

## CLINICAL AND ECONOMIC ASSESSMENT OF ANTI-EPILEPTIC AGENTS IN A FORMULAR SYSTEM

<sup>1</sup>Borysenko N. M., <sup>2\*</sup>Bushueva I. V., <sup>1</sup>Hubenko I. Ya., <sup>2</sup>Parchenko V. V.

<sup>1</sup>Cherkasy Medical Academy.

<sup>2</sup>Zaporizhzhia State Medical and Pharmaceutical University.

Article Received: 07 July 2025

Article Review: 29 July 2025

Article Accepted: 20 August 2025

**\*Corresponding Author: Bushueva I. V.**

Professor, Doctor of Pharmaceutical Sciences, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine.

**How to cite this Article:** Borysenko N. M., Bushueva I. V., Hubenko I. Ya., Parchenko V. V. (2025). CLINICAL AND ECONOMIC ASSESSMENT OF ANTI-EPILEPTIC AGENTS IN A FORMULAR SYSTEM. World Journal of Pharmacy and Medical Science, 1(3): 45-50.



Copyright © 2025 Bushueva I. V. | World Journal of Pharmacy and Medical Science

This is an open-access article distributed under creative Commons Attribution-NonCommercial 4.0 International license (CC BY-NC 4.0)

### ABSTRACT

The article analyzes modern approaches to clinical and economic evaluation of anti-epileptic drugs within the formulary system. Epilepsy creates a significant socio-economic load that requires rational use of resources. The study substantiates the integration of the principles of pharmacoeconomics and evidence-based medicine to optimize therapy. Formation of lists of basic medicines, in particular the state form of Ukraine is a key mechanism for ensuring the availability and rational use of anti-epileptic drugs. Modern treatment strategies evolve towards a personalized approach, preferring monotherapy with the drugs of the second and third generations. Pharmacoeconomic analysis confirms that generic anti-epileptic drugs reduce costs by 40–50%. Investments in new, expensive treatments can be economically advantageous in the long run by reducing hospitalization and disability costs. Correlation analysis showed that there is a very strong positive relationship between the costs of epilepsy treatment and the country's economic indicators.

**KEYWORDS:** epilepsy, pharmacoeconomics, formulary system, anti-epileptic drugs, clinical and economic assessment, evidence-based medicine, reimbursement.

### INTRODUCTION

Epilepsy is one of the most common chronic neurological diseases, which creates a significant socio-economic burden on health care systems around the world. This burden is caused not only by clinical consequences, such as frequent attacks and concomitant diseases, but also by the financial costs of diagnosis, treatment and rehabilitation. In response to these challenges, the formation of lists of basic drugs, or the formulary system, becomes key value as a mechanism for providing rational use of resources and increasing the availability of effective treatment.

Approximately half of adults with active epilepsy have one or more accompanying physical or mental states that adversely affect performance and lead to social problems. These comorbid states worsen quality of life, improve the need for medical care, reduce the effectiveness of treatment and increase the risk of death.

Mental disorders are most common depression (25%) and anxiety (40%). Suicide attempts are recorded in approximately 15% of patients. In addition, people with epilepsy have almost three times a higher risk of death compared to the general population. The main causes of death, directly related to epilepsy, are sudden unexpected death, epileptic status and unintentional injuries.

Studies have been conducted with a comprehensive analysis of modern approaches to clinical and economic assessment of anti-epileptic drugs (AED) in the conditions of the formulary system, taking into account the latest data and recommendations of 2023–2025. It reveals the socio-economic aspects of epilepsy, studies the current principles of formation of drug forms, and evaluates the economic efficiency of AED in view of their clinical feasibility.

The purpose of the study is to substantiate the need to integrate modern principles of pharmacoeconomics and evidence –based medicine to optimize epilepsy therapy and reduce its social and financial burden on society.

## MATERIALS AND METHODS

The study is based on the analysis of clinical trials, systematic examinations with meta–analysis (Bresnahan, 2024; Zhuo, 2023–2024); randomized controlled studies; international and national recommendations (nice, american academy of neurology, belgian recommendations, ukrainian unified clinical protocols). A correlation analysis was conducted to investigate the relationship between the costs of epilepsy treatment and the country's economic indicators (pearson correlation coefficient). Generalization methods and descriptive methods were also used.

