

# The Effect of Treatment for Epilepsy Associated with Malignant Neoplasms of the Brain: a Literature Review

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## Abstract

**Introduction.** Epilepsy is a frequent complication in patients with malignant neoplasms of the brain. However, despite an extensive number of studies, anticonvulsants with antitumor activity have not been studied enough. The purpose of this study was to evaluate the efficacy and tolerability of brivaracetam and levetiracetam as an additional therapy in patients with malignant brain tumors, as an anticonvulsant and antitumor agent. **Materials and methods.** The search was carried out in the electronic databases PubMed/MEDLINE, EMBASE, Cochrane Library until June 2023. Screening and selection of studies was carried out according to the recommendations of PRISMA. The search included a combination of queries related to “glioma”, “epilepsy”, “antiepileptic drugs” and “efficacy”. From all the relevant articles, three different results were extracted for both mono- and polytherapy: adult patients with brain malignancies; ≥55 % of patients with proven or suspected glioma using histological examination; ≥10 patients receiving the same AED. **Results.** The data regarding levetiracetam are contradictory. In terms of research, this drug has shown not only anticonvulsant activity, but also antitumor activity. Other researchers point to the absence of antitumor activity in levetiracetam. Brivaracetam is an effective anticonvulsant drug that has shown antitumor activity in studies, but there are not enough studies to make an adequate conclusion. **Discussion.** The results obtained on the antitumor activity of levetiracetam are quite contradictory. Perhaps this is due to the heterogeneity of patient populations in terms of morphological examination of the tumor, different patients receiving concomitant treatment, and the prevalence of the tumor process. With regard to brivaracetam, it is not possible to give an adequate conclusion about an effective combination of antitumor and anticonvulsant activity due to the insufficient number of studies to date. **Conclusion.** Levetiracetam and brivaracetam have shown high efficacy in the symptomatic treatment of epilepsy associated with brain tumors. However, data on the presence of antitumor activity in these drugs is contradictory and requires further research.

**Keywords:** anticonvulsants, antiepileptic drugs, epilepsy, malignant neoplasms of the brain, efficacy, levetiracetam, brivaracetam

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# Эффективность лечения эпилепсии, ассоциированной со злокачественными новообразованиями головного мозга: обзор литературы

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## Аннотация

**Введение.** Эпилепсия является частым осложнением у пациентов, имеющих злокачественные новообразования головного мозга. Однако несмотря на обширное количество исследований, противосудорожные препараты, обладающие и противоопухолевой активностью, изучены недостаточно. Целью данного исследования явилось оценить эффективность и переносимость бриварацетама и леветирацетама в качестве дополнительной терапии у пациентов со злокачественными новообразованиями головного мозга как противосудорожных и противоопухолевых средств. **Материалы и методы.** Поиск проводился в электронных базах данных PubMed/MEDLINE, EMBASE, Cochrane Library до июня 2023 г. Скрининг и отбор исследований проводился согласно рекомендациям PRISMA. Поиск включал комбинацию запросов, связанных с «глиомой», «эпилепсией», «противоэпилептическими препаратами» и «эффективностью». Из всех подходящих статей были извлечены три различных результата как для моно-, так и для политерапии: взрослые пациенты со злокачественными новообразованиями головного мозга;  $\geq 55$  % пациентов с доказанной или подозреваемой глиомой при помощи гистологического исследования;  $\geq 10$  пациентов, получавших один и тот же препарат. **Результаты.** Данные в отношении леветирацетама противоречивы. В части исследований данный препарат показал не только противосудорожную, но и противоопухолевую активность. Другие же исследователи указывают на отсутствие у леветирацетама противоопухолевой активности. Бриварацетам — эффективный противосудорожный препарат, который показал в исследованиях противоопухолевую активность, однако исследований недостаточно, чтобы сделать адекватный вывод. **Обсуждение.** Полученные результаты о противоопухолевой активности леветирацетама достаточно противоречивы. Возможно, это связано с неоднородностью популяций больных с точки зрения морфологического исследования опухоли, разного приема пациентами сопутствующего лечения, распространенности опухолевого процесса. В отношении бриварацетама дать адекватное заключение об эффективной комбинации противоопухолевой и противосудорожной активности не представляется возможным ввиду недостаточного количества исследований на сегодняшний день. **Заключение.** Леветирацетам и бриварацетам при симптоматической терапии эпилепсии, ассоциированной с опухолями головного мозга, показали высокую эффективность. Однако данные о наличии противоопухолевой активности у данных препаратов противоречивы и требуют дальнейших исследований.

