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THE IMPACT OF ANTIEPILEPTIC DRUGS ON COGNITIVE FUNCTIONS IN EPILEPSY. LITERATURE REVIEW

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Abstract

Background: Epilepsy affects more than 70 million people worldwide. Antiepileptic drugs (AEDs) represent the basis of treatment; however, 30-40% of patients develop drug resistance. In addition, cognitive impairments are frequently observed in the context of polytherapy.

Objective: To analyze the literature on the effects of antiepileptic drugs on cognitive functions assessed using EpiTrack tool in patients with epilepsy.

Materials and methods: A literature search was performed in PubMed, Scopus, and Google Scholar databases. Eligible studies included full-text publications in English and Russian over the past 15 years that investigated the effect of antiepileptic drugs on cognitive functions.

Results: A total of 1,066 records were identified in the PubMed, Scopus, and Google Scholar databases. After screening, 5 full-text articles met the inclusion criteria and were analyzed.

Conclusions: The review highlights that the cognitive impact of AEDs depends on both the quantity and the pharmacological profile of the drugs used.

Keywords: *epilepsy, antiepileptic drugs, cognitive functions, neuropsychological testing, EpiTrack.*

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Резюме

ВЛИЯНИЕ ПРОТИВОЭПИЛЕПТИЧЕСКИХ ПРЕПАРАТОВ НА КОГНИТИВНЫЕ ФУНКЦИИ ПРИ ЭПИЛЕПСИИ. ОБЗОР ЛИТЕРАТУРЫ

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Во всем мире эпилепсией страдают более 70 миллионов человек. Как известно, основой лечения являются противоэpileптические препараты (ПЭП), однако при применении ПЭП у 30-40% пациентов развивается лекарственная устойчивость. И на фоне политерапии часто развиваются когнитивные нарушения.

Цель: анализ литературных источников, в которых изучалось влияние противоэpileптических препаратов на когнитивные функции, оцененные с помощью EpiTrack у пациентов с эпилепсией.

Материалы и методы. Поиск литературных источников проводился в базах данных PubMed, Scopus, Google Scholar. В исследование были включены полнотекстовые публикации на английском и русском языках за последние 15 лет, в которых изучены влияние противосудорожных препаратов на когнитивные функции.

Результаты. В результате поиска было идентифицировано 1066 источников в базах данных PubMed, Scopus, Google Scholar. После проведения скрининга было отобрано и включено в исследование 5 полнотекстовых статей.

Выводы. Таким образом, анализ литературных источников показал, что влияние антиэпилептических препаратов на когнитивные функции может быть обусловлено количеством применяемых препаратов, видом и механизмом действия препарата.

Ключевые слова: эпилепсия, противосудорожные препараты, когнитивные функции, нейропсихологическое тестирование, EpiTrack.

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Түйіндеме

ЭПИЛЕПСИЯ КЕЗІНДЕГІ КОГНИТИВТІК ФУНКЦИЯЛАРҒА ЭПИЛЕПСИЯҒА ҚАРСЫ ДӘРІЛЕРДІҢ ӘСЕРІ. ӘДЕБИЕТТІК ШОЛУ.

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Дүниежүзінде 70 миллионнан астам адам эпилепсиямен ауырады. Білетініміздей, емдеудің негізі - эпилепсияға қарсы препараттар (ЭП) болып табылады, алайда ЭП қолданған кезде 30-40% пациенттерде дәріге төзімділік дамиды. Политерапия фонында когнитивті бұзылулар жиі дамиды.

Мақсат. Эпилепсияға қарсы препараттардың эпилепсиямен ауыратын пациенттерде EpiTrack көмегімен бағаланған когнитивті функцияларға әсерін зерттейтін әдебиеттерді талдау.

Материалдар мен әдістер. Әдеби дереккөздерді іздеу PubMed, Scopus, Google Scholar дерекқорларында жүргізілді. Зерттеуге эпилепсияға қарсы препараттардың когнитивті функцияларға әсерін зерттеген соңғы 15 жылдағы ағылшын және орыс тілдеріндегі толық мәтінді жарияланымдар енгізілді.

Нәтижелер. Іздеу нәтижесінде PubMed, Scopus, Google Scholar дерекқорларында 1066 дереккөз анықталды. Скринингтен кейін 5 толық мәтінді мақала іріктеліп, зерттеуге енгізілді.

