

UDC 615.21:616.853-08-053.2](477+100)

DOI: 10.15587/2519-4852.2023.286425

## PHARMACEUTICAL PROVIDING OF THE TREATMENT OF CHILDREN WITH EPILEPSY IN UKRAINE AND ABROAD

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**The aim:** to investigate the pharmaceutical providing for the treatment of epilepsy in children in Ukraine and abroad and to conduct a marketing analysis of the domestic market of antiepileptic drugs.

**Materials and methods:** Ukrainian and foreign Internet sources, medical and technological documents on a specific research topic, the regulatory and legal base of Ukraine, materials of the State Formulary of Medicines, the State Register of Medicines of Ukraine were the objects of the study. The methods of marketing analysis, graphic, documentary and analytical generalization were used.

**Results:** a comparative analysis of clinical protocols (France, Great Britain and Ukraine) for the treatment of epilepsy in children showed that there are only 12 INNs out of 37 INNs in the country. The analysis of the formulary lists of drugs of Great Britain and Ukraine showed that the BNFC has 32 INNs, and the domestic – 10 INNs. As of October 2022, 287 names of antiepileptic drugs are registered in Ukraine, and 164 of them are allowed in children's practice. The main producers of antiepileptic drugs are India and Ukraine. Children's drugs forms are mainly represented by tablets and capsules – more than 90 %. A comparison of the lists of drugs for the treatment of epilepsy from the National List of Essential Medicines of Ukraine, BNFC, WHO Model List of Essential Medicines and WHO Model List of Essential Medicines for Children showed that out of 37 INNs, only 11 INNs are listed in all documents.

**Conclusions:** the results prove the need of improvement of pharmaceutical providing of epilepsy treatment in Ukraine. The nomenclature and variety of dosage forms for children's practice need to be expanded. In order to increase the economic availability of epilepsy treatment, it is advisable to update the National List of Essential Medicines of Ukraine and include new drugs in it, which will make it possible to purchase them at the expense of the State Budget of Ukraine

**Keywords:** epilepsy, antiepileptic drugs, pharmaceutical provision, clinical protocols, registration, economic availability, national pharmaceutical market, marketing analysis

### How to cite:

Sholoiko, N., Hala, L., Kosyachenko, K., Hubar, M. (2023). Pharmaceutical providing of the treatment of children with epilepsy in Ukraine and abroad. ScienceRise: Pharmaceutical Science, 4 (44), 28–38. doi: <http://doi.org/10.15587/2519-4852.2023.286425>

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### 1. Introduction

The World Health Organization (WHO) in its report “Epilepsy” dated June 20, 2019, recognizes epilepsy as one of the serious problems of the health care system. Almost 50 million people worldwide suffer from epilepsy – a chronic non-infectious brain disease that affects people of all age groups, it is one of the most common global neurological diseases – and creates a major social problem for the health care system [1].

According to WHO estimates, up to 70 % of people suffering from epilepsy could live without seizures if properly diagnosed and treated [1].

The greatest and most severe risks of developing epilepsy are observed in the case of its occurrence in childhood, and under the influence of the same factors, the risk of developing epilepsy in children is higher than in adults. Treatment of such children places a heavy burden (financial and moral) on the family and the national health care system.

The incidence of epilepsy depends on age. The highest incidence rate (from 100 to 233 per 100,000) is observed in children under 1 year of age with a peak in the

first week of life. Later in early childhood, this rate drops to about 60 per 100,000; in adolescents and adults, the incidence rate is 30–40 per 100,000, and in the elderly after the age of 65, it increases again to 100–170 per 100,000 [2].

Almost 80 % of people with epilepsy live in low- and middle-income countries [1].

In Ukraine at the beginning of 2018, 52,482 patients with epilepsy were registered (0.12 % of the total population), which corresponds to an incidence rate of 123.7 per 100,000 people [3].

The incidence of epilepsy in children in Ukraine ranges from 4.7 to 5.9 per 10 thousand, prevalence – 33.0 to 37.8 per 10 thousand. 4.4–5.0 per 10 thousand children have disabilities. The highest frequency of convulsions and attacks in children is observed at the age of 15 [4].

The economic consequences of epilepsy can vary depending on the duration and severity of the disease, the response to treatment, and the conditions for providing medical care. Economic studies in India have shown that state financing of first- and second-line drugs reduces the financial burden on families of epilepsy patients and is a cost-effective measure [5].

There are a large number of international professional organizations and international bureaus, national committees, foundations and public associations, government departments and institutions working on education, prevention, diagnosis, treatment, rehabilitation and control of epilepsy patients. In particular, the European Academy of Neurology, which has united more than 45 thousand participants since 2014 [6]; The American Neurological Association is the main professional society of academic neurologists and neurobiologists since 1875 in the United States of America [7]; British Pediatric Neurology Association is a charitable professional organization of doctors specializing in the care of children with neurological disorders [8]; The Epilepsy Foundation is a charity that has been promoting awareness and understanding of people with epilepsy for over 50 years, advocating for laws that matter to people with epilepsy, and funding epilepsy research [9]; The French Epilepsy Association (Association Epilepsie-France) is a voluntary national association, according to the law of 1901, recognized as a public benefit and has a national authorization to represent users in hospitals and health care bodies [10].

