before the development of AIDS to 3–4 years [12]. There are more than 190,000 HIV-infected people in Ukraine, and only 150,000 of them receive ART. Therefore, more than 21% of HIV-infected people are at risk of rapid AIDS development in the forecast period. They will need constant pain relief for at least the last two months of life. In the last stages, AIDS progresses quite quickly, therefore, in order to assess the impact of the correct organization of medical care on the quality of life and the adequacy of palliative analgesia in patients diagnosed with HIV/AIDS, it is YLL that should be taken into account.

According to the same principle, among vascular crises, which are responsible for the highest mortality in the world, the YLL indicator is more relevant for the assessment of strokes, and the YLD indicator of heart attacks. After all, by the end of the year, 20% of victims of myocardial infarction in Ukraine survive. After strokes, 30–40% of patients die in the first 30 days, another 50% die within a year. Of those who survive, up to 40% become dependent on assistance (often living with chronic pain), and only 10% return to a full life [13]. In general, disability from cerebrovascular diseases in the world increased from 2.3 million cases in 1990 to 4.3 million in 2010 [7].

Trends in onset and duration of disability, calculated by YLD, have multidirectional vectors, which must be taken into account when planning the volumes of necessary analgesia. Thus, YLD due to neonatal conditions in the world during 1990–2010 decreased by 13.5% (from 159 per 100 thousand population to 137 per 100 thousand population). On the contrary, YLD due to oncopathology, which has a significant burden of pain and is treated palliatively in stages 2 and 4, increased from 2.5 million first registered cases in 1990 to 4.5 million cases in 2010.

A global study of YLL and YLD in the world during 1990–2010 also showed that national health systems are not sufficiently responding to the challenges of palliative diseases. The strategies of the PHC organization are insufficiently effective, first of all, in matters of determining the list of palliative diseases, creating centers for coordinating the routes of palliative patients in the

system of medical institutions, and organizing adequate analgesia. The majority of palliative care patients do not receive the necessary analgesia due to strict drug restrictions, lack of political will of governments, insufficient qualification of medical professionals and lack of scientific research. This is also evidenced by the data of Ukrainian researchers [14–17]. Therefore, the issue of pain relief is insufficiently studied, both at the world and national levels.

The aim of the study was to determine the need for different types of analgesia in palliative patients depending on the main palliative diagnosis.

Materials and Methods

To carry out this study, we used the method of systematic analysis and bibliosemantic (searching for sources by keywords on PubMed and Google Scholar). The aggregation method [18] summarizes information on types of pain in various palliative diagnoses and painkillers recommended in Ukraine. The need for various painkillers for adults and children with palliative diagnoses was assessed.

In our calculation and forecast of the need for PHC in Ukraine, made according to the improved methodology (2021–2024) [19] of the Ukrainian Center for Social Data (2019) [20], the indicator hovered around the figure of 200 thousand and included malignant neoplasms, cardiovascular diseases, tuberculosis, diabetes, HIV/AIDS in adults and children; dementia, rheumatoid arthritis, fibrosis and cirrhosis of the liver, kidney disease in adults; congenital malformations, severe perinatal conditions, cerebral palsy, severe and profound mental retardation, inflammatory diseases of the central nervous system, chronic hepatitis, phenylketonuria, cystic fibrosis, mucopolysaccharidoses in children. Obtaining statistical data on congenital malformations [21], severe and profound mental retardation in children; chronic obstructive pulmonary disease [22], dementia in adults was complicated. Complications were related to the collection of disease statistics. We also consider it necessary to expand the list of palliative diseases to include epilepsy in adults and children, as well as multiple sclerosis in adults [23].

Results and Discussion

Painless dying is considered from the perspective of human dignity [24]. Even under adequate anesthesia, it is difficult for palliative patients to overcome the emotional problems associated with the awareness of imminent death. In the presence of chronic pain, the psychological state of patients

deteriorates to the point of clinical depression with suicide attempts, therefore, the treatment of many palliative diseases relies on the use of sedatives, tranquilizers, neuroleptics, anticonvulsants, which simultaneously have analgesic properties [25].

