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The use of opioid analgesics in palliative care in Ukraine: Changes in legislation and availability

Abstract

Introduction: The main task of palliative care is to improve the quality of life of a patient, and the therapy of chronic pain with opioids is a significant problem for palliative care patients in Ukraine. Therefore, this study aimed to assess the opioid availability for palliative care patients in Ukraine.

Methods: Analysis of the list and consumption of opioids according to the scientific publications and legal documents.

Results: It was found that in Ukraine as of June 2021, 12 international non-proprietary names of opioids were registered, most of which are represented by several dosage forms, which makes it possible for patients to receive adequate pain relief through non-invasive therapy with oral forms. It was shown that two thirds (63.2%) of trade names of opioids registered in Ukraine were of domestic origin. Based on a comparative analysis of the range of opioids, available in current regulatory documents, it was established that in the State Register of Medicines of Ukraine and the Unified clinical protocol there is an almost identical list of opioids (12 drugs). However, in the State Drug Formulary and the National List of Essential Medicines, this list is much smaller (8 and 5 drugs, respectively). Since 2013 changes in the regulatory documents on the medical use of opioids in Ukraine have occurred, and oral morphine was registered for the first time, allowing access to adequate pain relief. Analysis of the morphine consumption level by dosage forms has shown that before 2013, the pharmacies sold only morphine in injections, and since 2013, the consumption of oral morphine increased.

Conclusions. Changes in regulatory documents partially simplified the complicated process of obtaining opioids by patients. However, more than 80% of patients still do not receive adequate pain therapy due to the hesitancy of doctors to prescribe opioids and an extremely insufficient number of pharmacies (1.8%) that sell opioids for the population.

Palliat Med Pract 2022; 16, 2: 93–102

Key words: palliative care, palliative care patient, chronic pain, opioid analgesics, range, regulatory document

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Palliative Medicine in Practice 2022; 16, 2, 93–102

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DOI: 10.5603/PMPI.2022.0004

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Introduction

According to the Order of the Ministry of Health of Ukraine (MHU) "On improving the organization of palliative care in Ukraine" dated June 4, 2020, No 1308 the main task of palliative care is to improve the quality of life of a patient with an incurable disease and his family members, caring for him, due to early detection, careful assessment and treatment of pain, associated symptoms and complications, and also the solution of patient's physical, psychological, spiritual and social problems [1]. In particular, the document defines the main components of palliative care:

- physical (medical, pharmaceutical) — symptomatic drug treatment therapy, non-pharmaceutical management, prevention and effective treatment of chronic pain;
- social (including the provision of social palliative care services);
- spiritual;
- psychological — support of the patient and his family, other persons caring for the patient.

The main goals of proper pain management are to reduce pain and improve daily function while monitoring for adverse effects. Also, it should be noted that there are different approaches to pain management for all types of patients (e.g. with reduced prognosis or not) and diseases such as malignant, acute or some chronic non-cancer pain. An especially significant problem is the treatment of chronic pain in patients receiving palliative care with cancer and non-cancer diseases [2]. However, it should be noted that there are different approaches to pain management for all types of diseases, such as malignant, acute or some chronic non-cancer pain. According to the world's recommendations (WHO, ESMO, EAPC) [3–5], opioids are the gold standard in the treatment of severe pain. However, inappropriate prescribing, lack of knowledge regarding adverse events associated with long-term use, opioid misuse, abuse and addiction, and prescription of opioids for chronic non-cancer pain for long-term use are factors that prove that opioids need careful consideration and the dose should be tailored to the individual's need: start low and then be adjusted (titrated up or down) according to response [6].

Opioids are remarkable drugs that can provide good pain relief, but also opioid use is associated with mental and behavioural disorders, including the following conditions or diseases according to ICD-10: acute opioid intoxication (F11.0), opioid dependence (F11.2), withdrawal state (F11.3) [7, 8]. That is why opioids are included in the list of narcotic drugs and their circulation is limited and additionally controlled [9].

The use of evidence-based prescribing by physicians (including limiting the prescribed opioid to the lowest effective dose), regular monitoring and reassessment of the pain intensity and drug dose, increasing of knowledge level about pain and addiction, sharing of last world guidelines on pain management between medical practitioners are key issues to minimize the risks associated with long-term opioid use and improve the treatment of chronic pain [10, 11]. Given the above, the monitoring of opioid supply level of patients with chronic pain is extremely important for health care professionals who are constantly engaged in pain relief therapy. Therefore, this study aimed to assess the opioid availability for palliative care patients in Ukraine.