They are all united in the “International League Against Epilepsy”, which positions itself as a global association of medical professionals and scientists working to create a world where epilepsy does not limit the life of any person [11].

**The aim:** to investigate the pharmaceutical providing for the treatment of epilepsy in children in Ukraine and abroad and to conduct a marketing analysis of the Ukrainian market of antiepileptic drugs.

## 2. Planning (methodology) of the research

To achieve the goal of the study, the following research stages were planned:

I – to compare the lists of drugs recommended for the treatment of epilepsy in children, according to selected foreign clinical recommendations (France, Great Britain) with Ukrainian protocols and data of the State Formulary of Medicines by groups of drugs, codes of anatomic-therapeutic (ATC) classification and international non-proprietary name (INN).

II – to analyze the nomenclature of registered medicines for the treatment of epilepsy by INN and trade name using information from the State Register of Medicines of Ukraine.

III – distinguish Ukrainian and foreign manufacturers of antiepileptic drugs that are allowed in medical practice in Ukraine.

IV – to calculate the share of children’s antiepileptic drugs from the total number of registered antiepileptic drugs in Ukraine and to investigate the breadth of the assortment of antiepileptic drugs and dosage forms approved for use in children.

V – to compare the list of drugs for the treatment of epilepsy with the National List of Essential Medicines of Ukraine, the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children in order to assess the economic availability of drugs for the treatment of epilepsy.

## 3. Materials and methods

The object of the study was Ukrainian and foreign professional literary and the Internet sources on the topic of the study, the regulatory and legal framework of Ukraine that regulates the availability of drugs for the population, materials of the State Formulary of Medicines, statistical data of the Ministry of Health (MOH) of Ukraine, the State Register of Medicines of Ukraine.

Research methods:

– documentary and analytical – for research and analysis of clinical Ukrainian and foreign guidelines for the treatment of epilepsy, the State Register of Medicines of Ukraine;

– marketing analysis – to analyze the national pharmaceutical market and to determine the economic availability of drugs for the treatment of epilepsy in pediatric practice;

– graphical – for analyzing the depth and breadth of the assortment of antiepileptic drugs;

– generalization – for formulating conclusions, explanations and discussions.

## 4. Research results

For a comparative analysis of the lists of drugs recommended for the treatment of epilepsy in children, the clinical recommendations (CR) of the French National Authority for Health (Haute Autorité de Santé – HAS) were determined: “Treatment of children and adults with epilepsy” (Recommandation Épilepsies : Priz en charge des enfants et des adultes) (CR France), approved by the French Higher Council of Public Health and updated in October 2020 [12], and the guideline of the National Institute for Health and Care Excellence of Great Britain (NICE) “Epilepsies in children, young people and adults”, updated in April 2022 [13]. This document is structured in such a way that when choosing a drug, there is a reference to the British National Formulary for Children (BNFC), therefore, for comparison, we also included information from the BNFC [14]. BNFC and CR of France are used to create national clinical guidelines of many countries of the world and contain the most complete and up-to-date lists of drugs for the treatment of epilepsy.

The following Ukrainian medical and technological documents were also selected:

1. «Unified clinical protocol of primary, emergency, secondary (specialized) and tertiary (highly specialized) medical care «Epilepsy in children», approved by the order of the Ministry of Health of Ukraine dated 04/17/2014 No. 276 [15].

2. The 14<sup>th</sup> edition of the State Formulary of Medicines (SFM), approved by the order of the Ministry of Health of Ukraine No. 1011 dated 13.06.2022 [16].

The comparison was made by drug groups, ATC codes and INN. The results of the comparison are shown in Table 1.

The greatest variety of drugs for the treatment of epilepsy is shown by the BNFC and the NICE guideline (32 and 31 names, respectively). The State Formulary of Medicines includes 10 INNs, and the domestic clinical protocol – only 12 names. French clinical guidelines provide for the use of 27 INNs.

Table 1

Comparison of the lists of antiepileptic drugs of the clinical protocol of Ukraine and the clinical recommendations of France, the guidelines of Great Britain (NICE), the State Formulary of Medicines of Ukraine and the British National Formulary