Қорытынды. Сонымен, әдеби дереккөздерді талдау - эпилепсияға қарсы препараттардың когнитивті функцияларға әсері қолданылатын препараттардың санына, препараттың түрі мен әсер ету механизміне байланысты болуы мүмкін екенін көрсетті.

Түйін сөздер: эпилепсия, эпилепсияға қарсы препараттар, когнитивті функциялар, нейропсихологиялық тестілеу, EpiTrack.

Дәйексөз үшін:

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Introduction

Epilepsy is characterized by a persistent predisposition to the occurrence of epileptic seizures [4] and at least two unprovoked seizures with an interval of more than 24 hours [13].

According to the literature, more than 70 million people worldwide suffer from epilepsy [23]. Currently, the treatment of epilepsy includes both drug therapy and surgical treatment. As a rule, the choice of method depends on the

type and form of the disease, as well as on the individual characteristics of the organism. Antiepileptic drugs are the basis of treatment, however 30-40% of patients develop drug resistance when treated with antiepileptic drugs (AEDs) [10]. It is known that drug-resistant epilepsy (DRE) is defined as the lack of control over seizures after using two or more adequately selected antiepileptic drugs at sufficient doses and for sufficient duration [5]. Pharmacoresistance is an indication for surgical treatment.

Nevertheless, cognitive impairment is not excluded in both drug-based and surgical treatment. Long-term follow-up of more than 5 years showed that, with complete control of seizures, the risk of verbal memory decline after left-sided resection decreases to 3–17%, whereas with ongoing seizures – 37% on the left side and 20% on the right [7]. However, the nature and severity of memory impairments vary depending on a number of epilepsy-related factors, such as the side of the seizure focus, the duration of the disease, and other specific characteristics.

In the treatment with antiepileptic drugs, regardless of the number of medications prescribed, achieving a favorable profile requires doctors not only to be aware of the potential side effects of antiepileptic drugs, but also to carefully monitor cognitive changes in their patients. Relying solely on patient complaints is often insufficient, as patients may not realize the presence of impairments or cognitive alterations, or may mistakenly attribute their difficulties to epilepsy or normal aging. In addition, patients, like healthcare professionals, may have different perceptions about cognitive functions, which can easily lead to misunderstanding [5,6,9]. In this regard, an adequate neuropsychological assessment is an essential prerequisite for the correct identification of cognitive changes.

Several instruments are available for the assessment of cognitive functions in epilepsy. The Montreal Cognitive Assessment (MoCA) can be considered a simple and reliable test, recommended for screening cognitive impairments in patients with epilepsy in outpatient settings. Research findings on the assessment of cognitive functions in patients with epilepsy using MoCA have shown that their total MOCA scores were significantly lower compared with the control group (23.3, SD 4.5 vs. 27.5, SD 1.9; $p < 0.001$). However, it should be noted that this assessment tool has been validated primarily for cognitive screening in Alzheimer's disease and vascular dementia [21].

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a concise neuropsychological battery validated for the evaluation of patients with dementia and epilepsy. Some researchers have reported that RBANS is useful for assessing cognitive functions in patients with epilepsy and allows for differentiation between patients with temporal lobe epilepsy (TLE) and those without it. In addition, the authors found that the number of antiepileptic drugs (AEDs) is associated with general cognitive functions in adults with epilepsy [17].

Considering that all these tools are widely used, Helmstaedter and Lutz developed in 2005 a screening tool called EpiTrack [16], which is specifically designed for use in epilepsy. EpiTrack is a 12–15-minute test for monitoring cognitive side effects. It consists of six subtests (verbal fluency, reaction inhibition, working memory, anticipation, speed, and flexibility) which are aimed at checking attention and executive functions. The maximum score that patients can receive is 49 (after age correction). A total score from 29 to 31 indicates mild impairment, while the threshold for a significant impairment is <28 points. A significant change is defined as a gain of >3 points or a loss of >2 points. [19].

The purpose of this review is to analyze publications that have investigated the effects of antiepileptic drugs on cognitive functions, assessed using EpiTrack, in patients with epilepsy.