Methods

Analysis of the list and consumption of opioids according to the scientific publications and legal documents, in particular: the State Register of Medicines of Ukraine (further — the Register) [12], the National List of Essential Medicines (further — the National List) [13], the State Drug Formulary, in particular, Annex 8 "Palliative and Hospice Care Drug Formulary" since 2nd Issue in 2010 (further — the Formulary) (2–13 issues) [14, 15], the Unified clinical protocol (further — the Protocol) for palliative treatment of chronic pain [2], the Analytical report on the use of opioids in Ukraine (2011–2016) (further — the Report) [16]. The Register contains information on all the opioids registered in Ukraine, the Formulary — the list of opioids with evidence-based efficacy for pain management. The National List provides information about opioids to meet the priority needs of medical care in health care facilities for treatment of patients at the expense of state and local budgets and the Protocol — the information on the diagnostics, assessment of pain intensity and treatment, as well as a list of medicines for the management of various types of pain. The Report is devoted to a study of the state's compliance with international obligations to ensure the availability and accessibility of opioids for patients, which was conducted with the support of the International Renaissance Foundation. Different methods, such as graphics, documentary and marketing, were used in the study. As the study does not constitute medical experiment involving patients ethical approval was not required.

Results

Documents and availability of opioids

The analysis of data of the Register as of June 2021 (Table 1) has found that 12 international non-proprietary names (INN) of opioids under 39 tra-

de names (TN) were registered in Ukraine in particular morphine, oxycodone, fentanyl, methadone, buprenorphine, butorphanol, nalbuphine, tramadol, trimeperidine, codeine, and two combinations: morphine + noscapine + papaverine + codeine + thebaine and morphine + noscapine + papaverine + codeine.

Almost all opioids, except codeine, buprenorphine and methadone, belong to the subgroup “N02A — Opioids” according to the Anatomical Therapeutic Chemical (ATC) Classification System. Codeine, even though it also interacts with opiate receptors and is a central analgesic, belongs to the subgroup “R05D — Cough

Table 1. Range of opioids according to the State Register of Medicines data

No.	Trade name	Dosage form	Manufacturer
Morphine N02AA01			
1	Morphine sulphate	Oral tablet (5, 10 mg)	InterChem, Ukraine
2	Morphine Calcex	Solution for injection, 10 mg/ml, 20 mg/ml, 1 ml ampoule	JSC Kalceks, Latvia
3	Oramorph	Oral solution, 2 mg/ml, 100 ml	Molteni Farmaceutici, Italy L. MOLTENI & C. DEI F.LLI ALITTI SOCIETÀ DI ESERCIZIO S.P.A.
4	Morphine hydrochloride	Solution for injection 1%, 1 ml ampoule	Zdorovye Narodu, LTD, Ukraine
5	Morphine-ZN	Tablets 5, 10 mg	
Oxycodone N02AA05			
1	Dolonica 10 (20, 40, 80) mg	Prolonged-release film-coated tablets (multiple-unit pellet system) 10, 20, 40, 80 mg	Acino Pharma AG, Switzerland
2	Oxycodone Kalceks	Solution for injection 10 mg/ml, 1 ml or 2 ml ampoule	JSC Kalceks, Latvia
Morphine + noscapine + papaverine + codeine + thebaine			
1	Omnopon-ZN	Solution for injection, 1 ml ampoule	Zdorovye Narodu, LTD, Ukraine
Morphine + noscapine + papaverine + codeine			
1	Omnopon neo	Solution for injection, 1 ml ampoule	Zdorovye Narodu, LTD, Ukraine
Fentanyl N02AB03			
1	Fentanyl M Sandoz®	Transdermal patch 25, 50, 75, 100 µg/h	Hexal AG, Germany
2	Durogesic®	Transdermal patch 25, 50, 75, 100 µg/h	Janssen Pharmaceutica NV, Belgium
3	Fentavera 12 (25, 50, 75, 100) mcg/hour	Transdermal patch 12, 25, 50, 75, 100 µg/h	Acino AG/Luye Pharma AG, Germany
4	Fentanyl Kalceks	Solution for injection, 50 µg/ml, 2 ml or 10 ml ampoule	HBM Pharma S.R.O., Slovakia, JSC Grindeks, Latvia, JSC Kalceks, Latvia
5	Fenstud	Solution for injection, 50 µg/ml, 2 ml ampoule	Rusan Pharma Ltd, India
6	Fentanyl	Solution for injection, 50 µg/ml, 2 ml ampoule	Zdorovye Narodu, LTD, Ukraine
Methadone N02AC52, N07BC02, R05DA06			
1	Metafin®	Tablets 5, 10, 25 mg	InterChem, Ukraine
2	Methadone-ZN	Oral solution, 1, 5 mg/ml	Zdorovye Narodu, LTD, Ukraine
3	Methadone-ZN	Tablets 5, 10, 25, 40 mg	
4	Methadone hydrochloride Molteni	Oral solution, 1, 5 mg/ml	Molteni Farmaceutici, Italy L. MOLTENI & C. DEI F.LLI ALITTI SOCIETÀ DI ESERCIZIO S.P.A.

