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# LEGAL FRAMEWORK FORPRESCRIBING OPIOIDS – OPIOPHOBIA

*In Serbia, around 32,000 new cases of malignant disease are diagnosed annually, while about 20,000 people die from cancer. Pain represents the most common and severe symptom, affecting up to 60% of patients, and 25–30% experience severe pain. Although the World Health Organization (WHO) method enables effective control of cancer pain in 70-90% of cases, in practice only about 50% of patients receive adequate treatment. The main barrier is opiophobia – an excessive fear of opioid use – present among physicians and the wider public. This leads to inadequate prescribing, underdosing, or early discontinuation of therapy. However, research shows that iatrogenic opioid addiction in cancer patients is rare, occurring in about 2% of cases, while physical dependence and tolerance are expected pharmacological effects, not pathological addiction. Effective pain management requires overcoming misconceptions about opioids, careful dosing, and management of side effects. Strengthening physician education, addressing regulatory barriers, and reducing opiophobia are essential steps toward improving the quality of palliative care and reducing unnecessary suffering in patients with malignant diseases.*

***Keywords**: cancer pain; opioids; opiophobia; palliative care.*

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Every year in the Republic of Serbia, about 32,000 new cases of malignant disease are diagnosed, and about 20,000 people die from cancer annually. Pain is the most common and severe symptom of a malignant disease, which scares the patient and family the most. Pain is defined as an unpleasant sensory and emotional experience, which is associated with existing or possible tissue damage or which we describe with words that correspond to that damage. It occurs in about 60% of patients, in all stages of the malignant disease, with the fact that the frequency and severity of pain increase as the disease progresses. About 25-30% of patients have severe pain.

According to data from the World Health Organization (WHO), cancer pain can be eliminated in most patients (70-90%). The WHO method is based on pharmacotherapy with drugs that are applied in the least invasive way (orally, in the first place), on an hourly basis, in accordance with the intensity of pain and the individual characteristics of the patient and the pain syndrome. Opioid analgesics are key drugs, without which successful therapy of moderately severe and severe cancer pain is not possible. According to the so-called according to the WHO analgesic ladder, any patient with pain intensity ≥ 5/10 on a numerical scale for pain intensity (0: no pain, 10: worst possible pain) should be treated with opioids.

Recommendations for the treatment of cancer pain (WHO and the National Guide for Palliative Care), as well as appropriate drugs are available to all doctors. There are both weak (tramadol) and strong opioids (morphine, hydromorphine, Fentanyl TD and methadone) on our market. However, we have witnessed that in everyday practice, the treatment of cancer pain is not satisfactory. This is confirmed by WHO statistics, according to which the treatment of cancer pain is successful only in about 50% of cases. Therefore, there is a large gap between what can be done and what is actually done.

There are many reasons for failure in the treatment of cancer pain, and one of the most important is opiophobia, which is defined as an excessive fear of the therapeutic use of opioids. The risk of opioid analgesics is assessed as too great in relation to the therapeutic benefit. Instead of being used, opioids are avoided, resulting in pain management failure and unnecessary suffering for patients and their families. Opiophobia is very widespread and is present at all levels, from doctors to the general public.

Surveys conducted among doctors show that they fear the development of addiction, tolerance and side effects of opioids. They are also afraid of the restrictive regulations that control the prescription of opioids as narcotics. That is why doctors do not prescribe opioids when indicated by the severity of pain, prescribe them in smaller doses than necessary (so-called underdosing), extend opioid dosing intervals or discontinue them as soon as the pain is relieved, regardless of whether the cause of the pain is still

present. In this way, patients are deprived of opioids, which are the most effective and safest drugs for the long-term treatment of cancer pain.

## Iatrogenic opioid dependence

Doctors fear that by prescribing opioid analgesics to treat cancer pain, they will iatrogenically cause opioid addiction. A WHO expert committee found that opioids, when used to treat pain, cause physical dependence and tolerance. However, in 2006, this Committee further clarified that the appearance of physical dependence and/or tolerance in patients who take opioids for the treatment of pain for a long time does not mean pathological dependence on opioids at the same time. Namely, physical dependence and tolerance are the expected consequences of the drug's effect and are not sufficient in themselves for the diagnosis of addiction. The presence of other phenomena, which make up the so-called addiction syndrome. In patients who use opioids to treat pain, these phenomena rarely occur, so the criteria for establishing the diagnosis of addiction syndrome are rarely met. Research has shown that iatrogenically induced addiction to opioid analgesics in patients with cancer pain is very rare and occurs in about 2% of patients. Therefore, the risk of developing iatrogenic addiction is too small to deny the patient, due to the fear of addiction, treatment of cancer pain with the most effective drugs, i.e. opioids.

In order to avoid equating physical dependence with drug dependence, the WHO replaced the term physical dependence with the term withdrawal syndrome.

The term psychological dependence has been dropped. The modern WHO terminology uses only the terms abstinence syndrome and addiction syndrome (in the old terminology drug dependence, i.e. addiction).