According to the results of a systematic review of ten prospective studies of palliative sedation, found by Arantzamendi M. et al. (2021) in the PubMed, CINAHL, Cochrane, MEDLINE and EMBASE databases for the period 2014–2019 [26], 25–65% of palliative patients required chronic pain treatment. Most of them were cancer patients. (Our own observations in the Kharkiv hospice [27] are similar). Evaluation of the effectiveness of sedation according to the conclusions of Arantzamendi M. et al. performed according to the Glasgow Coma Scale, Ramsay Sedation Scale, Richmond Agitation Sedation Scale, and Bispectral Index monitoring. The most used drugs were midazolam, phenobarbital, promethazine and the anesthetic propofol.

But according to the WHO three-stage pain treatment strategy [28], adopted as a basis in Ukraine [29], the main drugs for pain relief are narcotic and non-narcotic analgesics. The three levels of pain relief are based on the intensity of the pain. For mild pain, non-narcotic painkillers are used (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), acetaminophen (paracetamol), adjuvant drugs); with moderate – weak opioids (hydrocodone, codeine, tramadol); in severe cases, strong opioids (morphine, methadone, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with the addition of adjuvants if necessary.

Opioid pharmacotherapy is the basis of cancer pain treatment [30]. It can be supplemented by treatment with adjuvant analgesics, psychotherapy and physiotherapy. In order to choose methods that will be effective in the complex for the vast majority of patients, it is necessary that clinicians are well aware of methods of pain assessment and therapeutic strategies that must consider the balance between the effectiveness of analgesia and the side effects of analgesics. The choice of drugs is based on understanding the pathophysiology of pain. But if it is not about hospice in a medical institution, but about a home for the elderly, in which a palliative patient ends his life, or about "hospice at home", the choice of drugs for pain relief is usually insufficient [31]. The situation is often complicated by comorbidity, which increases the need in drug treatment, its duration, number of drugs, necessary doses, risk of polypharmacy [32].

Specialized hospice facilities and palliative care units often have more options than home hospices and nursing homes in terms of drug delivery routes, which affects their effectiveness. Thus, for example, morphine is 2–3 times more effective when administered intravenously and subcutaneously than when administered orally [33]. The need for long-term analgesia in palliative medicine prompts to pay considerable attention to the possible side effects of painkillers, to change these drugs to those that do not have side effects, to combine them to reduce the dosage. From doctors who do not specialize in patients with a palliative profile, such actions require special knowledge and a lot of time to study the features of pain relief depending on the age of the patient and the main palliative diagnosis. Therefore, it is advisable to improve the protocols for the treatment of chronic pain: to include in them recommendations on the lists of painkillers for each diagnosis with the appropriate dosage depending on the severity of the disease, assessment of pain intensity, age, comorbidity. It is also necessary to indicate the possibility of replacing drugs in cases of pronounced side effects and the sequence of such replacement. The legalization of medical cannabis in Ukraine significantly expands the possibilities of pain relief [34]. A list of these drugs must be offered to the National Health Service for reimbursement under the "Affordable Medicines" medical guarantee program [35]. Currently, only valproic acid, haloperidol, carbamazepine, acetylsalicylic acid, clozapine, lamotrigine, morphine, phenytoin, and fluoxetine are included in the list of reimbursement drugs that can be used in palliative medicine in the presence of chronic pain (with reimbursement of 43–100% of the cost) [36].

We have compiled a *Table* of the correspondence of palliative diseases of adults and children to the types and possible intensity of pain, indicating the groups of drugs with an analgesic effect. Types of pain are listed in accordance with national standards of care and evidence-based clinical guidelines for chronic pain syndrome in adults and children [37]. Nerve irritation causes nociceptive pain, damage – neuropathic. We will describe the pathogenetic mechanisms of pain in palliative diseases selected by us for inclusion in the list that can be recommended by the Ministry of Health of Ukraine from the WHO list.