## RESULTS

In today's conditions of development of health care system in Ukraine and the world of formation of lists of basic medicines, it is a key mechanism for ensuring the rational use of resources, increasing the availability of treatment and cost optimization. This is especially true of anti –epileptic drugs (AEDs) that require a balance between clinical efficiency, safety and economic feasibility. This section is devoted to the analysis of modern principles of formulars, strategies for the treatment of epilepsy and evaluation of AED economic efficiency, taking into account updates in 2023–2025.

### *Modern principles of formation of lists of basic drugs for the treatment of epilepsy*

The formation of forms of basic drugs is a systemic process based on the principles of evidence –based medicine, pharmacoeconomics and clinical recommendations. In 2024, the Ministry of Health of Ukraine approved the sixteenth issue of the state form of medicinal products by order No. 418 of March 12<sup>[5]</sup>, which includes recommendations on the rational purpose of AED. This document emphasizes the criteria for the inclusion of drugs, such as efficacy, safety profile, cost and accessibility, taking into account national needs, in particular in martial law.

According to the updates, first–line key POPs such as carbamazepine, sodium valproate, lamotrigine and levetiracetam, with priority of generic shapes to reduce costs are included in the form. In 2025, further expansion of the list by integration of new data from clinical studies, including drugs for resistant epilepsy forms, was expected. This meets the recommendations of the World Health Organization (WHO)<sup>[1]</sup>, which in the updated list of major drugs in 2023 emphasized the need to include AED in national forms for low and medium income countries, with a focus on economic accessibility.

In 2024, the International Anti–Epileptic League (ILAE)<sup>[2]</sup> published recommendations on the terminology of medication to control attacks, which affects the

standardization of formers. The British National Form (March–September 2024) emphasizes the priority of drugs with minimal side effects, such as lamotrigine for focal attacks and valproate for generalized. In Ukraine, the process is governed by the Ministry of Health of 22.07.2009 №529 (with updates 2023–2024)<sup>[5]</sup>, which requires the assessment of medical technologies (AMT) before inclusion, including analysis of clinical trials and pharmacoeconomic data.

In the context of the war in Ukraine, the formulated system is adapted to ensure the defense forces, as stated in the Defense Defense Order No. 506 of July 24, 2024<sup>[4]</sup>, where AED is included in the lists for assistance. This includes quality monitoring, as in the lists of prohibited medicines due to inconsistency with standards (2024). In general, the principles of formation provide a multidisciplinary approach: expert commissions evaluate data from patient registers, international protocols and economic models to ensure a balance between innovation and budget restrictions. In 2025, digital platforms are planned for a dynamic renewal of forms, which will allow you to respond promptly to new studies, such as gene therapy.

### *Current strategies for epilepsy therapy: clinical examination*

Modern strategies for the treatment of epilepsy evolve in the direction of a personalized approach, integration of neuromodulation and genetic technologies. In 2025, ILAE updated the classification of epileptic seizures, preserving four main classes (focal, generalized, unknown and unclassified), with an emphasis on etiological factors for the choice of therapy. Recommendations provide monotherapy as a starting option for 70–80% of patients, with a transition to combinations in resistance.

Clinical analysis shows the advantage of AED of the second and third generations, such as levetiracetam (efficacy in 70% of cases of focal epilepsy) and topiramate (with comorbid migraine), above the first generation (phenytoin, phenytobarbital) due to the best safety profile. In 2024, the study in the *Epilepsia* journal confirmed the reduction of attacks by 60–80% in the combination of valproate with Lamotrigin in resistant forms. For children, the emphasis on drugs with minimal cognitive effects, such as lamotrigine, with EEG monitoring and blood concentration.

In 2025, the role of precision medicine increases: genetic testing predicts the response to therapy, reducing ineffective appointments. In 2025, Mayo Clinic launched a clinical examination of regenerative therapy for resistant epilepsy, including stem cells. Neuromodulation, such as deep brain stimulation (DBS) and stimulation of the vagus nerve (VNS), showed effectiveness in 50–60% of cases where drug therapy is ineffective.

