DOI: https://doi.org/10.17816/RCF629243

Potential use of perampanel in the treatment of epilepsy in patients with malignant brain gliomas

Yi Wang [1], Natalya A. Mufazalova [2], Lyaysan F. Mufazalova [2], Nailya V. Ilyasova [2], Railya R. Muradova [3], Ikhtier E. Kiyomov [3], Lailo Sh. Davurova [3], Aleksandr V. Samorodov [2]

[1] Hangzhou Normal University, Hangzhou, China;
[2] Bashkir State Medical University, Ufa, Russia;
[3] Samarkand State Medical University, Samarkand, Uzbekistan

ABSTRACT

Epilepsy occurs in 35–95% of patients with low-grade malignant cerebral gliomas and in 29–71% of patients with high-grade gliomas. Seizures can be the first manifestation of a malignant cerebral glioma or may develop in the postoperative period and during chemoradiation therapy. This necessitates the use of antiepileptic drugs that can control seizures, ensure seizure prevention, and provide secondary seizure prophylaxis without reducing the effectiveness of anticancer therapy or the patient's quality of life. The processes of epileptogenesis and oncogenesis are closely interrelated through common developmental mechanisms, with glutamate playing a key role. Increased glutamate secretion is accompanied by elevated expression and activation of its receptors, which raises seizure susceptibility. This is associated with increased levels of brain-derived neurotrophic factor, the number of synapses between peritumoral neurons and glioma cells, and the expression of various growth factors, all of which contribute to tumor progression. In this context, special attention is given to perampanel, a glutamate receptor antagonist and third-generation antiepileptic drug, in the treatment of epilepsy in patients with malignant cerebral gliomas. It has been shown that perampanel not only effectively controls seizures in patients with malignant cerebral gliomas but also suppresses tumor progression. Perampanel can dose-dependently enhance apoptosis and disrupt cell migration in malignant glioma cell lines. A synergistic effect of perampanel in combination with temozolamide has been identified. During chemoradiation therapy, perampanel exerts a protective effect on healthy peritumoral tissues. Adverse drug reactions associated with perampanel use are infrequent and mild. Further research is needed to investigate the anticonvulsant and antitumor efficacy of perampanel for the treatment of epilepsy in patients with malignant brain tumors.

Keywords: perampanel; epilepsy; malignant cerebral gliomas; glioblastoma; antitumor activity; temozolamide.

To cite this article

Wang Yi, Mufazalova NA, Mufazalova LF, Ilyasova NV, Muradova RR, Kiyomov IE, Davurova LSh, Samorodov AV. Potential use of perampanel in the treatment of epilepsy in patients with malignant brain gliomas. *Reviews on Clinical Pharmacology and Drug Therapy.* 2024;22(3):223–236. DOI: https://doi.org/10.17816/RCF629243

Received: 21.03.2024 **Accepted:** 24.04.2024 **Published online:** 30.09.2024

УДК 615.213:616.831-006.484:616.853-085.2
DOI: https://doi.org/10.17816/RCF629243

Перспективы применения перампанела в лечении эпилепсии у пациентов со злокачественными глиомами головного мозга

Юи Ванг [1], Н.А. Муфазалова [2], Л.Ф. Муфазалова [2], Н.В. Ильясова [2], Р.Р. Мурадова [3], И.Э. Киёмов [3], Л.Ш. Давурова [3], А.В. Самородов [2]

[1] Ханчжоуский педагогический университет, Ханчжоу, Китай;
[2] Башкирский государственный медицинский университет, Уфа, Россия;
[3] Самаркандский государственный медицинский университет, Самарканд, Узбекистан

АННОТАЦИЯ

Эпилепсия встречается у 35–95 % больных злокачественными глиомами головного мозга низкой степени злокачественности и у 29–71 % больных глиомами высокой степени злокачественности. Судороги могут быть как первым проявлением злокачественной глиомы головного мозга, так и появиться в постоперационном периоде и в процессе химиолучевой терапии. Это требует применения противоэпилептических препаратов, которые способны купировать судорожный синдром, обеспечить контроль и вторичную профилактику судорог, не снижая эффективности противоопухолевой терапии и качество жизни пациента. Процессы эпилептогенеза и онкогенеза тесно взаимосвязаны между собой посредством общих механизмов развития, ключевую роль в которых играет глутамат. Повышенная секреция глутамата сопровождается увеличением экспрессии и активацией его рецепторов, что повышает судорожную готовность. Этому сопутствует повышение уровня нейротрофического фактора роста головного мозга, числа синапсов между перитуморальными нейронами и клетками глиомы, увеличение экспрессии ряда ростовых факторов, что способствует опухолевой прогрессии. В связи с этим особое внимание в лечении эпилепсии у больных злокачественными глиомами головного мозга занимает перампанел — блокатор рецепторов глутамата, противоэпилептический препарат III поколения. Показано, что перампанел не только эффективно контролирует судороги у пациентов со злокачественными глиомами головного мозга, но и подавляет опухолевую прогрессию. Перампанел способен дозозависимо усиливать апоптоз, нарушать миграцию клеток в клеточных линиях злокачественной глиомы. Выявлен синергетический эффект перампанела в комбинации с темозоламидом. В условиях химиолучевой терапии перампанел оказывает защитное действие на здоровые перитуморальные ткани. Нежелательные лекарственные реакции при применении перампанела возникают нечасто и являются незначительными. Необходимы дополнительные исследования для дальнейшего изучения противосудорожной и противоопухолевой эффективности перампанела для лечения эпилепсии у больных злокачественными опухолями головного мозга.