The nature of pain in *malignant neoplasms* can change with the progression of the disease. Nociceptive pain predominates in the early stages, and neuropathic pain in the later (palliative) stages.

Nociceptive pain can be caused by the pressure of a growing tumor on the adjacent tissues (nerves, bones), irritation of nerves by products of inflammation accompanying the neoplastic process, tumor growth into nerves. Long-term compression of nerves disrupts their functionality; thus, the pain can be considered neuropathic. Nerve damage can be caused by surgery, radiation therapy, or the effects of certain anticancer drugs (cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, vincristine, vinblastine, and others). Pain increases the development of osteoporosis [38–40].

Pain in *cardiovascular diseases* is mainly nociceptive. It occurs due to ischemia of the myocardium, stretching of the aneurysm walls, inflammation of the pericardium and endocardium, blockage of blood vessels by blood clots. Severe pain is characteristic of angina pectoris, myocardial infarctions and strokes. The intensity of pain in heart failure is usually moderate. Pathogenetic therapy with nitroglycerin in angina pectoris reduces the level of pain [41].

Pain in *pulmonary tuberculosis* is mainly nociceptive, caused by inflammation of lung tissue, formation and disintegration of cavities with pleural irritation. When bones and kidneys are affected by tuberculosis, neuropathic pain is added. Pain reduction occurs as a result of pathogenetic treatment with antibiotics and analgesia using paracetamol, NSAIDs, and weak opioids [42].

Most often, pain in *diabetes* has a neuropathic character, which is reflected in the name of a common complication of diabetes "diabetic neuropathy" (E10.4, E11.4 according to the ICD-10), which is more characteristic of adult patients. Pain, paresthesias, and numbness are initially localized in the feet and lower legs, with possible spread higher up the lower limb. The intensity of pain in diabetic neuropathy ranges from mild to severe. The presence of arthritis and osteoporosis increases pain [43; 44], while the normalization of the blood sugar level lowers it. Treatment of pain in diabetes is pathogenetic (non-narcotic analgesics of central action (pregabalin, gabapentin) (first therapeutic line); carbamazepine (effective in some types of neuropathic pain); tricyclic antidepressants (amitriptyline); sugar-lowering drugs, insulin, diet) and symptomatic (weak and strong opioids (tramadol, codeine, morphine, oxycodone), alpha-lipoic acid, capsaicin). Physiotherapy, reflexology, acupuncture, and cognitive-behavioral therapy are effective [45–49].

In *HIV/AIDS*, pain is most often mixed: it includes nociceptive pain (from inflammatory pro-

Table. Palliative diagnoses of adults and children, corresponding types of pain and analgesia

The main palliative diagnosis	Codes according to ICD-10	Age*	Predominant types of pain			Groups of pharmaceutical drugs depending on the intensity of chronic pain		
			NP	NC	Md	mild	moderate	severe
Malignant grade 3–4 neoplasms	C00–C97, D00–D48	Adults	+	+	+		WO	SO
	C00–C97	Children						
Cardiovascular diseases	I00–I99	Adults		+			PT, WO, NSAIDs, NA	PT, SO
		Children						
Tuberculosis	A15–A19	Adults		+	+	PT, NSAIDs, NA	PT, WO, NSAIDs	
		Children						
Diabetes	E10–E14	Adults	+			PT	NA, PT, AC, AD, WO	NA, PT, AC, AD, SO
		Children						
HIV/AIDS	B20–B24	Adults			+	NSAIDs	WO, AC, AD	SO, AC, AD
		Children						
Epilepsy	G40–G41	Adults			+	AC, NSAIDs, NA	AC, AD, NSAIDs, NA	AC, AD, NA
		Children						
Dementia	F00–F09	Adults			+	NSAIDs	NSAIDs, AC, AD	AC, AD, SO
Multiple sclerosis	G35				+	NSAIDs, PT	WO, PT, AC, AD	SO, PT, AC, AD
Rheumatoid arthritis	M05–M06			+		NSAIDs, PT	NSAIDs, PT	NSAIDs, PT, AD, NA
Fibrosis and liver cirrhosis	K74				+	PT, NA, NSAIDs	PT, NA, NSAIDs	PT, NA, NSAIDs
COPD	J43–J47				+	NSAIDs, NA	NSAIDs, NA, AC, AD	
Kidney disease	N00–N15, N20–N23				+	NSAIDs, NA	NSAIDs, NA, WO, PT	NSAIDs, NA, SO, PT
Congenital malformations	Q00–Q99			+	+	+	NSAIDs, NA	NSAIDs, NA, WO, PT
Perinatal conditions	P05–P96		+	+	+	NSAIDs, NA	NSAIDs, NA, WO, PT	SO, PT
Children's cerebral palsy	G80	Children			+	NSAIDs, NA	NSAIDs, NA, WO, PT, AC, AD	NSAIDs, NA, SO, PT, AC, AD
Mental retardation (heavy and deep)	F72–F79		+	+	+	NSAIDs, NA	NSAIDs, NA, WO, PT, AC	NSAIDs, NA, SO, PT, AC
Inflammatory diseases of the CNS	G00, G03, G04, G06, G08, G09				+	PT, NSAIDs, NA	PT, NSAIDs, NA, WO	PT, NA, SO
Phenylketonuria	E70.0		+			PT, NSAIDs, NA	PT, NSAIDs, NA, WO	