ATC code	Availability (+/-)					
	INN	CP of Ukraine	CR of France	NICE guideline	SFM	BNFC
H02AB – Glucocorticoids						
H02AB06	Prednisolone	–	–	+	–	+
N01AF – Barbiturates, plain						
N01AF03	Thiopental sodium	+	–	–	–	+
N03AA – Barbiturates and derivatives						
N03AA02	Phenobarbital	+	+	+	+	+
N03AA03	Primidone	–	+	+	–	+
N03AB – Hydantoin derivatives						
N03AB02	Phenytoin	+	+	+	+	+
N03AB05	Fosphenytoin	–	–	–	–	+
N03AD – Succinimide derivatives						
N03AD01	Ethosuximide	–	+	+	–	+
N03AE – Benzodiazepine derivatives						
N03AE01	Clonazepam	+	+	+	+	+
N03AF – Carboxamide derivatives						
N03AF01	Carbamazepine	+	+	+	+	+
N03AF02	Oxcarbazepine	+	+	+	–	+
N03AF03	Rufinamide	–	+	+	–	+
N03AF04	Eslicarbazepine acetate	–	+	+	–	+
N03AG – Fatty acid derivatives						
N03AG01	Valproate acid	+	+	+	+	+
N03AG04	Vigabatrin	–	+	+	–	+
N03AG06	Tiagabine	–	+	+	–	+
N03AX – Other antiepileptics						
N03AX03	Sulthiame	–	–	+	–	–
N03AX09	Lamotrigine	+	+	+	+	+
N03AX10	Felbamate	–	+	+	–	+
N03AX11	Topiramate	+	+	+	+	+
N03AX12	Gabapentine	+	+	+	+	+
N03AX14	Levetiracetam	+	+	+	–	+
N03AX15	Zonisamide	–	+	+	–	+
N03AX16	Pregabalin	+	+	+	+	+
N03AX17	Stiripentol	–	+	+	–	+
N03AX18	Lacosamide	–	+	+	–	+
N03AX22	Perampanel	–	+	+	–	+
N03AX23	Brivaracetam	–	+	+	–	+
N03AX24	Cannabidiol	–	+	+	–	+
N03AX25	Cenobamate	–	–	+	–	–
N03AX91	Potassium bromide	–	–	+	–	–
N05BA – Benzodiazepine derivatives						
N05BA01	Diazepam	–	+	–	+	+
N05BA06	Lorazepam	–	–	–	–	+
N05BA09	Clobazam	–	+	+	–	+
N05CC – Aldehydes and derivatives						
N05CC05	Paraldehyde	–	–	–	–	+
N05CD – Benzodiazepine derivatives						
N05CD02	Nitrazepam	–	–	+	–	–
N05CD08	Midazolam	–	+	–	–	+
N06BX – Other psychostimulants and nootropics						
N06BX03	Piracetam	–	–	+	–	–

The examined Ukrainian medical and technological documents do not include such INNs as prednisolone,

primidone, fosphenytoin, ethosuximide, rufinamide, eslicarbazepine acetate, vigabatrin, tiagabine, sultiame,

felbamate, zonisamide, stiripentol, lacosamide, perampanel, brivaracetam, cannabidiol, cenobamate, potassium bromide, lorazepam, clobazam, paraldehyde, nitrazepam, midazolam.

In the clinical recommendations of the French National Authority for Health: “Treatment of children and adults with epilepsy” [12] and the United Epilepsy Council of Great Britain and Ireland, which regulates the inclusion of drugs in the BNFC, separately prescribed recommendations for the use of the British company GW Pharmaceuticals Epidiolex based on highly purified cannabidiol in the form of a solution for oral use.

The effectiveness of this drug was proven as a result of four randomized, double-blind, placebo-controlled clinical trials involving more than 700 patients with Lennox-Gastaut and Dravet syndrome aged 2 to 55 years. During research, it was established that the combination of this drug together with other antiepileptic drugs contributes to a significant reduction in the frequency of seizures (atonic, tonic, tonic-clonic) in infants and was maintained from the beginning of treatment during the 14–16-week course of therapy. In 2019, the drug Epidiolex was registered by the EMA under a centralized procedure, and therefore allowed in all countries of the European Union [17].

The National Institute for Health and Care Excellence (NICE) of Great Britain recommended to include cannabinoid-based drugs Epidiolex and Sativex in the list of drugs for reimbursement of treatment costs by the National Health Service (NHS) [18]. The introduction of cannabis-based drugs into the national medical neurological practice requires changes to a number of regulatory acts related to the circulation of controlled substances on the territory of Ukraine, as pointed out by Ukrainian researchers [19–21].

In 2016, the Ministry of Health of Ukraine, by its order No. 1422 dated 29.12.2016, which entered into force on 28 April 2017 [22], allowed the use of international clinical guidelines adapted in Ukraine by national professional medical associations and associations of member states of the European Union (membership is determined as of 01 January 2017), the United States of America, Canada and the Australian Union. Guided by this Order, Ukrainian doctors have the right to use the best global recommendations, those supported and recommended by the International League against Epilepsy. But, as the analysis showed, the Ukrainian pharmaceutical market lacks a significant number of modern drugs for the treatment of epilepsy in children, which makes it impossible to use international clinical protocols completely.

*Availability for use in medical practice (registration in Ukraine).*

The pharmaceutical market of Ukraine is a very saturated consumer product market. Today, Ukraine has registered about 17,000 domestic and foreign production medicines.

The marketing analysis of the pharmaceutical market of drugs for the treatment of epilepsy in children (Table 2) was carried out using the database of registered drugs posted on the website of the “State Register of Medicines of Ukraine” (Resolution of the Cabinet of Ministers of Ukraine No. 411 of 31.03.2004) [23] as of October 2022. The State Register of Medicines of Ukraine contains information about drugs approved for medical use in Ukraine [24]. According to the data of the State Register of Medicines of Ukraine, 287 trade names (TN) of drugs for the treatment of epilepsy in various dosage forms and doses were registered on the Ukrainian market according to the ATC classification (13 groups).