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Table 1. cont. Range of opioids according to the State Register of Medicines data

No.	Trade name	Dosage form	Manufacturer
Buprenorphine N02A 01, N07BC01			
1	Bupren®	Sublingual tablets 0.2; 0.4; 2; 4; 8 mg	InterChem, Ukraine
2	Buprenorphine hydrochloride	Solution for injection, 0.3 mg/ml, 1 ml ampoule	Zdorovye Narodu, LTD, Ukraine
3	Buprenorphine hydrochloride	Sublingual tablets 2, 4, 8 mg	
Butorphanol N02AF01			
1	Butolar®	Solution for injection, 2 mg/ml, 1 ml ampoule	PJSC SIC Borshchahivskiy CPP
Nalbuphine N02 F02			
1	Nalbuphine Farmex	Solution for injection, 10 mg/ml, 1 ml or 2 ml ampoule	LLC Farmex Group / Zdorovye Narodu, LTD, Ukraine
2	Nalbuphine-ZN	Solution for injection, 10 mg/ml, 1 ml or 2 ml ampoule	Zdorovye Narodu, LTD, Ukraine
3	Nalbuk	Solution for injection, 10 mg/ml, 1 ml or 2 ml ampoule	Joint Stock Company Farmak
4	Nalbuphine	Solution for injection, 10 mg/ml, 1 ml or 2 ml ampoule	LLC Yuria-Pharm, Ukraine
5	Nalbaxone	Solution for injection, 10 mg/ml, 1 ml or 2 ml ampoule	Myungmoon Pharm. Co., Ltd., South Korea
6	Nofa	Solution for injection, 10 mg/ml, 1 ml or 2 ml ampoule	Steril-Gene Life Sciences (P) Ltd, India
7	Nalbuphine injections 10 (20) mg	Solution for injection, 10,20 mg/ml, 1 ml ampoule	Rusan Pharma Ltd, India
Tramadol N02AX02			
1	Tramadol-ZN	Solution for injection, 50 mg/ml, 1 ml or 2 ml ampoule	Zdorovye Narodu, LTD, Ukraine
2	Tramadol-ZN	Capsules 50 mg	
3	Tramadol Kalceks	Solution for injection, 100 mg/2 ml, 2 ml ampoule	HBM Pharma S.R.O., Slovakia, JSC Grindeks, Latvia, JSC Kalceks, Latvia
4	Tramadol hydrochloride	Solution for injection 5%, 2 ml ampoule	JSC Farmak, Ukraine
5	Tramadol	Capsules 50 mg	JSC Farmak, Ukraine
6	Tramadol-M	Solution for injection, 50 mg/ml, 1 ml or 2 ml ampoule	Zdorovye Narodu, LTD, Ukraine
Trimeperidine N02			
1	Promedol-ZN	Solution for injection, 20 mg/ml, 1 ml ampoule	Zdorovye Narodu, LTD, Ukraine
2	Promedol Kalceks	Solution for injection, 20 mg/ml, 1 ml ampoule	HBM Pharma S.R.O., Slovakia, JSC Grindeks, Latvia, JSC Kalceks, Latvia
Codeine R05DA04			
1	Codeine phosphate	Tablets 0.03 g	InterChem, Ukraine

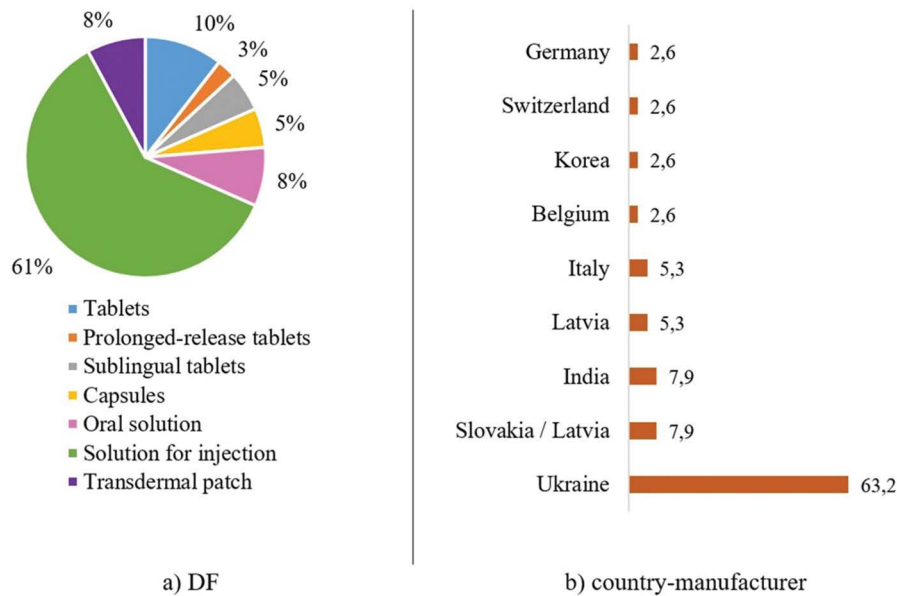


Figure 1. The structure of registered trade names of opioids in percentage, as of 2021

and cold preparations”, because the main therapeutic effect is its antitussive effect. Methadone and buprenorphine have several ATC codes and belong to both subgroups “N02A” and “N07BC — Drugs used in opioid dependence”, due to their therapeutic indications.