Continuation of the Table

The main palliative diagnosis	Codes according to ICD-10	Age*	Predominant types of pain			Groups of pharmaceutical drugs depending on the intensity of chronic pain		
			NP	NC	Md	mild	moderate	severe
Cystic fibrosis	E84	Children		+		NSAIDs, NA	NSAIDs, NA, WO, PT	NSAIDs, NA, SO, PT
Mucopolysaccharidoses	E76				+	PT, NSAIDs, NA	NSAIDs, NA, CO, PT	NSAIDs, NA, SO, PT
Chronic hepatitis	K73, K75.2, K75.3			+		PT, NSAIDs, NA	PT, NSAIDs, NA	
Notes:	COPD - chronic obstructive pulmonary disease; CNS - central nervous system; ICD-10 – International Statistical Classification of Diseases and Related Health Problems 10 th revision; *Children: age 0–17 years (according to WHO); NP - neuropathic; NC - nociceptive; Md - mixed (neuropathic-nociceptive)					NSAIDs – non-steroidal anti-inflammatory drugs; NA – non-narcotic analgesics; WO – weak opioids (hydrocodone, codeine, tramadol); SO – strong opioids (morphine, methadone, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone); PT – pathogenetic therapy; AC – anticonvulsant drugs; AD – antidepressants		

cesses, tumors, and treatment complications) and neuropathic pain (from the direct effect of the virus or opportunistic infections (cytomegalovirus, cryptococcosis) on the nervous system in neuroAIDS). The intensity of pain in HIV/AIDS ranges from mild to severe. The presence of tuberculosis, cryptococcosis, or Kaposi's sarcoma can increase pain. NSAIDs (ibuprofen, naproxen – for nociceptive pain), weak (codeine) and strong (morphine) opioids, anticonvulsants (pregabalin, gabapentin – for neuropathic pain), antidepressants (amitriptyline, duloxetine) are used to treat pain.

Kluger B.M. et al. [50] write about the treatment of patients with epilepsy as palliative patients with this disease. The disease is accompanied by convulsions of varying degrees of manageability [51; 52]. Treatment should cover both the attacks themselves and their anticipation (anxiety, fatigue, depression) [53; 54]. Adequate treatment of sleep disorders, cognitive disorders, psychotic manifestations, anxiety symptoms, rage attacks also contribute to reducing the level of pain in epilepsy. Drug therapy of epilepsy can be supplemented with psychotherapy. The cognitive clarity it achieves can get rid of attacks, make them less frequent and last longer. Reducing the frequency and strength of attacks reduces the risk

of sudden death by 2–4 times, the intensity of chronic pain by 30–60% [55–61]. Family members of epilepsy patients (caregivers) have high rates of anxiety, depression, and premature mortality due to chronic stress and fatigue [62–65]. Their condition negatively affects the quality of care and support for patients.