**Ключевые слова:** противосудорожные средства, противоэпилептические препараты, эпилепсия, злокачественные новообразования головного мозга, эффективность, леветирацетам, бриварацетам

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## INTRODUCTION

One of the initial symptoms of brain tumors are convulsions, which occur in about 40 % of patients. Patients with convulsive syndrome associated with brain neoplasms are difficult cases for curation, requiring an interdisciplinary approach [1–3]. At the same time, the issue of the treatment of this complication from the point of view of the choice of antiepileptic drugs is quite difficult due to resistance to these drugs in this population of patients [4–6].

Today, there is a wide range of AED on the market, having various mechanisms of action and affecting an extensive number of targets, while most representatives have not been fully studied in terms of their direct endpoints of action [7–10].

The mechanism of epileptogenesis in neoplasms of the central nervous system is neither sufficiently studied. In these patients, convulsions may occur with tumors of different localization: infiltrative or deforming. At the same time, convulsive activity does not occur directly due to the presence of the tumor itself, but from the peritumoral cortex in most patients. The exception is glioneuron tumors, which contain neuronal elements [11–13].

Due to the high incidence of epilepsy in patients with malignant neoplasms of the brain, the choice of the most appropriate therapeutic tactics to manage a patient should not only be determined by the effectiveness of the drug, subject to the occurrence of various types of seizures, high rates of individual tolerability and the potential for drug interaction [14–17]. Modern ideas about antiepileptic drugs in the context of the treatment of seizures in this population of patients include, in addition to anticonvulsant action, also the ability to provide antitumor activity [18]. However, despite an extensive number of studies, anticonvulsants with antitumor activity have not been studied enough.

The purpose of this study is to retrospectively evaluate the efficacy and tolerability of brivaracetam and levetiracetam as additional therapy in patients with brain malignancies.

## MATERIALS AND METHODS

The literature review was carried out in the electronic databases PubMed/MEDLINE, EMBASE, Cochrane Library until June 1, 2023. Screening and selection of studies was carried out according to the recommendations of PRISMA. The search included a combination of queries related to “glioma”, “epilepsy”, “antiepileptic drugs” and “efficacy”. Articles were selected out independently by title and abstract of all potentially significant full-text articles. The search for additional sources in the literature lists from the included full-text articles was carried out manually. The inclusion criteria were: (1) adult patients with brain malignancies, (2)  $\geq 55$  % of patients with proven or suspected glioma using histological examination, (3)  $\geq 10$  patients receiving the same AED. The exclusion criteria were: (1)  $\geq 55$  % of patients receiving perioperative prophylaxis of AED, and the lack of information on the outcomes of treatment of seizures in relation to this group of patients and patients receiving symptomatic treatment, (2) lack of documentation on the outcomes for each AED, (3) articles on the treatment of epileptic status. The information was obtained from

interventional (randomized and non-randomized) and observational studies (cohort, case-control and case series).

## RESULTS AND DISCUSSION

Levetiracetam is often used as the first-line drug of the epilepsy monotherapy regimen. [19, 20]. Although its exact mechanism of action is not fully understood, it is reliably known that it exerts its anticonvulsant effect by binding the SV2A protein in synaptic vesicles. This drug has a wide therapeutic range, rapid activation of pharmacodynamic mechanisms, as well as good tolerability [18].

Kim et al. have shown that levetiracetam can contribute to a longer survival of patients with glioma [21], whereas the analysis of four clinical trials did not show the advantages of using levetiracetam in terms of increasing the survival of patients with brain tumors [22].

In the study, as mentioned above, it remains controversial which of the AED is the best option to ensure not only anticonvulsant, but also antitumor efficacy against glioma cells.

Lange F. Et al. have investigated the molecular biological mechanisms of the effect of four antiepileptic drugs on brain tumor cells: levetiracetam, valproic acid, per and carbamazepine. To simulate native conditions directly inside the tumor, the researchers have used a glioblastoma cell line obtained from the patient. As a result of the experiment, the findings show that of the four studied drugs, only perampamil inhibited cell growth in the studied glioblastoma cell lines, whereas levetiracetam did not show antitumor activity [18].