It should be noted that most opioids were represented by several dosage forms (DF) that allowed the doctor to prescribe medicines in compliance with the Protocol. The Protocol was registered as the Order of the MHU dated April 25, 2012 No 311 and developed based on adapted clinical guidelines “Pain Control”, based on the principles of evidence-based medicine, taking into account modern international recommendations [2]. However, not all opioids were used to treat chronic pain, such as methadone or buprenorphine, which were primarily used for opioid substitution therapy. The turning point in the formation of the opioids range was the registration in Ukraine:

In 2013, morphine sulphate in the form of tablets [17], enabled patients to receive adequate analgesia with non-invasive dosage forms, as well as the state’s compliance with obligations to incurable patients in terms of providing adequate medical care.

In 2016, oxycodone (prolonged-release tablets), was used as an alternative analgesic for patients intolerant to morphine.

In 2017, morphine in the form of an oral solution was the drug of choice for pain relief in children.

As of 2021, all opioids on the Ukrainian market were represented by different DF such as parenteral (solution for injection), oral (tablets, capsules), and

transdermal drug delivery systems (patches) (Fig. 1a). Almost two thirds (61%) of the range were parenteral DF, almost a third (31%) — were oral DF and the smallest group (8%) — had transdermal patches.

Opioids registered in Ukraine were represented by manufacturers of different countries. Almost two thirds (63.2%) of the range of medicines were of Ukrainian origin. The rest of the opioids was produced by Slovakia / Latvia (joint production) and India (3 or 7.9% of drugs each), Latvia and Italy (2 or 5.3% each), Belgium, Korea, Switzerland and Germany (1 or 2.6% each) (Fig. 1).

Among domestic producers, the dominant position (58.3% of TN) was occupied by Zdorovye Narodu, LTD (Kharkiv), the other producers were, in particular: InterChem (16.6%), JSC Farmak (12.5%), LLC Farmex Group (4.2%), PJSC SIC Borshchahivskiy CPP (4.2%), LLC Yuria-Pharm (4.2%) (Fig. 2).

The need to develop various applications and clinical recommendations was related to the peculiarities of therapy of some categories of patients (patients with tuberculosis, HIV/AIDS, cancer), specific groups of medicines used and their interactions. Due to the growing number of patients with limited life expectancy and incurable diseases, the issue of creating special formularies and clinical protocols for palliative care is extremely important. Specialists of the “Institute of palliative and hospice medicine of the MHU” have formed a list of medicines, recommended for the treatment of chronic pain in palliative oncology, as well as adjuvant drugs for symptomatic therapy. This list

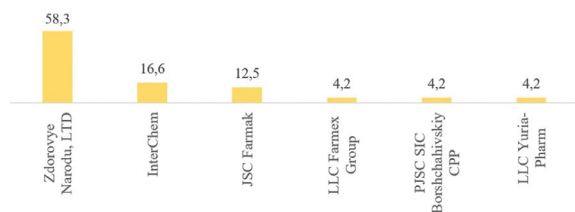


Figure 2. Rating of domestic producers by the number of registered trade names of opioids (in percentage)

became the basis for the draft of the Drug Formulary for Palliative and Hospice Care (2009) and was included for the first time in the Formulary (2nd issue, 2010) in the form of Annex 8 “Palliative and Hospice Care Drug Formulary”. As of 2021, thirteen issues of the Formulary have been published in Ukraine, which contains recommendations on the rational use of medicines, considering efficacy, safety and economic feasibility [14, 15].

Therefore, the next stage of the present study was the analysis of the formulary range of opioids in the dynamics, for which was selected the Formulary Annex 8 of 2–13 issues (2010–2021). The range of subgroup “N02A Opioids” until the 6th issue did not change and had 10 opioids INN (Table 2). It should be noted that for the first time in the 5th Formulary issue the changes to the formulary chapter “Morphine” were made (the dosage for the use of morphine sulphate in tablets was included).

From the 6th to the 9th Issue of the Formulary, due to the expiration of the hydromorphone registration certificate, the range of opioids was reduced to 9 INN. The 10th and 11th Issues of the Formulary contained 9 INN of opioids (due to the registration certificate expiration the combination of tramadol with paracetamol was excluded), the 12th and 13th — 8 INN of opioids (due to the registration certificate expiration the combination of paracetamol, dicycloverine and dextropropoxyphene was excluded).