A combination of nociceptive and neuropathic pain is often observed in epilepsy. Nociceptive pain can be associated with injuries sustained during seizures (for example, when falling), or with muscle pain after intense seizures. Neuropathic pain is caused by epilepsy itself or by side effects of antiepileptic drugs. The intensity of the pain ranges from mild to severe. Having a migraine or fibromyalgia increases the pain. Drug therapy is used to treat pain, and neurostimulation and blockades are used for severe pain. For the treatment of neuropathic pain, anticonvulsants are used (pregabalin, gabapentin – drugs of the first therapeutic line; carbamazepine – for treatment of trigeminal neuralgia; lamotrigine), antidepressants (including tricyclic antidepressants (amitriptyline, nortriptyline) – for night pains and related sleep disorders; selective serotonin and norepinephrine reuptake inhibitors (duloxetine and venlafaxine)). NSAIDs (ibuprofen, naproxen, ketoprofen) and

paracetamol are used to treat nociceptive pain. Physiotherapy, thermal procedures, massage, physical therapy, psychotherapy are also effective.

Starting from 2019, Ukraine no longer collects statistical data on the number of dementia patients (in adults) and severe and profound mental retardation (in children) [66; 67]. This fact significantly complicates the calculation of the need for PHC for these nosological units, but still requires clarification regarding the necessary analgesia.

In *dementia*, the predominant type of pain is mixed, which consists of nociceptive pain from infections, injuries, bedsores, as well as neuropathic pain due to degeneration of the nervous system. In Alzheimer's disease, beta-amyloid plaques have a toxic effect on nerve cells. NSAIDs are used to treat nociceptive pain, and anticonvulsants and antidepressants are used to treat neuropathic pain. Non-medicinal methods are also effective: physiotherapy, massage, thermal procedures. Bedridden patients need special anti-bedsores care. In some patients with dementia, the pain sensitivity threshold may change, ranging from overestimation to underestimation. The intensity of the pain ranges from mild to severe. Pain is increased by comorbid arthritis, osteoporosis, some pharmaceutical drugs for the treatment of dementia (haloperidol, biperiden, prednisone, dexamethasone, lamotrigine, gabapentin, pregabalin). Severe headache is often present with vascular dementia. For the treatment of severe pain in dementia, strong opioids (morphine, oxycodone) are used with caution (given the difficulty of determining the level of pain in patients with cognitive disorders) [68–71].

In *multiple sclerosis*, pain has a mixed nature, the neuropathic component of which is associated with disturbances in the conduction of nerve impulses due to demyelination and inflammatory processes that damage nerve fibers. The nociceptive component is also associated with inflammatory processes or with injuries due to muscle spasms, contractures or other concomitant diseases. It is more pronounced in the early stages of the disease. In the later stages, neuropathic pain is more pronounced. The nature and strength of the pain depends on the stage of the disease and the localization of the damage to the nervous system. The disease mainly affects women (up to 80%) aged 20–35. The onset of the disease in most men occurs at the age of 35–45. After 10 years from the onset of the disease about a third of patients, and after 15 years half of patients are unable to move without assistance. The loss of the ability to move

often correlates with an increase in pain from mild in the initial stages of the disease to very severe in the last stages [72; 73]. Many complications of the disease are accompanied by pain: spastic conditions, contractures, bedsores, delayed urination and defecation, swallowing disorders, aspiration pneumonia. Some medical and diagnostic procedures (catheterization, epicystostomy, and others) are also painful [74; 75].

Early initiation of treatment using pathogenetic therapy using glucocorticosteroids, plasmapheresis, interferons, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethylfumarate, ocrelizumab improves the prognosis: delays the development of disability [76–78]. The presence of deficient chronic viral diseases, stress, obesity, depression and vitamin D deficiency increase the level of pain; adequate physical therapy, thermal procedures, massage, transcutaneous electronic neurostimulation, yoga, meditation, acupuncture, other methods of complementary medicine – reduce [79–81].