Materials and Methods

This systematic review included studies aimed at investigating cognitive functions in patients with epilepsy receiving antiepileptic drugs, evaluated using EpiTrack. Literature searches were conducted in PubMed, Scopus, and Google Scholar databases. The following keywords were applied when searching in English-language databases: 'The EpiTrack Cognitive Assessment' OR/AND 'EPITRACK' OR/AND 'Cognition' OR 'Memory' OR/AND 'Executive function' OR/AND 'Attention' AND 'Pharmacoresistant epilepsy' OR/AND 'Epilepsy' OR/AND 'Seizures' AND 'Medical treatment' OR/AND 'Anti-epileptic drugs'. For the Russian-language search in the Google Scholar, the following keywords were used: 'Epilepsy, antiepileptic drugs, cognitive functions', 'Epilepsy, the effect of drugs on cognitive functions, EpiTrack'.

This review was in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. A comprehensive search strategy was developed in collaboration with a medical specialist.

Exclusion criteria were as follows: conference materials, abstracts, short reports, clinical case description, reviews; studies including participants younger than 16 years; animal studies; publications whose titles referred to other neurological disorders; recurring publications; as well as meta-analyses, systematic or literary reviews. Publications with titles indicating only "assessment of cognitive functions" were selected only after reviewing the abstract.

Subsequently, screening was performed based on the content of the abstracts. In several studies, cognitive functions were assessed using methods other than EpiTrack. These articles were not included in the review, as our analysis focused on data obtained with EpiTrack.

Ethical aspects

Ethical approval was not required for this study, as it involved the analysis of previously published data and did not include any new data collection on humans or animals.

Results

A total of 1,066 publications were identified, of which 28 full-text articles were selected as a result of screening. In addition, 2 publications were identified from the reference list and included in the review.

Following further screening based on abstract review, 18 publications were excluded from the study for the following reasons:

- Studies that investigated disorders other than epilepsy -4;
- Studies in which the participants were children- 10;
- Studies that applied other cognitive function assessment tools (not EpiTrack) -3;
- Non-full-text article - 1.

Further, after reviewing the full-text publications, five articles were excluded as they assessed cognitive functions in the context of other types of treatment (non-pharmacological) -5. Thus, the final number of publications after screening was five, all of which focused on investigating cognitive functions in relation to antiepileptic drug use.

As a result, five articles were included in the review. The main drugs studied for their effect on cognitive functions were Topiramate, Lacosamide, Perampanel, Zonisamide, and Lamotrigine. The largest number of study

participants in publications was 834 people, while the smallest number was 70 people (Table 1). In one of the studies, neither the names nor the number of drugs were specified. The analysis of the included publications is

presented below depending on the effect of drugs that researchers have identified on cognitive functions: positive effect, adverse effect, or no effect.

Table 1.

Publications included in the review.

Authors, year, country	Research design	Number of patients	The purpose of the study
Niina Lähde et al [12]	A retrospective cross-sectional study	94	The aim of this study was to use EpiTrack to evaluate cognitive functions, particularly attention and executive functions in patients with refractory epilepsy, taking into account therapeutic interventions such as antiepileptic drug (AED) modification and/or neuromodulation therapy.
Carolin Meschede, Juri-Alexander Witt et al [19]	A retrospective cohort study	94	The aim of this study was to compare the long-term cognitive and behavioral side effects of adjunctive antiepileptic therapy with perampanel (PER) and lacosamide (LCM), two third-generation antiepileptic drugs with presumed favorable cognitive profiles.
Dominika Jarcuskova et al [9]	A cross-sectional study	206	The aim of the study was to evaluate the impact of demographic and clinical characteristics of epilepsy, anxiety, depressed mood, sleep, and quality of life on predicting cognitive decline in patients with epilepsy.
Helmstaedter C. et al [8]	A retrospective controlled study	70	In this retrospective controlled study, the effect of adjunctive therapy with lacosamide (LCM) on cognitive function in patients with epilepsy was evaluated and compared with that of topiramate (TPM) and lamotrigine (LTG) under natural outpatient conditions.
Juri-Alexander Witt et al [23]	A retrospective cross-sectional study	834	The study was conducted to evaluate the impact of the overall drug load of antiepileptic pharmacotherapy on cognitive functions.

For the study groups that demonstrated a positive or negative effects of antiepileptic drugs, results with $p < 0.05$ were considered. In contrast, for the groups of studies that did not reveal any effect of drugs on cognitive functions, the results with $p > 0.05$ were also analyzed, since in this context a statistically insignificant p-value reflects 'the absence of drug effects'.

Drugs with a positive effect on cognitive functions

Among the analyzed publications, two publications reported the positive effects of drugs. Assessment of cognitive functions using EpiTrack in the study by Niina Lähde showed that EpiTrack scores were higher in patients treated with two drugs (32 points), excluding Topiramate or Zonisamide, compared with patients treated with 3-4 drugs (28 points) that included Topiramate or Zonisamide.