The above-mentioned Protocol is important in the proper appointment of opioids. The National List plays a significant role in the state regulation of drug prices, as well as in drug availability to the population, as this list includes qualitative, safe and cost-effective drugs needed to provide medical care in health care facilities of all types of ownership [5]. Therefore, the next stage of the present study was a comparative analysis of the range of opioids included in the current regulations — the Register, the Protocol, the Formulary (13th issue) and the National List (Table 3).

The list of opioids registered in Ukraine was almost identical to that in the Protocol (12 drugs). However, in the Formulary and the National List the number of opioids was much lower (8 and 5 drugs, respectively). It should be noted that oxycodone was not included in the Formulary and the National List, which was probably due to the recent state registration, as well as its use as a second-line drug. Hydromorphone was listed only in the Protocol, as of 2021 it was not

Table 2. Comparative analysis of the range of formulary opioids for palliative and hospice care

No.	International non-proprietary name of opioid	Issue of State Drug Formulary (SDF)											
		2	3	4	5	6	7	8	9	10	11	12	13
1	Buprenorphine	+	+	+	+	+	+	+	+	+	+	+	+
2	Butorphanol	+	+	+	+	+	+	+	+	+	+	+	+
3	Hydromorphone	+	+	+	+	-	-	-	-	-	-	-	-
4	Morphine	+	+	+	+	+	+	+	+	+	+	+	+
5	Morphine + noscapine + papaverine + codeine + thebaine	+	+	+	+	+	+	+	+	+	+	+	+
6	Nalbuphine	+	+	+	+	+	+	+	+	+	+	+	+
7	Paracetamol + dicycloverine + dextropropoxyphene	+	+	+	+	+	+	+	+	+	+	-	-
8	Tramadol	+	+	+	+	+	+	+	+	+	+	+	+
9	Tramadol + paracetamol	+	+	+	+	+	+	+	+	-	-	-	-
10	Trimeperidine	+	+	+	+	+	+	+	+	+	+	+	+
11	Fentanyl	+	+	+	+	+	+	+	+	+	+	+	+
Total INN		11	11	11	11	10	10	10	10	9	9	8	8

Table 3. List of international non-proprietary names of opioids for the treatment of chronic pain in regulatory documents

No.	International non-proprietary name of opioid	State Register of Medicines	Unified clinical protocol	State Drug Formulary (13th issue)	National List of Essential Medicines
1	Morphine	+	+	+	
2	Hydromorphone	–	+	–	+
3	Codeine	+	+	–	–
4	Oxycodone	+	+*	–	+
5	Morphine + noskapine + papaverine + codeine + thebaine	+	+	+	–
6	Morphine + noskapine + papaverine + codeine	+	–	–	–
7	Fentanyl	+	+	+	–
8	Methadone	+	+**	–***	+
9	Buprenorphine	+	+	+	+
10	Butorphanol	+	+	+	+
11	Nalbuphine	+	+	+	–
12	Tramadol	+	+	+	–
13	Trimeperidine	+	+	+	–
Total number of INN		12	12	8	5

*In the text of the clinical guidelines there is information about oxycodone, however, due to the lack of drugs on the market at the time of the creation of the Protocol, it was not specified in the list of recommended opioids; **The text of the Protocol and the clinical guidelines indicates the use of methadone only as an alternative, due to the difficulty of correct dose titration when changing opioid; ***Methadone in the Formulary is listed in the section „Opioid receptor agonists“ as a drug primarily for the treatment of opioid dependence

registered in Ukraine, and, accordingly, could not be included in the Formulary or the National List.

The use of opioids

In Ukraine, information on opioid consumption has not been properly systematized for a long time, and the first steps toward careful data collection began in 2014. Thus, the analysis of domestic statistics revealed that the rate of morphine consumption in Ukraine in 2014 per capita was almost 8 times lower than the world average and 16 times than in Europe [18].

In 2016–2018, specialists from the NGO “Institute of Analytics and Advocacy” with the support of the International Renaissance Foundation conducted a study of data on opioid consumption in Ukraine [16]. According to the data obtained for 2012–2016, the volume of morphine use in healthcare facilities increased slightly (in 2015) and subsequently decreased in 2016 (Fig. 3).

Analysing data on the prescription dispensing of morphine DF in pharmacies, the rapid trend of growth was noticeable (Fig. 4).

Analysis of the morphine consumption level by DF has shown that before 2013, the pharmacies sold only morphine in injections, and since 2013, due to the registration of the tablet DF, the consumption of oral morphine began to grow rapidly (Fig. 5).

Unmet needs

Comparing the range of opioids on the Ukrainian market with the range in leading world recommendations (WHO, IAHP, EAPC) [5, 19, 20], it should be noted that its content was fully consistent with the above lists, that is all opioids indicated in the guidelines are registered in Ukraine (Table 4).