For the treatment of neuropathic pain in multiple sclerosis, anticonvulsants (gabapentin, pregabalin), tricyclic antidepressants, selective serotonin reuptake inhibitors, and opioids are used. NSAIDs can reduce nociceptive pain. With the right treatment, the life expectancy of patients can be the same as that of other people without multiple sclerosis. But in Ukraine, unfortunately, correct and timely treatment of multiple sclerosis is rarely carried out. Correct treatment is also hampered by the high cost of therapy [26; 27; 82].

In *rheumatoid arthritis*, the pain is mainly nociceptive, caused by inflammation of the synovial membrane of the joints and the destruction of their tissues, which irritates pain receptors. Only with a long course due to complications, neuropathic pain can be added. The intensity of pain usually increases with the progression of the disease from mild to severe, and correlates with the strength of the inflammatory process. It starts from one joint and later spreads to others, more in the case of damage to large joints, the presence of osteoarthritis and fibromyalgia. As with all other diseases, the intensity of pain depends on the threshold of individual sensitivity. But with predominant nociceptive pain, the objective assessment in points on standard scales depends more on individual perception than with neuropathic pain. For the treatment of pain in rheumatoid arthritis at all levels of its intensity, NSAIDs (ibuprofen, naproxen) are used, in moderate and severe cases – glucocorticosteroids. The key drugs of pathogenetic treat-

ment are basic antirheumatic drugs (methotrexate, sulfasalazine, which inhibit the inflammatory reaction), biological drugs (cytokines, tumor necrosis factor inhibitors, which slow down the destruction of joints). Non-medicinal methods (physical therapy, massage, thermal procedures), ergotherapeutic devices to facilitate movement, yoga, meditation are effective. A healthy diet, sufficient sleep, and moderate physical activity also have a positive effect on the course of the disease, reduce pain and delay the onset of disability. Tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors are used to treat severe pain in rheumatoid arthritis. The use of opioids is limited and not long-term [83–85].

In *fibrosis and cirrhosis of the liver*, pain is of a mixed type. Its nociceptive component is associated with stretching of the liver capsule (visceral pain) and appears already in the early stages of the disease. The neuropathic component occurs when the nerves of the liver are damaged, against a background of hepatic encephalopathy or vitamin deficiency. The intensity of pain ranges from mild in the early stages to severe in the later stages. Pain can be aggravated by hepatic encephalopathy, ascites, portal hypertension, varicose veins of the esophagus. Pathogenetic pharmacotherapy (entecavir, tenofovir, interferons, sofosbuvir, ledipasvir, simeprevir, essentials, karsil, vitamin E, obelirosan, cencrelide, TGF- β inhibitors, aldosterone inhibitors, etc.) or donor liver transplantation is used for treatment. For pain relief, non-narcotic analgesics and NSAIDs (paracetamol, ibuprofen), antispasmodics (buscopan, no-spa, drotaverin) are used; with ascites – diuretics (verospiron, furosemide). For the treatment of fibrosis and cirrhosis of the liver and their complications, thermal procedures and physiotherapy are used. Patients are recommended a diet and restrictions on physical activity [86–88].

In *Chronic Obstructive Pulmonary Disease* (COPD), pain is mostly of a mixed nature. Its nociceptive component is associated with inflammation of the respiratory tract, chronic cough, suffocation with accelerated breathing, which causes overstrain of the respiratory muscles, and chronic hypoxemia. Neuropathic pain occurs as a result of nerve damage caused by chronic inflammation, compression of nerves by enlarged lymph nodes or tumors. Osteoarthritis, a frequent concomitant disease, contributes to the development of pain in COPD. The pain can be mild to moderate, with localization in the chest (due to coughing and muscle tension), in the back (also due to coughing and

incorrect posture), in the joints (due to lack of oxygen). Headache may be caused by chronic hypoxemia and/or neck muscle tension. For the treatment of neuropathic pain, anticonvulsants (gabapentin, pregabalin, carbamazepine), muscle relaxants (baclofen, tizanidine) and antidepressants are effective, and for nociceptive pain in muscles and joints – NSAIDs (ibuprofen, naproxen), paracetamol. Physiotherapy, massage, heat treatments (mustards, warming compresses), acupuncture, cognitive-behavioral therapy, removal of lung tumors, oxygen therapy are also effective for reducing pain [22; 89–91].