Table 2  
Analysis of the nomenclature of drugs registered in Ukraine for the treatment of epilepsy by INN and trade name

ATC group	INN number	TN number	Allowed for children
H02AB – glucocorticoids	1	3	3
N01AF – barbiturates	1	2	2
N03AA – barbiturates and their derivatives	1	5	3
N03AB – hydantoin derivatives	0	0	0
N03AD – succinimide derivatives	0	0	0
N03AE – benzodiazepine derivatives	1	3	3
N03AF – carboxamide derivatives	3	29	29
N03AG – fatty acids derivatives	1	13	13
N03AX – other antiepileptics	7	200	100
N05BA – benzodiazepine derivatives	2	10	8
N05CC – aldehydes and derivatives	0	0	0
N05CD – benzodiazepine derivatives	1	3	3
N06BX – other anxiolytics	1	19	0
Total	19	287	164

The analysis of the main manufacturers of drugs listed in the State Register of Medicines of Ukraine showed that most INNs are produced by foreign manufacturers (Table 3). However, drugs containing prednisolone, sodium thiopental, phenobarbital, clonazepam and lorazepam are only of Ukrainian production.

Ten groups of drugs for the treatment of epilepsy, available on the Ukrainian pharmaceutical market, are represented by foreign and domestic manufacturers (Fig. 1). The main foreign suppliers are pharmaceutical companies from India – 87 trade names, Slovenia and Poland – each with 16 TN (Fig. 1).

In order to determine the drugs allowed for use in children’s practice, an analysis of the actual instructions for the use of drugs from the registration materials posted in the State Register of Medicines of Ukraine was carried out, which showed that more than half of the entire list of registered drugs are allowed for use in children – 164 names of drugs from 287 (Fig. 2).

In terms of the number of trade names, the range of drugs with different INNs is heterogeneous (Fig. 3). Pregabalin group has the widest assortment (94 trade names), sodium thiopental has the smallest assortment – 2 names.

The treatment of any disease will be successful if the patient is ready (compliant, committed) to follow the treatment regimen, the conditions for the rational use of prescribed drugs. To achieve compliance in children, it is important that dosage forms are comfortable to use. The children’s nomenclature of drugs has its own peculiarities because a baby cannot take a pill, children are afraid of injections, they are put off by the unpleasant smell and taste. Therefore, if possible, doctors and parents prefer drugs in the form of syrups, granules, sprays, and chewable tablets. For this reason, it is imperative that children’s dosage forms for the treatment of epilepsy are available on the pharmaceutical market.

Children’s dosage forms of antiepileptic drugs must meet the following requirements:

- easy to dose and adjust. This is especially relevant when the drug requires slow titration from the initial dose to the therapeutic dose (carbamazepine, lamotrigine, topiramate), and it is necessary to increase it gradually (in mg), compared to adult patients;

- have a pleasant taste;
- easy to swallow;
- be convenient to use (ideally, children’s dosage form (DF) should provide for 1–2 doses per day);
- be bioequivalent to an adult drug.

Today, in medical practice, the following pharmaceutical forms of antiepileptic drugs are used for children or acceptable for use by children:

- syrups, suspensions;
- oral solutions, drops;
- tablets (chewable and soluble) with a small amount of active substance, compared to adult DF;
- divided tablets (tablets with a notch for division);
- special dosage forms for taking with food (granules).

Table 3  
Analysis of drug manufacturers allowed in medical practice in Ukraine

INN	TN amount	Ukrainian manufacturers	Foreign manufacturers
Prednisolone	3	3	0
Sodium thiopental	2	2	0
Phenobarbital	5	5	0
Clonazepam	3	3	0
Carbamazepine	22	9	13
Oxcarbazepine	4	0	4
Eslicarbazepine acetate	3	0	3
Valproic acid	13	3	10
Lamotrigine	33	6	27
Topiramate	12	5	7
Gabapentin	14	5	9
Levetiracetam	38	3	35
Zonisamide	3	0	3
Pregabalin	94	22	72
Lacosamide	6	0	6
Diazepam	7	5	2
Lorazepam	3	3	0
Midazolam	3	0	3
Piracetam	19	12	7
Total	287	86	201

In the opinion of foreign and domestic researchers, drugs in the form of granules are the most promising, because according to their pharmacokinetic parameters, they are close to adult drugs [25–27].