Despite the increase in the range of opioids, the territorial availability, namely a small number of pharmacies licensed to retail narcotic and psychotropic drugs, still remains the problematic barrier to obtaining adequate pain relief for palliative patients. Thus, according to the State Service of Ukraine on Medicines and Drugs Control, there are 21,294 pharmacies in Ukraine licensed to dispense medicines, and only 378 pharmacies (1.8%) have a license to sell narcotic drugs [21].

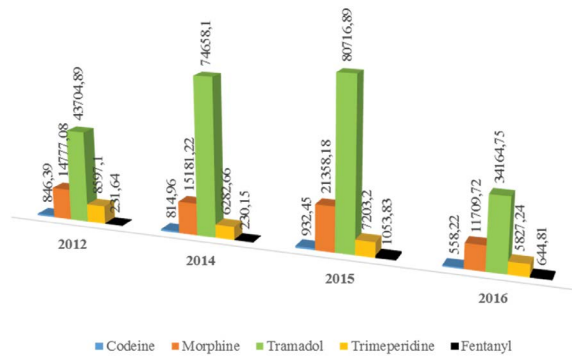


Figure 3. Opioid consumption in the healthcare facilities in Ukraine (in grams)

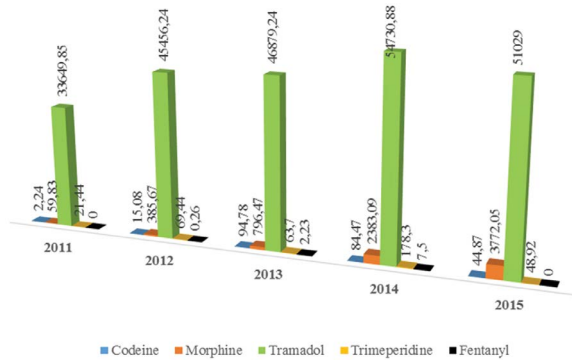


Figure 4. The dynamics of prescription dispensing of opioids in pharmacies (in grams)

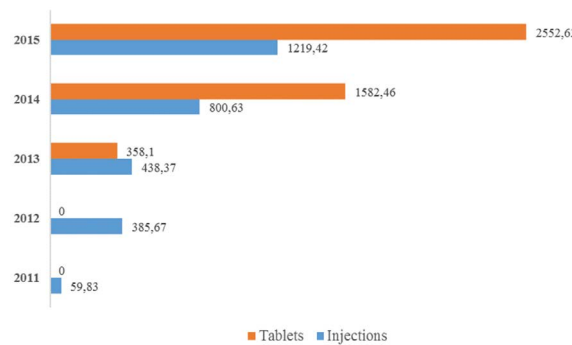


Figure 5. The dynamics of prescription dispensing of morphine (injections and tablets) in pharmacies (in grams)

Over the last 10 years, especially since 2013, the changes in the regulatory documents on the medical use of opioids in Ukraine have occurred [22], in particular regarding the writing of prescriptions on

opioids for palliative care patients: the maximum dose of dispensing on one prescription and the local attachment of a pharmacy to health care facility have been cancelled. The purpose of these changes was to simplify the complicated process of obtaining adequate pain relief for patients so that this was a turning point in the context of opioid circulation and prescribing.

Discussion

Analysis of the range of opioids in the pharmaceutical market of Ukraine showed that since 2013 in Ukraine there have been several changes, both in terms of registration of new drugs and in terms of changes to regulations on opioids circulation. Therefore, it is safe to say that there was a significant breakthrough in the availability of opioids for patients, as evidenced by the registration of oral morphine, as well as the improvement of domestic legislation on opioid circulation.

The results of the analysis have shown that 12 INN of opioids were registered in Ukraine, and all of these opioids were included in the Protocol. However, only 8 INN (66.7%) of opioids were included in the Formulary of the latest edition. This legal document was characterized by a tendency to reduce opioid quantity during 12 editions — from 11 to 8 INN. The National List contained only 5 opioids, which is 62.5% of the amount in the Formulary. This indicates that physical and economic accessibility to opioids was insufficient for patients with chronic pain during inpatient treatment at the expense of state social guarantees. According to the Lancet Commission main barriers to increased access to palliative care and pain relief are [23]:

- The focus of existing measures of health outcomes on extending life and productivity with little weight given to health interventions that alleviate pain or increase dignity at the end of life;
- Opiophobia, which refers to prejudice and misinformation about the appropriate medical use of opioids;
- The focus, in medicine, on the cure and extending life and concomitant neglect of caregiving and quality of life near death;
- Limitations on patient advocacy due to the seriousness of illnesses;
- The focus on preventing non-medical use of internationally controlled substances (such as opioids) without balancing the human right to access medicines to relieve pain, unbalanced laws and excessive regulation.