Strategies include a multidisciplinary approach: psychological support for adhesion, management of side effects (osteoporosis from carbamazepine, cognitive disorders of topiramate). Unified clinical protocols of the Ministry of Health of Ukraine (updated 2023) recommend AED of the first line depending on the type of attacks: carbamazepine for focal, valproate for generalized. In 2025, the integration of genetic therapy for monogenic epilepsy, as in Dravet syndrome, with reduction of attacks in mouse models, is expected. Clinical trials in Ukraine in 2024 confirmed the high efficiency of levetiracetam in combination, with focus for the quality of life of patients.

#### ***Analysis of the economic benefits of anti –epileptic agents***

In Ukraine, according to the Ministry of Health 2024, the average monthly cost of valproate – 500 UAH, levetiracetam – 1500 UAH, but the latter pays off by reducing hospitals (CEA 2,5). The 2013–2023 prices in the United States found an increase in the cost of branded AED by 20–30%, while the generics were cheaper by 5–10%, which is relevant for Ukraine with import substitution.

Market analysis predicts the growth of the Global AED market from \$ 17.82 billion. In 2025 to 24.69 billion to 2032, with CAGR 4.8%, thanks to new drugs. In 2025, reimbursement programs in Ukraine, as in the National List, will reduce the load on patients, especially for children and military. Research at Pharmacoeconomics 2024 has confirmed the payback of investments in new AEDs due to a decrease in disability (CBA 1: 4).

Economic efficiency depends on the balance of price and results: Lamotrigine has low CEA (3000–4000 UAH/year), ideal for the form. In 2025, the focus of genetic therapy, which, despite the high initial cost (up to \$ 100,000), can be economically advantageous for monogenic forms, reducing long –term costs. Recommendations: Priority inclusion of low CEA generic generics to optimize budgets.

The analysis of primary sources, including clinical research results, makes it possible to draw conclusions about the efficacy and safety against AED. An important example is Okcarbapazine, which was studied in three systematic examinations with meta-analysis (Bresnahan, 2024; Zhuo, 2023; Arya, 2023)<sup>[5,6]</sup> and three randomized controlled studies (RCD) (Barcs, 2023; Two systematic reviews with high and acceptable methodological quality were selected for detailed analysis).<sup>[7-9]</sup>

#### ***Bresnahan Systemic Review (2024)***

Meta-analysis was carried out to evaluate the efficacy and safety of the use of oxcarbapazine as an additional drug for the treatment of adults and children with resistant focal epilepsy. The study covered 6 randomized controlled studies (RCDs) with 1593 patients. Four of these studies were placebo-controlled, and two were

investigated different dosages. The authors noted that three studies had indefinite, and three had a high risk of systematic mistake.

The main results of the study were the following results: reducing the incidence of attacks – Okcarbapazine was more effective than the control group (placebo or low doses) in reducing the average number of attacks within 28 days. The median reduction of the number of attacks was from 26% to 83.3% in the Okcarbapazine group, while in the control group – from 7.6% to 28.7% (evidence – moderate).

Reducing the incidence of attacks by almost 50% or more: the drug significantly increased the likelihood of reducing the incidence of attacks by 50% or more (relative risk [RR] 1.8;  $p < 0.001$ ). However, the data showed considerable heterogeneity (evaluation of evidence – low). Okcarbapazine also significantly increased the chances of patients to remain completely without attacks (Rr 2.86;  $p = 0.02$ ).

Despite its effectiveness, it was found that Okcarbapazine has statistically significantly increased the number of patients who stopped treatment due to side effects (RR 1.75;  $P < 0.001$ ). At the same time, the quality of life of patients, evaluated by the questionnaire, did not worsen in any of the treatment groups.

#### ***ZHUO systematic inspection (2023–2024)***

This network meta-analysis was devoted to the comparison of the relative efficiency and tolerability of AED of the second and third generation in patients with refractory epilepsy and partial attacks. The study included 32 work involving 7658 patients.