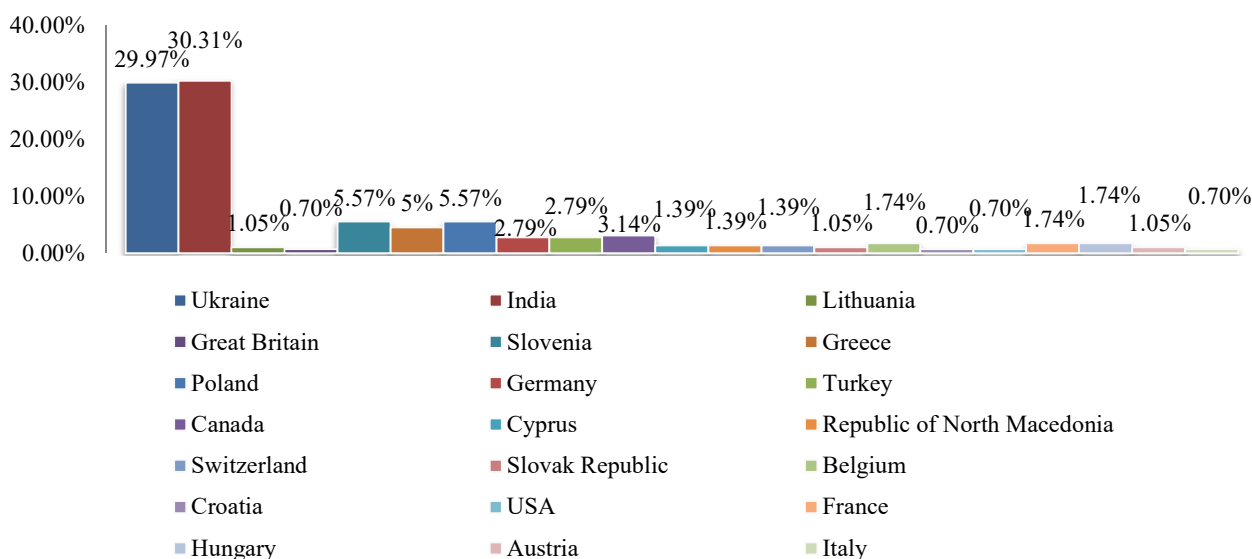


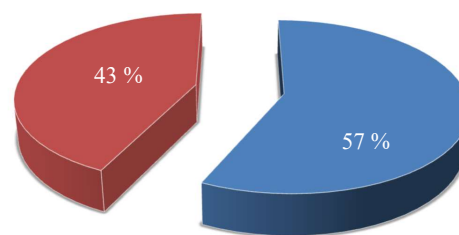
Fig. 1. Supplier countries of antiepileptic drugs to Ukraine (according to the State Register of Drugs of Ukraine)



The analysis of dosage forms of drugs allowed in children’s practice showed that most drugs for the treatment of epilepsy in the Ukrainian market are presented in the form of tablets and capsules (Fig. 4).

Tableted dosage forms make up almost 52 % of the entire assortment, and capsules – almost 40 %. There is also a small amount of solutions for injections – 5.23 %, oral solutions – 1.74 %, syrups and lyophilisates for solutions for injections – 0.7 % each, oral suspensions and concentrates for solutions for infusions – 0.35 % each.

Such a low number of DF for children’s age indicates an opportunity for manufacturers to expand the range of drugs at the expense of children’s dosage forms.



■ Antiepileptic drugs approved for use in children  
 ■ Antiepileptic drugs not approved for use in children

Fig. 2. The share of children’s antiepileptic drugs from the total number of registered antiepileptic drugs