In palliative *kidney diseases*, the pain is mainly of a mixed nature. Its nociceptive component can be associated with renal colic, inflammatory processes (pyelonephritis), tumors. The neuropathic component of pain in kidney diseases can be associated with ureterohydronephrosis, diabetic nephropathy, nerve damage during surgery. The intensity of the pain ranges from mild to severe. Pharmacotherapy of pain involves the use of NSAIDs, paracetamol, antispasmodics, diuretics (to remove stones and reduce pressure in the kidneys), weak and strong opioids (codeine, morphine). Physiotherapy (electrophoresis, ultrasound), massage, heat procedures or, on the contrary, cold (in case of acute inflammation), acupuncture, psychotherapy, epidural anesthesia, neurostimulation, changing the position of the body during treatment to reduce the load on the kidneys, physical therapy, diet, relaxation techniques (yoga, meditation) are also effective [92–94].

In *congenital malformations*, the pain can be equally neuropathic, nociceptive or mixed, from mild to severe (for hydrocephalus, spina bifida (split spine) in intensity, depending on the nature and localization of the defect. Pain can be constant and periodic, disappear in periods of remission. Determining the level of pain is difficult in young children who cannot describe their feelings. The pain is aggravated by the presence of spasms, contractures, and infection. Narcotic and non-narcotic pain killers, blockades, anticonvulsants, antidepressants, physiotherapy (massage, thermal procedures, physical exercises, electrical stimulation), surgical interventions, orthopedic devices (orthoses) [21; 95; 96].

Pain in *severe perinatal conditions* that cause palliative illnesses can range from mild to severe in intensity, nociceptive, neuropathic and mixed in origin. Narcotic and non-narcotic pain relievers (paracetamol, ibuprofen, opioids), anticonvulsants (gabapentin, pregabalin), antidepressants,

epidural anesthesia, physiotherapy (massage, heat procedures, physical exercises, electrical stimulation), compression therapy (bandages, stockings), positional therapy (change in body position), surgical interventions [97–101].

In children with *cerebral palsy*, the pain is mostly mixed. Its nociceptive component is associated with muscle contracture, spasticity, bedsores. The intensity of the pain ranges from mild to severe. In all forms of the disease, the headache is associated with increased intracranial pressure or spasms of blood vessels. Increased muscle tone often causes muscle and joint pain. Contractures limit the mobility of the joints, which, moreover, are often deformed and require surgical treatment. The treatment uses analgesic anti-inflammatory NSAIDs (ibuprofen, naproxen, ketorolac), weak and strong opioid analgesics (tramadol, morphine), muscle relaxants of central (baclofen, tizanidine) and peripheral (dantrolene) action, anticonvulsant drugs (gabapentin, pregabalin – for neuropathic pain), antidepressants (amitriptyline, venlafaxine – for chronic pain), botulinum toxin (reduces spasticity), physical therapy, massage, kinesiotherapy, psychotherapy [102–105].

Pain in *mental retardation (severe and deep)* is associated with complications of diseases that occur or progress faster in such children: cardiovascular (heart failure, strokes), respiratory system (pneumonia, bronchitis, food aspiration), epilepsy, infectious diseases in combination with weakened immunity (with sepsis), with complications after surgical interventions, bedsores. Therefore, nociceptive, neuropathic and mixed types of pain of all degrees of intensity are inherent in this disease. NSAIDs, opioid analgesics, muscle relaxants, anticonvulsants, physiotherapy, acupuncture, positional therapy, art therapy, psychotherapy are used to treat pain [106–109].