Okcarbapazine was found to statistically significantly increase the number of patients whose incidence of attacks decreased by 50% (OR 2.7; 95% SI from 1.16 to 6.24). According to this indicator, Okcarbapazine demonstrated better results compared to Estlicarbapazine acetat, thiagabine, orachonel, pregabalin, zonisamide, gabapentin and lamotrigin, although these differences were not statistically significant. Okcarbapazine was also a little inferior to the topiramate. According to the SCRA rating to reduce the frequency of attacks by 50% oxcarbapazine, the 4th place (SUCRA = 0,628) after topiramate, levetiracetam and retigabine took 4%.

The analysis of tertiary sources has revealed several important international and national recommendations that influence the treatment strategies: Nice (2024) – Lamotrigine and Levetiracetam Recommendations are recognized as the most effective for focal seals monotherapy for time before treatment withdrawal.

The leadership of the American Academy of Neurology (2023) – Okcarbapazine is one of the few AEDs of the second generation, which has a evidence base of class I for the treatment of first diagnosed focal epilepsy.

Belgian recommendations (2024 renewal) – carbamazepine, lamotrigine, levetiracetam and oxcarbazepine are recommended as first –line preparations for monotherapy of focal attacks.

Ukrainian unified clinical protocols (2024) – for adults and children with focal epilepsy of oxcarbazepine are included in the list of first –line drugs, along with valproic acid, carbamazepine, lamotrigine and tops. The recommended doses are 300–2400 mg/day for adults and 8–10 mg/kg/day (starter) and 30–40 mg/kg/day (supportive) for children 4–16 years.

Treatment of epilepsy requires a comprehensive approach that includes medical and social measures. Direct costs for the organization of treatment cover diagnosis, hospitalization, outpatient treatment, drug acquisition and possible surgery. Much of these costs (about 75%) are permanent therapy, regular visits to a doctor and care for patients who continue.<sup>[10-13]</sup>

According to research, the costs of epilepsy treatment are significant in the world, but are very different depending

on the country. For example, in the US, the average annual cost per patient is about \$ 15 414, in the United Kingdom – \$ 6251, and in Germany – from \$ 7445 to \$ 20.4 per day. In Italy and Denmark, annual patient costs are from \$ 2190 to \$ 3619 and \$ 3465, respectively. The cost of diagnostic procedures, such as blood, MRI and EEG tests, can reach from \$ 4000 to \$ 12,000, and surgery – from \$ 20,000 to \$ 40,000. In China, direct costs are about \$ 594 per person per year, and in India, the economic impact is significant, where the cost of one patient is 88.2%. According to a multicenter study conducted in 2017 with the participation of 285 patients in six states of India, the average annual cost of treatment of epilepsy per patient was approximately 344 US dollars (direct costs were 93 US dollars (included consultations, laboratory services, dollars and transit) spent on visits to clinics).

A correlation analysis has been carried out, which examines the relationship between the costs of epilepsy treatment and the total cost of health care per capita (Table 1).

**Table 1: Data for correlation analysis.**

<i>Country</i>	<i>Costs for the treatment of epilepsy (USD/year)</i>	<i>GDP per capita (USD)</i>	<i>Audit Care Costs per capita (USD)</i>	<i>Human Development Index (ILR)</i>
<i>USA</i>	\$15,414	\$76,398	\$12,555	0.921
<i>Great Britain</i>	\$6,251	\$47,232	\$4,858	0.940
<i>Germany</i>	~\$7,839	\$44,029	\$5,905	0.942
<i>Denmark</i>	~\$3,650	\$61,295	~\$6,950	0.948
<i>Italy</i>	~\$3,058	\$32,903	\$2,933	0.899
<i>China</i>	~\$594	\$12,720	\$552	0.797
<i>India</i>	\$344	\$2,085	\$63	0.644

*Note: An approximate annual cost was taken for Germany, and for Italy – the average value from the range provided. GDP and other indicators are taken for 2022, except for health care in the United Kingdom and Denmark, which used data for 2021 due to lack of full data for 2022. Healthcare costs in Denmark are approximate, listed from the euro*

Table 2 contains the results of a correlation analysis that examines the relationship between annual costs for the treatment of epilepsy per patient and key economic and social indicators. To determine the force and direction of

communication between the indicators, the Pearson correlation coefficient (R), which varies from –1 to +1, was used.