A second study related to the positive effects of antiepileptic drugs on cognitive function revealed the beneficial effects of Lacosamide in the form of significant improvements in EpiTrack and memory performance. Similarly, Helmstaedter C. et al. confirmed the positive cognitive profile of Lacosamide, noting that its cognitive side-effect profile is comparable to LTG and superior to TPM (Table 2).

Drugs with adverse effects on cognitive functions

In the analyzed publications, two studies similarly reported adverse effects of antiepileptic drugs on cognitive functions. According to Helmstaedter C. et al., Topiramate treatment was associated with impaired executive functions and a significant decline in EpiTrack scores. Another study investigating the impact of more than 20 different drugs on cognitive functions, with the primary aim of evaluating the effect of the overall antiepileptic drug burden. The authors

reported that a lower number of medications was associated with better cognitive performance, whereas the addition of each new drug resulted in a significant reduction in EpiTrack scores. However, they also noted that patients treated with Levetiracetam (LEV) and Lamotrigine (LTG) demonstrated better executive function outcomes compared to those who did not receive these two drugs. The data is presented in Table 2.

Drugs with no effect on cognitive functions

As can be seen from Table 2, analysis of the literature revealed that three publications did not establish an association between antiepileptic drugs and cognitive functions. According to Niina Lähde, Clobazam does not affect the average EpiTrack scores. Studies investigating Lacosamide and Perampanel demonstrated that Perampanel does not improve cognitive function. According to other authors, there is no relationship between the amount of drugs administered and cognitive functions

Discussion

Thus, the analysis of literature has demonstrated that the number of drugs administered, their type, and mechanism of action may determine the impact of antiepileptic drugs on cognitive functions. Despite the fact that the use of no more than two drugs is mainly associated with more favorable cognitive effect compared to polytherapy involving 3-4 drugs, this effect largely depends on the type of drug itself. Thus, the use of Topiramate or Zonisamide, as one of the two drugs in the treatment, may exert an adverse effect on cognitive functions. It should also be noted that the mechanism of action of drugs does not necessarily explain whether a drug exerts beneficial or adverse cognitive effects.

Table 2.

The impact of different antiepileptic drugs on cognitive functions.

Authors	Number of patients	The investigated drugs	Positive effect	Adverse effect	No effect
EpiTrack is a feasible tool for assessing attention and executive functions in patients with refractory epilepsy <i>Niina Lähde et al.</i>	94	Topiramate (TPM) Zonisamide (ZNS) Clobazam (CLB) Lacosamide (LCM) Lamotrigine (LTG) Levetiracetam (LEV) Oxcarbazepine (OXC) Valproic Acid (VPA) Pregabalin (PGB) Carbamazepine (CBZ) Clonazepam (CZP)	EpiTrack scores were significantly higher in the group of patients treated with 2 AEDs excluding TPM or ZNS compared with the group with 3-4 AEDs, which included either TPM or ZNS, $p=0.023$		There were no significant differences in mean EpiTrack scores between patients receiving Clobazam (CLB) and those not treated with it.
Evaluating the longer-term cognitive effects of adjunctive perampanel compared to lacosamide in a naturalistic outpatient setting <i>Carolin Meschede et al.</i>	94	Lacosamide (LCM) Perampanel (PER)	A significant improvement in EpiTrack scores ($p = 0.009$) and memory performance ($p = 0.02$) was observed in the Lacosamide (LCM) treatment group.		No improvement in EpiTrack scores or memory performance was observed during treatment with Perampanel (PER) $p=0.89$.
Which clinical and neuropsychological factors are responsible for cognitive impairment in patients with epilepsy? <i>Dominika Jarcus`kova` et al.</i>	206	The names of the drugs are not specified.			No association was found between the number or type of drugs and cognitive functions ($p=0.19$).
The longer-term cognitive effects of adjunctive antiepileptic treatment with lacosamide in comparison with lamotrigine and topiramate in a naturalistic outpatient setting <i>Helmstaedter C. et al.</i>	70	Zonisamide (ZNS) Lacosamide (LCM) Topiramate (TPM) Lamotrigine (LTG)	The results of this study demonstrate for the first time that the profile of cognitive side effects of LCM is comparable to that of LTG and surpasses that of TPM.	Subjective cognitive complaints increased in 5 out of 9 patients whose seizures were treated with Topiramate (TPM) $p<0.01$, with executive functions worsening under TPM treatment ($p = 0.001$). Patients whose seizures were treated with TPM showed a significant decrease in EpiTrack scores.	
Adverse cognitive effects of antiepileptic pharmacotherapy: each additional drug matters <i>Juri-Alexander Witt et al.</i>	834	More than 20 drugs		With each additional drug, a significant decrease in EpiTrack scores was observed. Considering the EpiTrack threshold values, untreated patients and patients receiving two drugs demonstrated mild impairment, whereas patients with three or more concomitant drugs demonstrated severe impairment.	