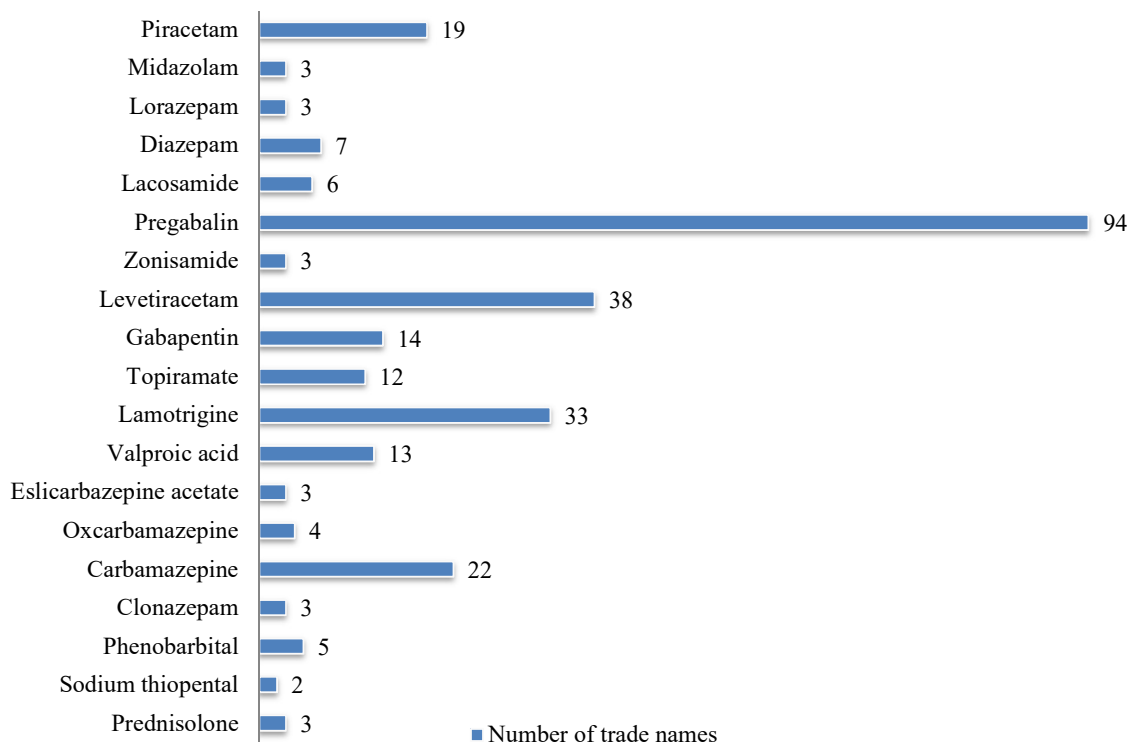


Fig. 3. Analysis of the assortment of antiepileptic drugs

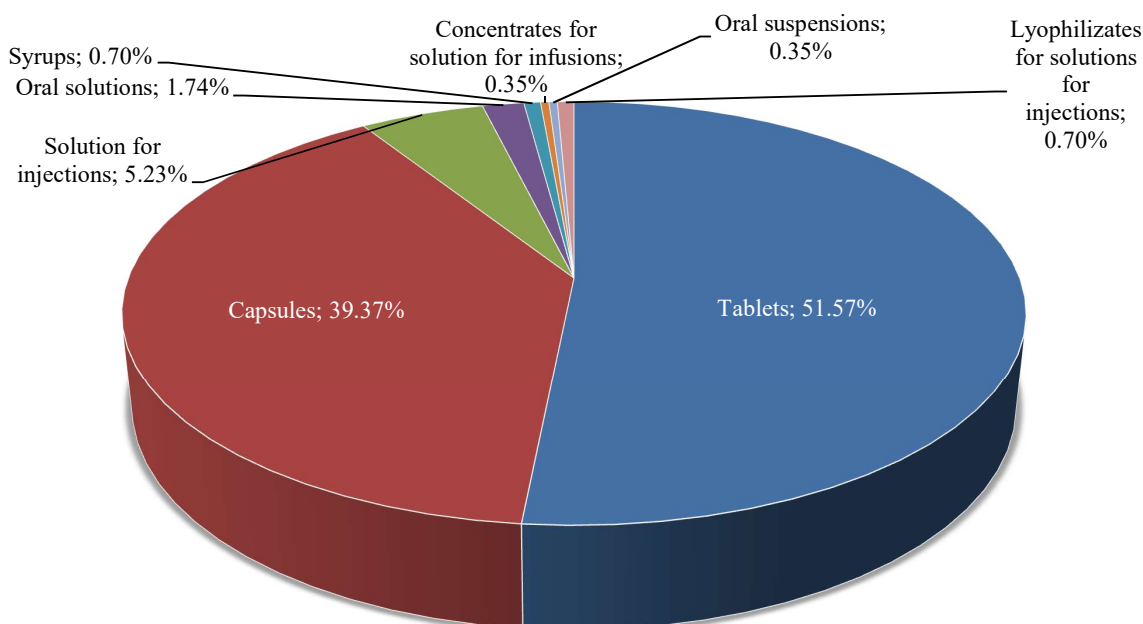


Fig. 4. Analysis of dosage forms approved for use in children

*Economic availability of medicines.*

Treatment of epilepsy is a great financial and moral burden for the family. In the case when a child is sick, one of the family members is forced to leave work and take care of the sick child. As a rule, the income of such families is quite limited, and therefore it is difficult to overestimate the importance of implementing state programs to provide epilepsy patients with the necessary drugs. Some authors indicate that about 500 million relatives and colleagues of the patient in one way or another participate in solving problems related to epilepsy [28].

According to the estimates of domestic authors, state costs for the treatment of epilepsy patients are estimated at 1.1 % of the total costs for health care, and this figure directly depends on the level of the disease in a certain country [29].

Employees of the State University “Institute of Neurology, Psychiatry and Narcology of the National Academy of Sciences of Ukraine” (Kharkiv) under the leadership of Professor A. E. Dubenko. determined the cost of illness (COI), which includes direct and indirect costs of epilepsy treatment, considering the human capital index and other indicators. Based on the analysis, it was established that the total cost of the disease is more than UAH 100,000 per patient. The largest share of costs falls on indirect costs – 75 % [30]. Therefore, the indicator of the economic availability of drugs is very important, if the state fully or partially reimburses the cost of drugs. For this purpose, we analyzed the Model List of Essential Medicines [31] recommended by the WHO, for national health care systems to perform their functions, which was first approved in 1977 [32].

In Ukraine, the free and subsidized dispensing of drugs is regulated by a number of laws of Ukraine, in particular the Law of Ukraine “On Medicines” [33], the Law of Ukraine “Basics of the Legislation of Ukraine on Health Care” [34] and a number of by-laws at the level of Resolutions of the Cabinet of Ministers of Ukraine and Orders of the Ministry of Health of Ukraine.