Table 4. List of international non-proprietary names of opioids in the State Register of Medicines of Ukraine and leading world recommendations (WHO, IAHPC and Essential Package of palliative care)

No.	The international non-proprietary name of opioid	State Register of Medicines of Ukraine	WHO's Essential Medicines List	Essential Package of palliative care and pain relief health services	IAHPC list of essential medicines for palliative care
1	Morphine	+	+	+	+
2	Hydromorphone	-	+	-	-
3	Codeine	+	+	-	+
4	Oxycodone	+	+	-	+
5	Morphine + noskapine + papaverine + codeine + thebaine	+	-	-	-
6	Morphine + noskapine + papaverine + codeine	+	-	-	-
7	Fentanyl	+	+	-	+
8	Methadone	+	+	-	+
9	Buprenorphine	+	-	-	-
10	Butorphanol	+	-	-	-
11	Nalbuphine	+	-	-	-
12	Tramadol	+	-	-	+
13	Trimeperidine	+	-	-	-
Total number of INN		12	6	1	6

An Essential Package of palliative care and pain relief health services, developed by the Lancet Commission, contains the inputs for safe and effective provision of essential palliative care and pain relief, including lists of medicines (based on WHO's Essential Medicines List), equipment and human resources. One of the authors' most important recommendations is that immediate-release morphine is made available in both oral and injectable formulations in the appropriate and necessary dose for any patient with moderate-to-severe pain or dyspnoea that cannot be relieved adequately by other means. However, it should be noted that only in 2013, the oral morphine was registered in Ukraine for the first time, allowing access to adequate pain relief.

As the morphine of immediate-release (injections and tablets since 2013) is present in the pharmaceutical market of Ukraine, it can be considered that recommendations of the Lancet Commission developed in the Essential Package of palliative care and pain relief health services were followed. Thus, it can be concluded that the liberalization of the legislation has improved the supply of opioids to patients, as well as the increased prescription dispensing of morphine tablets in pharmacies. However, due to the extremely insufficient number of pharmacies licensed to sell

opioids (1.8%) and the lack of pain management medical experts, more than 80% of patients still suffer from pain and are often unable to obtain medicines.

Conclusions

In Ukraine as of June 2021, 12 international non-proprietary names of opioids under 38 trade names were registered, most of which were represented by several dosage forms that made it possible for patients to receive adequate pain relief through non-invasive therapy with oral forms. It was shown that two-thirds (63.2%) of trade names of opioids registered in Ukraine were of domestic origin.

The dynamics of the range of subgroup "N02A Opioids" from the 2nd to the 13th issue of the Formulary was characterized by a decrease (from 11 to 8 international non-proprietary names) due to the exclusion from the 6th issue of hydromorphone, from the 10th issue — a combination of tramadol with paracetamol, from the 12th issue — a combination of paracetamol, dicyclerine and dextropropoxyphene.

In the Register and the Protocol, there was an almost identical list of opioids (12 drugs). However, in the Formulary and the National list, this list was much smaller (8 and 5 drugs, respectively). This indi-

cates that physical and economic access to effective opioids was insufficient for patients with chronic pain during inpatient treatment at the expense of state social guarantees.

Over the last 10 years, changes in the regulatory documents on the medical use of opioids in Ukraine have occurred, and this simplified the complicated process of obtaining adequate pain relief by patients and increased the prescription dispensing of morphine tablets in pharmacies. However, according to the Ministry of Health of Ukraine statistics, more than 80% of patients did not have access to analgesia due to the legislation over-regulation, the hesitancy of doctors to prescribe opioids and fear of criminal liability and extremely insufficient number of pharmacies (1.8%) that sell opioids for the population.

Declaration of conflict of interests

The authors declare that there is no conflict of interest.

Funding

None declared.