According to the analysis, it was revealed that among the sodium channel blockers there are drugs that have both beneficial (Lacosamide) and adverse effects (Topiramate, Zonisamide, Lamotrigine), while stimulants of the GABA-ergic system had no effect on cognitive functions.

Regarding the effect of Topiramate on cognitive functions, some experimental studies have revealed that Topiramate does not affect cognitive performance [7], while others, on the contrary, have demonstrated a moderate beneficial effect on cognitive functions, which was further confirmed histologically. Although these studies have been conducted in animal models, the observed patterns may nevertheless indicate a link between specific antiepileptic mechanisms of action and the occurrence of cognitive side effects. [1,22]

Consistent with the findings of the present analysis, Thompson et al. reported that Topiramate administration was associated with a significant cognitive impairment, particularly in tests of verbal fluency and verbal learning ($p < 0.001$) [24].

Regarding the effect of Lacosamide on cognitive functions, most studies are consistent with our findings and indicate that it carries a low risk of adverse events in relation to cognitive functions, both in monotherapy and in polytherapy [3,8,14].

It is known that cognitive status in epilepsy is recommended to be assessed as early as possible. However, the quality of the neuropsychological profile is of great importance and can have a significant impact on the subsequent treatment of patients with epilepsy. Effective anticonvulsant medications may be unreasonably reduced or discontinued, and the possibility of surgical intervention may be mistakenly excluded if patterns of widespread cognitive impairment are incorrectly identified [25]. This highlights the crucial role of timely and accurate cognitive assessment in the clinical practice of an epileptologists, not only for diagnosis, but also for selecting the most appropriate treatment strategy.

Taking into account the above, we recommend readers to interpret the conclusions of our analysis with caution, as the following limitations should be acknowledged: a small number of publications included in the analysis; difficulties in summarizing the results of studies carried out at different times, in different cohorts, and using non-identical methodologies; a systematic error in selecting only published works (some relevant work may not be represented in the analyzed databases). Although it was not within the scope of this review, it should be noted that not all analyzed studies specified clear inclusion and exclusion criteria. As is known, poor test performance and the risk of false neuropsychological test results may be associated with such factors as advanced age [15], impaired intelligence and memory [11,25] and the use of liberal thresholds [2,25]. Moreover, the sample sizes in the analyzed publications are relatively small and geographically limited, which restricts the generalizability of the findings to patients from other regions with different demographic or clinical characteristics.

Conclusion.

Despite its limitations, our study has its potential strengths. This review represents one of the few attempts to systematize and analyze publications investigating cognitive

functions in the context of different treatment approaches for epilepsy over time, with the application of the EpiTrack tool. Although the analysis of 5 publications can hardly be regarded as a full-scale systematization, it nevertheless provides a general overview in which a certain trend can be observed. It should also be emphasized that there was no bias in defining the study objective; we did not focus solely on a specific type or group of drugs, nor did we seek to demonstrate the advantages of particular drugs. The data obtained may contribute to further refinement of approaches to neuropsychological testing, particularly through using the EpiTrack tool.

It is necessary to develop specific recommendations for reporting results in a standardized and unified format that takes into account sample-specific characteristics. Furthermore, the establishment of clearly developed inclusion and exclusion criteria should be considered essential in order to minimize the risk of false positive and false negative results.

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Author contribution

Conceptualization: Nazira Bekenova (NB) and Balzhan Kassiyeva (BK); methodology: NB, Alisher Aitkaliyev (AA), Guldana Zhumabayeva (GZh); investigation: NB, BK, Akmaral B. Suleimenova (AS), Tamara A. Vochshenkova (TV), Mukhit A. Dossov (MD), (GZh); writing-original draft preparation: NB, BK, AS, GZh; writing-review and editing: NB, BK, AA, TV, GZh. All authors have read and agreed to the published version of the manuscript.

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