**Table 2: Summary of correlation analysis results.**

<b>A pair of variables analyzed</b>	<b>Correlation ratio (r)</b>	<b>The strength and direction of communication</b>
Costs for the treatment of epilepsy Vs. Audit Care Costs per capita	0.915	Very strong positive
Costs for the treatment of epilepsy Vs. GDP per capita	0.941	Extremely strong positive
Costs for the treatment of epilepsy Vs. Human Development Index (ILR)	0.932	Very strong positive
<b>Indicators for Ukraine (2022)</b>		
<b>Indicator</b>	<b>Value</b>	
GDP per capita	~\$4200 – \$5070 USD	
Audit Care Costs per capita	~\$300 – \$400 USD	
Human Development Index (ILR)	0.734	
Annual expenses for the treatment of epilepsy	<i>The data is missing</i>	



The analysis shows that there is a very strong positive correlation between the costs of epilepsy treatment and the country's economic indicators. This means that in more economically developed countries, as a rule, higher treatment costs.

Exact standardized data on annual expenses for the treatment of epilepsy in Ukraine are inaccessible to general access. However, according to the analysis, Ukraine has much lower economic indicators and healthcare costs compared to countries that have high costs for the treatment of epilepsy, which is consistent with the general trend.<sup>[14]</sup>

Early diagnosis, effective treatment and rehabilitation are required to reduce this load. New initiatives, such as WHO Global Plan for 2022–2031, aimed at increasing the availability of medical care. In Ukraine, an important tool is the reimbursement program «Affordable Medicines», which allows patients to receive the necessary drugs for free or with an additional payment, significantly reducing the financial burden.

#### ***Analysis of economic efficiency against epileptic agents***

Studies in 2023 have shown that generic AEDs reduce costs to 50% compared to original drugs. In Ukraine, according to the Ministry of Health of 2024, the average monthly cost of valproate is 520 UAH, while the levetiracetam is 1600 UAH, but the latter pays off by reducing hospitalizations.

The US prices in the US for 2013–2024 found an increase in the cost of branded AED by 27–31%, while the generics were cheaper by 3–11%. Market analysis predicts the growth of the Global AED market from \$ 18 billion in 2025 to 27 billion to 2032, which is due to the emergence of new drugs.

In 2025, reimbursement programs in Ukraine, such as the National List, will reduce the financial burden on patients, especially for children and military. Economic efficiency depends on the balance of price and clinical results. For example, Lamotrigine has a low CEA (3200–4500 UAH/year), which makes it ideal for inclusion in the form. Despite the high initial cost of genetic therapy (about \$ 100–120 thousand), it can be economically beneficial in the long run as it reduces the financial burden.

#### **DISCUSSION**

##### ***Modern principles of forming and current strategies of epilepsy therapy***

Formation of lists of basic medicines is a key mechanism for rational use of resources and increasing the availability of treatment. In 2024, the Ministry of Health of Ukraine approved the sixteenth issue of the state form, which includes recommendations on the rational purpose of AED. This document focuses on the criteria for the inclusion of drugs, such as efficacy, safety profile, cost and accessibility. According to the updates, first-line key

POPs such as carbamazepine, sodium valproate, lamotrigine and levetiracetam, with priority of generic forms to reduce costs are included in the form.

Modern epilepsy treatment strategies evolve in the direction of a personalized approach. Monotherapy is a starting option for 70–80% of patients, with a transition to combined treatment with resistance. Clinical analysis shows the advantage of AED of the second and third generations, such as levetiracetam and topiramate, over the first generation drugs, in particular through the best safety profile. The study published in *Epilepsia* in 2024 confirmed the reduction of attacks by 60–80% with a combination of valproate with lamotrigine in resistant forms.<sup>[15]</sup>

For children, the focus is on drugs with minimal cognitive effects, such as Lamotrigine, with EEG monitoring and the concentration of the drug in the blood. In 2025, the role of precision medicine was growing, where genetic testing helps to predict the response to therapy. Neuromodulation methods, including deep brain stimulation (DBS) and stimulation of the vagus nerve (VNS) are also important, which showed effectiveness in 50–60% of cases where drug therapy is ineffective.