References

1. Order of the Ministry of Health of Ukraine 1308 «On improving the organization of palliative care in Ukraine» [Internet] dated 04.06.2020. <https://zakon.rada.gov.ua/laws/show/z0609-20#Text>. (8 September 2021).
2. Order of the Ministry of Health of Ukraine 311 «On approval and introduction of medical and technical documents to standardize palliative medical care for chronic pain syndrome» [Internet] dated 25.04.2012. <https://zakon.rada.gov.ua/rada/show/v0311282-12#Text> (8 September 2021).
3. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents [Internet]. <https://apps.who.int/iris/bitstream/handle/10665/279700/9789241550390-eng.pdf>. (8 September 2021).
4. Fallon M, Giusti R, Aielli F, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org, ESMO Guidelines Committee. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018; 29(Suppl 4): iv166–iv191, doi: [10.1093/annonc/mdy152](https://doi.org/10.1093/annonc/mdy152), indexed in Pubmed: [30052758](https://pubmed.ncbi.nlm.nih.gov/30052758/).
5. Caraceni A, Hanks G, Kaasa S, et al. European Palliative Care Research Collaborative (EPCRC), European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012; 13(2): e58–e68, doi: [10.1016/S1470-2045\(12\)70040-2](https://doi.org/10.1016/S1470-2045(12)70040-2), indexed in Pubmed: [22300860](https://pubmed.ncbi.nlm.nih.gov/22300860/).
6. Yang J, Bauer BA, Wahner-Roedler DL, et al. The Modified WHO Analgesic Ladder: Is It Appropriate for Chronic Non-Cancer Pain? *J Pain Res*. 2020; 13: 411–417, doi: [10.2147/JPR.S244173](https://doi.org/10.2147/JPR.S244173), indexed in Pubmed: [32110089](https://pubmed.ncbi.nlm.nih.gov/32110089/).
7. Medical Care Standard “Mental and Behavioral Disorders Due to Opioid Use”. Order of the Ministry of Health of Ukraine 2555 dated 09.11.2020 [Internet]. <https://www.dec.gov.ua/mtd/psychichni-ta-povedinkovi-rozladny-syndrom-zalezhnosti-vnaslidok-vzhyvannya-opioyidyiv/>. (8 September 2021).
8. International Statistical Classification of Diseases and Related Health Problems 10th Revision [Internet]. <https://icd.who.int/browse10/2019/en>. (20 December 2021).
9. International Narcotics Control Board. Yellow List: List of Narcotic Drugs Under International Control [Internet]. <https://www.incb.org/incb/en/narcotic-drugs/Yellow-list/yellow-list.html>. (20 December 2021).
10. Nadeau S, Wu J, Lawhern R. Opioids and Chronic Pain: An Analytic Review of the Clinical Evidence. *Frontiers in Pain Research*. 2021(2): 1–15, doi: [10.3389/fpain.2021.721357](https://doi.org/10.3389/fpain.2021.721357).
11. Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015; 156(4): 569–576, doi: [10.1097/01.j.pain.0000460357.01998.f1](https://doi.org/10.1097/01.j.pain.0000460357.01998.f1), indexed in Pubmed: [25785523](https://pubmed.ncbi.nlm.nih.gov/25785523/).
12. State Register of Medicines of Ukraine [Internet]. <http://www.drz.com.ua>. (8 September 2021).
13. Resolution of the Cabinet of Ministers of Ukraine 333 from 25.03.2009 «On some issues of state regulation of prices for medicines and medicinal products» [Internet] [cited 2021 Sep 8]. Available from: <https://zakon.rada.gov.ua/laws/show/333-2009-%D0%B-F#n15>. (8 September 2021).
14. State Expert Center of the Ministry of Health of Ukraine. Archive of orders on approval of the State Drug Formulary of Ukraine [Internet]. <https://www.dec.gov.ua/materials/arhiv-nakaziv-pro-zatverdzhennya-derzhavnogo-formulyara-likarskih-zasobiv/?role=applicant>. (8 September 2021).
15. Order of the Ministry of Health of Ukraine dated 22.04.2021 792 “On approval of the 13th issue of the State Drug Formulary and ensuring its availability” [Internet]. <https://www.dec.gov.ua/materials/chinnij-vipusk-derzhavnogo-formulyara-likarskih-zasobiv/?role=applicant>. (8 September 2021).
16. The analytical report. The opioid consumption in Ukraine [Internet]. <http://budgetadvocacy.ua/wp-content/uploads/2018/12/opium-2011-2016-final.pdf>. (18 December 2021).
17. Order of the Ministry of Health of Ukraine dated 01.02.2013 77 «About the state registration (re-registration) of medicines and modification of registration materials» [Internet]. <https://zakon.rada.gov.ua/rada/show/v0077282-13#Text>. (8 September 2021).
18. World Standards for Cancer Pain Management. Health of Ukraine. Thematic issue Oncology, Hematology, Chemotherapy. 2021; 4 (71): 52–53. <https://health-ua.com/multimedia/6/7/2/0/3/1638534804.pdf>. (20 December 2021).
19. The WHO Model List of Essential Medicines. 22nd List (2021) [Internet]. <https://apps.who.int/iris/bitstream/handle/10665/345533/WHO-MHP-HPS-EML-2021.02-eng.pdf>. (20 December 2021).
20. IAHPC List of Essential Medicines for Palliative Care [Internet]. <https://hospicecare.com/what-we-do/projects/palliative-care-essentials/iahpc-essential-medicines-for-palliative-care/>. (20 December 2021).
21. State Service of Ukraine on Medicines and Drugs Control [Internet]. <https://www.dls.gov.ua/>. (3 January 2022).
22. Shunkina S, Hromovych B, Dorykevych K, et al. Access to opioid analgesics for palliative care patients in Ukraine: problems of past and present. *Palliative Medicine in Practice*. 2020; 13(4): 187–196, doi: [10.5603/pmpi.2019.0022](https://doi.org/10.5603/pmpi.2019.0022).
23. Knaul F, Farmer P, Krakauer E, et al. Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report. *The Lancet*. 2018; 391(10128): 1391–1454, doi: [10.1016/s0140-6736\(17\)32513-8](https://doi.org/10.1016/s0140-6736(17)32513-8).