Since 2017, the nationwide program “Dostupni Liki” (“Affordable Medicines”) [35] has been launched in Ukraine, which allows to significantly improve the medical care of certain categories of patients by reimbursing the full or partial cost of drugs in the presence of an electronic prescription (and with the introduction of martial law in Ukraine, a paper one). At first, it included only 3 diseases, and since October 2021, it has spread to epilepsy. As of now, this program covers the treatment of diseases that are well treated on an outpatient basis, but often lead to disability and death of patients, including cardiovascular diseases, bronchial asthma, type 1 and type 2 diabetes, mental and behavioral disorders, epilepsy, Parkinson’s disease, COPD, the need for immunosuppression [36].

We also included a separate WHO list for children up to 12 years of age in the analysis. Currently, the 8<sup>th</sup> list of WHO essential medicines for children– Model List of Essential Medicines for Children (MLEMC), updated in September 2021 [37] is relevant.

Our comparative analysis of the National List of Essential Medicines of Ukraine and the latest edition of the WHO Model List of Essential Medicines showed that the Ukrainian list contains a wider range of antiepileptic drugs according to INN ATC-classification (Table 4).

Table 4

Comparison of the list of drugs for the treatment of epilepsy from the National List of Essential Medicines of Ukraine, the British National Formulary for Children, the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children

ATC code	INN	National List of Medicines of Ukraine	BNFC	WHO Model List	WHO Model List for Children
1	2	3	4	5	6
H02AB – Glucocorticoids					
H02AB06	Prednisolone	+	+	+	+
N01AF – Barbiturates, plain					
N01AF03	Thiopental sodium	+	+	+	+
N03AA – Barbiturates and derivatives					
N03AA02	Phenobarbital	+	+	+	+
N03AA03	Primidone	–	+	–	–
N03AB – Hydantoin derivatives					
N03AB02	Phenytoin	+	+	+	+
N03AB05	Fosphenytoin	–	–	–	–
N03AD – Succinimide derivatives					
N03AD01	Ethosuximide	+	+	+	+
N03AE – Benzodiazepine derivatives					
N03AE01	Clonazepam	+	+	–	–
N03AF – Carboxamide derivatives					
N03AF01	Carbamazepine	+	+	+	+
N03AF02	Oxcarbazepine	–	+	–	–
N03AF03	Rufinamide	–	+	–	–
N03AF04	Eslicarbazepine acetate	–	+	–	–

Continuation of Table 4

1	2	3	4	5	6
N03AG – Fatty acid derivatives					
N03AG01	Valproate acid	+	+	+	+
N03AG04	Vigabatrin	–	+	–	–
N03AG06	Tiagabine	–	+	–	–
N03AX – Other antiepileptics					
N03AX03	Sulthiame	–	–	–	–
N03AX09	Lamotrigine	+	+	+	+
N03AX10	Felbamate	+	+	–	–
N03AX11	Topiramate	+	+	–	–
N03AX12	Gabapentine	–	+	–	–
N03AX14	Levetiracetam	–	+	–	–
N03AX15	Zonisamide	–	+	–	–
N03AX16	Pregabalin	+	+	–	–
N03AX17	Stiripentol	–	+	–	–
N03AX18	Lacosamide	–	+	–	–
N03AX22	Perampanel	–	+	–	–
N03AX23	Brivaracetam	–	+	–	–
N03AX24	Cannabidiol	–	+	–	–
N03AX25	Cenobamate	–	–	–	–
N03AX91	Potassium bromide	–	–	–	–
N05BA – Benzodiazepine derivatives					
N05BA01	Diazepam	+	+	+	+
N05BA06	Lorazepam	+	+	+	+
N05BA09	Clobazam	–	+	–	–
N05CC – Aldehydes and derivatives					
N05CC05	Paraldehyde	–	–	–	–
N05CD – Benzodiazepine derivatives					
N05CD02	Nitrazepam	–	–	–	–
N05CD08	Midazolam	+	+	+	+
N06BX – Other psychostimulants and nootropics					
N06BX03	Piracetam	–	–	–	–
Additional solutions for intravenous administration					
B05XA – Electrolyte solutions					
B05XA05	Magnesium sulfate	+	+	+	–

Comparing the British National Formulary for Children, international lists of the WHO and the National List of Essential Medicines of Ukraine, we make a conclusion that the following drugs (11) are prescribed by all the studied documents: prednisolone, sodium thiopental, phenobarbital, phenytoin, ethosuximide, carbamazepine, valproic acid, lamotrigine, diazepam, lorazepam, midazolam. Magnesium sulfate is included in all lists, except for the WHO list for children up to 12 years of age.

A greater number of INNs (15) were included exclusively in the BNFC (they are not listed in the National List of Essential Medicines of Ukraine and WHO lists): primidone, oxcarbazepine, rufinamide, eslicarbazepine acetate, vigabatrin, tiagabine, gabapentin, levetiracetam, zonisamide, stiripentol, lacosamide, perampanel, brivaracetam, cannabidiol, clobazam.

Clonazepam, felbamate, topiramate, pregabalin are included only in the BNFC and the National List of Essential Medicines.