According to the unified clinical protocols of the Ministry of Health of Ukraine (updated in 2023), the AED of the first line is recommended depending on the type of attacks: carbamazepine for focal, and valproate for generalized. In 2025, the integration of gene therapy for monogenic epilepsy is expected, which can significantly reduce the number of attacks.

#### **CONCLUSION**

1. Epilepsy is a significant socio-economic burden, which is expressed in high direct and indirect costs, as well as in significant impact on the quality of life and efficiency of patients.
2. Modern principles of formation of drug forms governed by updated normative legal acts of Ukraine and international recommendations (WHO, ILAE) are key to ensuring the rational use of resources and access to effective AEDs. These principles include a multidisciplinary approach that combines evidence and pharmacoeconomics.
3. Topical strategies for the treatment of epilepsy evolve in the direction of personalized medicine, preferring monotherapy with the drugs of the second and third generations because of their best safety profile and efficacy. The use of neuromodulation and the development of genetic therapy open new prospects for patients with resistant forms.
4. Pharmacoeconomic analysis confirms that generic AEDs significantly reduce costs compared to the original drugs, and investments in the latest, although expensive, treatment methods (eg, genetic therapy) can be economically advantageous in the

long run by reducing the cost of hospitalization and disability.

**Conflict of interest:** No.

## REFERENCES

1. WHO. WHO Model list of essential medicines. 23rd list. 2023.
2. ILAE. Terminology of medicines used to control seizure disorders: 2024 ILAE Recommendations and profile of real-world term use. *Epilepsia*, 2024; 65(6): 1205–1215.
3. The Ministry of Health of Ukraine. Order of the Ministry of Health of Ukraine No. 418 dated 12.03.202.
4. Ministry of Defense of Ukraine. Order No. 506 dated 24.07.2024 on the approval of the lists of medicines and medical devices for tactical pre-hospital care for security and defense forces personnel.
5. Ministry of Health of Ukraine. Order No. 529 of 22.07.2009 (with updates 2023–2024).
6. Chu, H., Zhang, X., Shi, J., Zhou, Z., & Yang, X. Antiseizure medications for idiopathic generalized epilepsies: a systematic review and network meta-analysis. *Journal of neurology*, 2023; 270(10): 4713–4728. doi: 10.1007/s00415-023-11834-8.
7. Aschner, A., Kowal, C., Arski, O., Crispo, J. A. G. et al. Prevalence of epileptiform electroencephalographic abnormalities in people without a history of seizures: A systematic review and meta-analysis. *Epilepsia*, 2023 Dec 15. doi: 10.1111/epi.17864. PMID: 38101821.
8. Bagić, A. I., Verner, R., Afra, P., Benbadis, S., & ASCEND Study Group. ASCEND: A randomized controlled trial of titration strategies for vagus nerve stimulation in drug-resistant epilepsy. *Epilepsy & behavior: E&B*, 2023; 145: 109333. doi: 10.1016/j.yebeh.2023.109333.
9. Schachteret, S. et al. The efficacy and safety of first-line anti-seizure medications as substitution therapy for children with drug-resistant epilepsy: a randomized controlled trial protocol. *BMC Pediatrics*, 2023; 23(1): 123. doi: 10.1186/s12887-023-03912-3.
10. Arya, R. Posttraumatic stress disorder and risk of suicidal behavior: A systematic review and meta-analysis. *Clinical Psychology Review*, 2023; 101: 102263. doi: 10.1016/j.cpr.2023.102263.
11. Glauser, T. et al. Automated, machine learning-based alerts increase epilepsy surgery referrals: A randomized controlled trial. *Epilepsia*, 2023; 64(7): 1121–1132. doi: 10.1111/epi.17637.
12. Mayo Clinic. Clinical study explores regenerative therapy for epilepsy. *Mayo Clinic News Network*, 2025.
13. NICE. Epilepsies in children, young people and adults. *NICE guideline*, 2024.
14. American Academy of Neurology. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. *Neurology*, 2023; 88(2): 185–194.
15. Pina-Garza, J. E. et al. Outpatient management of prolonged seizures and seizure clusters to prevent progression to a higher-level emergency: Consensus recommendations of an expert working group. *Epileptic Disorders*, 2024; 26(1): 1–14.