According to a study carried out by Pim B. van der Meer, levetiracetam shows higher therapeutic efficacy compared to enzyme-inducing antiseizure medications. A retrospective observational cohort study included patients with grade 2–4 glioma with a maximum follow-up duration of 36 months. At the same time, cases of unsuccessful therapy due to uncontrolled convulsions were twice as common in the group receiving EIASM (36 % vs. 18 %). In addition, the ineffectiveness of therapy in the levetiracetam group for other reasons was also much less common. Thus, in patients with glioma, the prescription of levetiracetam to combat convulsions seems more rational [23].

In another review study, a team of researchers from the Netherlands analyzed the effectiveness of levetiracetam in comparison with phenytoin and pregabalin among a similar population of patients: suffering from epilepsy associated with CNS tumors, more than 50 % of patients had histologically confirmed tumors of neuroectodermal origin (gliomas). It was concluded that levetiracetam, phenytoin and pregabalin are effective in the treatment of epilepsy associated with brain tumor damage, however, the use of levetiracetam is characterized by the greatest effectiveness and the lowest frequency of unsuccessful therapy [24].

A review made by Jia-Shu Chen et al., showed data to conclude that the use of levetiracetam does not improve the prognosis of life in the entire population of patients with glioblastomas, however, among patients with certain molecular patterns, levetiracetam may be the optimal treatment for epilepsy [25].

A group of researchers from Germany, on the contrary, concluded in their review that the early start of the use of antiepileptic drugs contributes to an increase in survival and a decrease in progression of glioblastomas. At the same time, a significant relevance was found only between survival (overall and progression-free survival) and levetiracetam intake. In addition, the researchers cite data that may indicate the possible antitumor activity of levetiracetam, probably due to epigenetic suppression of the MGMT enzyme and subsequent increase in the effectiveness of TMZ [26].

A relatively new anticonvulsant drug is brivaracetam, a representative of the racetam class, an analogue of levetiracetam, which is also a selective high-affinity ligand for synaptic vesicular protein 2A (SV2A) [27].

This drug is approved as an additional therapy and monotherapy for focal seizures in patients with epilepsy in the United States, and also as an additional drug for focal seizures in patients with epilepsy in the European Union [28].

Brivaracetam has shown high efficacy in cancer patients as an additional line of therapy for uncontrolled focal seizures, while a fairly low incidence of behavioral and cognitive disorders has been reported against the background of therapy.

However, there is no data on the efficacy and tolerability of this drug in patients with brain neoplasms.

Maschio M. et al. have investigated the antitumor activity of brivaracetam in vitro. The findings show that the anticonvulsant has a dose-dependent cytostatic effect on different glioma cell lines, which is accompanied by modification of a number of microRNAs (miRNAs). In their previous studies, the authors evaluated these results as an opportunity to use these data as a predictor of convulsions, as well as tumor progression in patients with brain neoplasms [29]. The efficacy of RVS as an adjunctive therapy in cancer patients with uncontrolled focal seizures was evaluated in randomized placebo-controlled studies [5, 30].

In this review, we have provided generalized information on current literature data on the effectiveness of antiepileptic drugs in a population of patients with brain neoplasms combining both anticonvulsant and antitumor activity. However, the results obtained on the antitumor activity of levetiracetam are quite contradictory. Perhaps this is due to the heterogeneity of patient populations in terms of morphological examination of the tumor, different patients receiving concomitant treatment, and the prevalence of the tumor process. One cannot exclude the simultaneous administration of antitumor drugs to this population of patients, which may also affect subsequent results in different studies. With regard to brivaracetam, it is difficult to give an adequate conclusion about an effective combination of antitumor and anticonvulsant activity due to the insufficient number of studies to date. Also, studies by different authors on this issue should be interpreted with caution due to the fact that the effectiveness of antiepileptic drugs has not always been the main result in studies, or such studies evaluated different time points or different effectiveness criteria.

## CONCLUSION

Thus, modern antiepileptic drugs are a safe tool to treat epilepsy in patients with tumors of the central nervous system. Most publications note not only the high effectiveness of modern drugs, such as levetiracetam and brivaracetam, in the symptomatic treatment of epilepsy associated with glioblastomas, but also their positive effect on the prognosis of the patient's life. Besides, there are data that prove the antitumor activity of these drugs. However, these data are contradictory and require further research.

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