## Abstinence syndrome (so-called physical dependence)

The term physical dependence is used to describe the state of adaptation of the organism to the presence of an opioid drug, which is manifested by withdrawal syndrome when the drug is suddenly stopped, when the dose or concentration of the drug in the blood is suddenly reduced, and/or when an opioid receptor antagonist is used. Physical dependence develops if opioids are used regularly for 3-4 weeks. However, physical dependence is not an obstacle to withdrawing the opioid analgesic when it is no longer needed, for example, if the cause of the pain is removed with antineoplastic therapy or the intensity of the pain is reduced. We have such cases after successful chemotherapy or

irradiation of painful bone metastases. The dose of the opioid analgesic should be gradually reduced (eg by 50% every 3 days) and then the drug should be discontinued. It is not recommended to increase the interval between doses.

## Opioid addiction syndrome

According to the international classification of diseases, the diagnosis of addiction syndrome can be made when a person meets at least 3 of the 6 criteria listed in the Table.

In patients treated with opioids, the diagnosis of addiction syndrome can only be made if the patient, in addition to tolerance and abstinence syndrome, meets at least one of the remaining four criteria, which relate to compulsive behavior and substance use despite harmful consequences. Once good pain control and a regular supply of opioids are established, the behavior characteristic of pseudo-addiction also stops.

## Tolerance

Tolerance implies a reduction in the analgesic effect of opioids after repeated administration of a certain dose of that drug. Tolerance to the analgesic effect of opioids does not develop quickly. A large number of patients are on a stable dose for weeks and months. The need to increase the dose of analgesics is most often the result of an increase in pain, and not true pharmacological tolerance (the so-called pseudo-tolerance).

Intensification of pain most often occurs due to an increase in painful stimulation (due to the complication/progression of a malignant disease) or due to a change in the factors that affect the patient's experience of pain (eg psychological, social, spiritual factors). Before attributing the reduction in opioid analgesic effect to tolerance to the drug, other possible reasons for increased pain should be considered. This is useful in many ways. First, increasing pain is one of the first signs of progression/relapse of the underlying disease or complications that may follow. In addition, by removing the cause of the pain, it is possible to reduce the pain and restore the analgesic effect of the drug.

Tolerance to the analgesic effect of opioids is not an obstacle to the use of these drugs in practice. First of all, tolerance can be overcome by switching from a weak to a strong opioid or by increasing the dose of a strong opioid. Unlike weak, strong opioids do not have the so-called the maximum dose and the dose of the drug can be increased as much as necessary until the pain stops or the side effects appear that cannot be controlled. Tolerance to a strong opioid can also be overcome by switching from one strong opioid to another (so-called opioid rotation), as cross-tolerance between opioids is not complete.

Side effects can be prevented by careful selection of the initial dose of the drug and gradual individual titration. The patient should be warned of mild nausea and sedation, which subsides during the first week. If necessary, an antiemetic (eg metoclopramide) can be prescribed, especially if the patient has a history of nausea and vomiting due to opioids. He should also be advised to avoid other sedative drugs, alcohol and driving.

We should also not forget that the patient may have disturbed sleep due to unrelieved pain, and therefore needs to get enough sleep to make up for the missed time. If sedation is maintained, comorbid conditions (eg hypercalcemia or brain metastases) or the influence of other drugs (most often benzodiazepines) should be ruled out. Initial confusion is rare. It occurs in patients with advanced malignant disease, in old people, patients with kidney failure or if the patient is dehydrated. Constipation should be approached prophylactically, which means that every patient receiving an opioid should be prescribed a laxative at the same time and immediately. A combination of a stool-softening laxative (eg lactulose) and a stimulant laxative (bisacodyl, senna) is recommended.

Among healthcare workers, there is a great fear of respiratory depression when opioids are administered. Respiratory depression is a potentially fatal side effect of opioids, but tolerance to this effect develops rapidly. In addition, pain counteracts the respiratory depressant effect of opioids. Therefore, respiratory depression is extremely rare when pain is present and the opioid dose is carefully and individually titrated. Respiratory depression does not develop suddenly and is usually preceded by other side effects, such as nausea, vomiting, and drowsiness. Combinations of opioids with other drugs that have a depressant effect on breathing, especially with benzodiazepines, should be avoided. There is no difference in the respiratory depressant effect among the individual opioids. The exception is methadone, whose complicated pharmacokinetics exposes the patient to a greater risk of drug accumulation and side effects. Due to the possible reduction of analgesia, the administration of naloxone is recommended only in case of threatening or symptomatic respiratory depression (number of respirations less than 8/min).

Successful opioid therapy requires that the desirable analgesic effects outweigh the possible adverse effects. When already manifested, the unwanted effects of opioids can be alleviated by reducing the dose of opioid analgesic (with the use of so-called adjuvant analgesics or non-pharmacological methods to reduce pain, e.g. radiation), by changing the method of opioid administration (e.g. to switch from oral to transdermal), by using opioid receptor antagonists (e.g. peripheral antagonists for the treatment of constipation), by rotating opioids or by symptomatic therapy of side effects.