The use of fosphenytoin, sulthiam, cenobamate, potassium bromide, paraldehyde, nitrazepam, and piracetam is not provided for in any of the studied documents.

It is known that drugs that are included in the National List of Essential Medicines of Ukraine and the program of medical guarantees [38] are subjects for payment from the State Budget of Ukraine, and domestic health care institutions are allowed to purchase drugs that are not included in the National list with budget funds only in the case of full provision of a medical facility from the National List. Thus, if the doctor prescribes drugs that are not included in the List, patients or their guardians are forced to buy these drugs at their own expense (Table 3). Therefore, the availability of medical equipment for socially vulnerable groups of the population of Ukraine is limited to 16 INN according to the ATC classification.

### 5. Discussion of research results

Many researchers in Ukraine are studying the problems of pharmaceutical care for patients with various socially significant diseases, in particular, hypertension [39], dementia [40], bronchial asthma [41], and diabetes [42].

A comparative analysis of treatment protocols (France, Great Britain and Ukraine) for epilepsy in children showed that according to the INN and ATC



classification of 37 drugs used in the world for the treatment of epilepsy, less than half (12 names) are allowed in Ukraine, and some groups of drugs are not even provided for by national medical and technological documents. Considering the results of researchers in 2015 [43], we can say that in 7 years the number of INNs registered in Ukraine has decreased by 2 positions (from 14 to 12).

Analysis of the current formulary list of drugs of Great Britain and the 14<sup>th</sup> edition of the State Formulary of Medicines of Ukraine showed that the British formulary has 32 INNs of drugs, and the Ukrainian – 10 INNs. The missing drugs are mostly new drugs and unregistered in Ukraine. Foreign treatment protocols include drugs based on highly purified cannabis, which are reimbursed (Great Britain), and are allowed for use in the European Union, but the Ukrainian legal framework does not allow the use of these drugs, which indicates the need to make changes to the legislative framework.

As of October 2022, 287 names of Ukrainian and foreign drugs are registered in Ukraine, of which only 164 names of drugs are allowed in children's practice.

The main producers of antiepileptic drugs are India and Ukraine. Children's drugs are mainly represented by tablets and capsules – more than 90 %, and the remaining 10 % are solutions for injections, oral solutions, syrups and lyophilisates for solutions for injections, oral suspensions and concentrates for solutions for infusions. This trend indicates the possibility of expanding the range of medicines at the expense of drugs are allowed in children's practice.

Tableted dosage forms make up almost 52 % of the entire assortment, and capsules – almost 40 %. There is also a small amount of other dosage forms in much smaller amounts.

A comparison of the list of drugs for the treatment of epilepsy from the National List of Essential Medicines of Ukraine, the British National Formulary for Children, the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children to determine the economic availability of drugs showed that out of 38 INNs, only 11 INNs are provided by all the studied documents. A significantly larger number (15) of INNs were included exclusively in the BNFC (they are not listed in the National and WHO lists). Clonazepam, felbamate, topiramate, pregabalin are included only in the BNFC and the National List of Essential Medicines of Ukraine. The use of fosphenytoin, sulthiam, cenobamate, potassium bromide, paraldehyde, nitrazepam, and piracetam is not provided for in any of the studied documents.

**Study limitations.** The study used specific data from clinical treatment protocols in France, Great Britain and Ukraine. Of course, these documents are used to create national clinical guidelines of many countries of the

world and contain an exhaustive list of drugs for the treatment of epilepsy, but this does not allow to comprehensively characterize the current trends in the treatment of epilepsy abroad (in the USA, Eastern countries and Australia).

**Prospects for further research.** Considering the expansion of the National List of Essential Medicines of Ukraine and the introduction of the health technology assessment system, the study of clinical protocols and formularies of other countries, the price policy of antiepileptic drugs on the Ukrainian market and abroad, the assessment of pharmacoeconomic impact are promising and relevant.

## 6. Conclusions

The results of a comprehensive study indicate the need to improve pharmaceutical support for the treatment of epilepsy in Ukraine, compared to foreign practice. When according to the INN and ATC classification, the NICE clinical protocol provides for the use of 31 drugs, the CR of France – 27 drugs, Ukrainian has less than half (12 names), and some groups of drugs are not even indicated. Foreign treatment protocols include drugs based on highly purified cannabis, which are reimbursed (Great Britain), and are allowed for use in the European Union, but the Ukrainian legal framework does not allow the use of these drugs, which indicates the need to make changes to the legislative framework of Ukraine.

The nomenclature and variety of dosage forms for children's practice need to be expanded, which will ensure a higher patient's adherence to treatment and increase the effectiveness of pharmacotherapy.

In order to increase the economic availability of antiepileptic drugs, it is advisable to update the National List of Essential Medicines of Ukraine and include new drugs in it, which will make it possible to purchase them at the expense of the State Budget of Ukraine.

## Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

## Funding

The study was performed without financial support.

## Data availability

The manuscript has no associated data.

## Acknowledgements

We express our gratitude to the Bogomolets National Medical University for assistance and help in conducting this research.

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*Received date 21.11.2022*

*Accepted date 22.08.2023*

*Published date 31.08.2023*

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