In *inflammatory diseases of the central nervous system* in children, the pain is mainly of a mixed nature. The nociceptive component of pain is associated with increased intracranial pressure and brain swelling, the neuropathic component is associated with demyelination. Nociceptive pain is usually present from the beginning of the disease, neuropathic pain joins in the last stages. In meningitis, there is an intense headache, which is often accompanied by stiffness of the occipital muscles and photophobia. In encephalitis, there is also frequent headache, chronic neuropathic spinal pain, convulsions, and loss of consciousness. The pain gradually increases from mild to severe.

For the treatment of pain, etiotropic therapy (antibiotics and antiviral drugs), pathogenetic therapy (glucocorticoids), the entire range of painkillers [110–113] are recommended.

In *phenylketonuria* the pain is usually neuropathic, resulting from nerve damage during convulsions. The intensity of such pain does not exceed a moderate level. A mild headache and muscle pain may also be present after the seizure [114].

In *cystic fibrosis*, the pain is mainly nociceptive, associated with irritation of the nerves of the chest and throat during coughing and the abdominal cavity during pancreatitis or intestinal obstruction. In pancreatitis and pneumonia, the pain can be severe. Dehydration and muscle tension can lead to headaches. Pain reduction occurs in response to adequate analgesia (using NSAIDs, weak and strong opioids) and pathogenetic therapy (to improve lung function using postural drainage, breathing exercises, inhalations, mucolytics, antibiotics; treatment of pancreatitis and intestinal obstruction). Physiotherapy, massage, kinesiotherapy, relaxation techniques (yoga, meditation, breathing exercises), thermal procedures (mustards, warming compresses), psychotherapy are also effective [115–119].

In *mucopolysaccharidoses*, the pain is mostly mixed. Its nociceptive component is associated with joint inflammation, bone deformation, and compression of nerve roots. Neuropathic pain is associated with neurodegenerative processes. The intensity of the pain ranges from mild to severe. Mild persistent pain is often localized in the joints and worsens with physical exertion. Moderate chronic pain in the back is associated with deformation of the spine, in the abdomen – with an increase in internal organs. Severe acute pain often occurs when nerve roots are compressed or joints are inflamed. The reduction in pain level corresponds to the effectiveness of pathogenetic therapy (enzyme replacement therapy and correction of metabolic disorders) and analgesia (with frequent use of NSAIDs and infrequent opioids). Kinesiotherapy, massage, acupuncture, thermal procedures, psychotherapy are also effective [120–123].

In children with *chronic hepatitis*, the pain is mainly nociceptive, associated with stretching of the liver capsule, compression of neighboring organs and nerve endings by an enlarged liver. The presence of gallstones increases the pain. With the development of cirrhosis of the liver, neuropathic pain is added, due to the degeneration of the nerves

of the liver. Etiotropic and pathogenetic therapy (treatment of the main disease, for example, virostatic therapy, immunomodulators-suppressors) together with painkillers (NSAIDs, paracetamol), antispasmodics, physiotherapy (ultrasound, electrophoresis with pharmaceuticals, magnetic therapy) and diet (restriction of fatty, fried, smoked, spicy) help to reduce the level of pain [124–126].

Conclusions

The treatment of chronic pain in Ukraine is regulated by the treatment standard, which recommends following the WHO three-step protocol the use of non-steroidal anti-inflammatory drugs and non-narcotic analgesics for the treatment of mild pain, mild opioids for moderate pain, and strong opioids for severe pain. A significant number of diseases that are accompanied by chronic pain should be treated as palliative. But the treatment standard does not detail the use of painkillers according to nosological units.

The conducted research made it possible to determine the predominant types of pain, their possible intensity and corresponding groups of pharmaceutical drugs with an analgesic effect in noso-

logical units from the list of palliative diseases proposed by us. We also proposed to introduce clarifications to the national standard for the treatment of chronic pain in adults and children. The perspective of further studies is to detail the dosage of drugs with an analgesic effect and to calculate the need at the national level for reimbursement under the "Affordable Medicines" program.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

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