## Legal framework for prescribing opioids

Opioid analgesics have a dual nature. On the one hand, these drugs are crucial for the successful treatment of moderate and severe cancer pain. Morphine is on the WHO list of essential medicines, which confirms its value and importance in medicine. On the other hand, opioids as substances have the potential for abuse and can cause a dependence syndrome when abused, which is why they are classified as narcotics. Narcotic is a legal term meaning a substance subject to international control under the United Nations (UN) Single Convention on Narcotic Drugs (1961, as amended in 1972). The term narcotic includes substances that have a legitimate use in medicine (eg, opioid analgesics), but also substances that are not used as drugs (eg, cocaine, heroin). The production, circulation, prescription and dispensing of narcotics are regulated by special regulations.

The UN Single Convention on Narcotic Drugs recognizes the dual nature of narcotics. The preamble of this document states that narcotics used in medicine are indispensable for eliminating pain and suffering. Also, it is stated that the abuse of narcotics is a serious evil for the individual and for the society as a whole. The Single Convention calls on governments of signatory countries to strike a balance between the obligation to prevent drug abuse and the equally important obligation to ensure the availability of narcotics for treatment pain and elimination of suffering (WHO principle of balance in drug control). This Convention was ratified by our country.

Governments are urged to analyze the national drug control policy and determine whether there are unduly restrictive provisions in that policy that hinder the health system from providing effective pain management services and to take appropriate corrective measures. Analysis of laws and regulations in Serbia that control narcotics, according to WHO guidelines, showed that they are overly restrictive. Narcotics control policy is not balanced, which means that emphasis is placed on preventing abuse, while provisions ensuring the availability of narcotics for medical use are lacking. Measures to prevent misuse thus become an obstacle to the successful treatment of cancer pain and cause unnecessary patient suffering.

A single convention requires a prescription for prescribing and dispensing narcotics. However, the requirements that the prescription must meet should be seen in the light of the fact that the prescription, in addition to preventing abuse, simultaneously ensures the availability of narcotics to the patient for pain treatment. Here, we should recall the double goal of the Convention, which is to enable the use of narcotics for the treatment of pain, while simultaneously preventing the abuse of narcotics and their flow into illegal channels. There is a justification for double prescription and it is applied in most countries. However, the maximum number of opioids that can be prescribed to patients in

Serbia at the same time is one. Patients who are treated with long-acting opioids (Fentanil TD or SR hydromorphone) also need short-acting morphine for the treatment of the so-called breakthrough pain, so there is a need to prescribe at least two opioids to the patient at the same time. Also, the validity period of the prescription is 7 days. In countries with a balanced drug control policy, the prescription is valid for 30 days. In addition, opioids should be available to patients near their place of residence. All doctors who treat patients with malignant diseases, regardless of specialization, should have the right to prescribe opioids, provided that they are experts and have a certificate proving their education.

The Republic of Serbia adopted the National Strategy for Palliative Care, which includes the right of patients to relieve pain and recognizes opioid analgesics as necessary and irreplaceable drugs for successful removal of cancer pain and palliative care. This strategy recognizes the government's obligation to provide and ensure the availability of opioids for medical use. In this sense, the Commission for Palliative Care of the Ministry of Health made a proposal to amend the legal regulations, with the aim of modernizing the control of narcotics and establishing a control system that will prevent abuse, but at the same time ensure the availability of narcotics for pain treatment.

Cancer pain must and can be treated. At today's level of knowledge, no patient should either live or die in pain. Opioid analgesics are necessary and irreplaceable drugs for the successful elimination of moderate and severe cancer pain. There are no contraindications for the use of these drugs when there is pain and when the dose of the drug is carefully and individually titrated. It is unacceptable that unfounded opiophobia continues to be an obstacle to the successful removal of pain and the cause of the unreasonable suffering of a large number of patients. Opioid analgesics are there to be used, not to be permanently avoided. Therefore, we have to ask ourselves why we are still denying these medicines to the sick?

## What are we still afraid of?

BALANCED OPIOID CONTROL POLICY (principle of balance) Refers to the establishment of a balanced narcotic control system that prevents the abuse of narcotics and at the same time ensures their availability for use in medicine in order to eliminate pain and suffering. A balanced drug control policy was proclaimed by the UN Single Convention on Narcotic Drugs (1961 and the 1972 Protocol) and WHO recommendations (2000). The UN single convention calls on the governments of signatory countries to establish a balance between the obligation to prevent drug abuse and the equally important obligation to ensure the availability of narcotics for the treatment of pain and the elimi-

nation of suffering. Although they are classified as narcotics and subject to control, opioids are also essential drugs for patients with cancer pain. Opioid control should not jeopardize their availability as medicines. Opioids used for therapeutic purposes must be available to patients who need them.

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