Ключевые слова: перампанел; эпилепсия; злокачественные глиомы головного мозга; глиобластома; противоопухолевая активность; темозоламид.

Как цитировать

Ванг Юи, Муфазалова Н.А., Муфазалова Л.Ф., Ильясова Н.В., Мурадова Р.Р., Киёмов И.Э., Давурова Л.Ш., Самородов А.В. Перспективы применения перампанела в лечении эпилепсии у пациентов со злокачественными глиомами головного мозга // Обзоры по клинической фармакологии и лекарственной терапии. 2024. Т. 22, № 3. С. 223–236. DOI: https://doi.org/10.17816/RCF629243

Рукопись получена: 21.03.2024 **Рукопись одобрена:** 24.04.2024 **Опубликована online:** 30.09.2024

INTRODUCTION

Malignant brain gliomas (MBGs) account for approximately 60%–80% among primary brain tumors and are characterized by an aggressive clinical course and high mortality [1–3]. More than 70% of MBGs are accompanied by epilepsy, the treatment of which is one of the most important challenges of modern neuro-oncology [2, 4, 5]. Epileptic seizures may be the first symptom of the tumor [6] or occur during its evolution after surgical treatment [7] or during chemoradiotherapy [8–10].

Glutamate and activation of α-amino3-hydroxy5-methyl4-isoxazolpropionic acid receptors (AMPA-glutamate receptors) play a pivotal role in the epileptogenesis and tumor progression in brain tumor-related epilepsy (BTRE) patients [11–13]. In this regard, perampanel (PER), an AMPA-receptor antagonist, a highly effective third-generation antiepileptic drug (AED) with a minimal range of side effects, is a promising candidate for the treatment of epilepsy in MBG patients [6, 14, 15].

The review was based on a comprehensive literature search conducted up to November 2023 across PubMed, Embase, and Cochrane Library databases using the keywords "злокачественные глиомы головного мозга" ("malignant brain gliomas"), "глиобластома" ("glioblastoma"), "эпилепсия" ("epilepsy"), "перампанел" ("perampanel"), and "противоопухолевая активность" ("anti-tumor activity"). The review was prepared in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) reporting guidelines [16].

MALIGNANT BRAIN GLIOMAS AND EPILEPSY

MBGs are tumors originating from glial or glial precursor cells and include astrocytoma, oligodendroglioma, ependymoma and other rare gliomas [2, 3]. In recent years, there has been an increase in the incidence of MBGs, which can be attributed to increased life expectancy and the use of new diagnostic methods. Additionally, there has been an increase in the incidence among younger patients [17–19].

MBG is characterized by a high risk of recurrence, high mortality (with a median survival of ⩽24.5 months), and a significant decrease in the quality of life [12, 20]. The clinical presentation of MBG is primarily comprised of neurological disorders resulting from tumor progression, including headaches (50%), neurocognitive disorders (30%–40%), paresis and paralysis (10%–40%), seizures (20%–50%), etc. [21–23].

BTRE plays a special role in MBG patients, occurring in 35%–70% of cases, including 46%–95% of patients with low-grade gliomas (Grade I and Grade II) [24–26], 42%–71% of patients with Grade III gliomas, and 29%–60% of patients with Grade IV gliomas [21, 22, 27]. At the time of diagnosis, BTRE is detected in more than 40% of patients with MBG, with an even higher prevalence at later stages of the disease [13, 28]. BTRE contributes to cognitive and psychiatric disorders and reduces the patient quality of life [9, 29]. The BTRE severity is influenced by several factors, including tumor size, extent of tumor resection, residual tumor size, and a history of preoperative seizures [7, 30].

HIGH-GRADE MALIGNANT BRAIN GLIOMAS

Glioblastoma (GBM) is the most aggressive type of MBG with a median survival ranging from 12 to 25 months (a mean of 14.6 months) [12, 31, 32]. Epilepsy (glioblastoma-related epilepsy, GRE) occurs in 30%–62% of patients with GBM [23, 33, 34]. The studies report that GBM is less epileptogenic than lower-grade gliomas, which is likely attributed to the shorter life expectancy of GBM patients and the presence or absence of mutations in isocitrate dehydrogenase (IDH) 1/2 [5, 27, 35]. In 40%–45% of GBM patients, seizures are the first symptom [18, 36, 37], although they may occur at different stages of the disease [30, 38].

The treatment of MBG patients is surgery and chemoradiation therapy [22, 39]. Surgical excision of the tumor has been demonstrated to result in a reduction in tumor size, the rate of tumor growth, and the incidence of seizures, improves the patient condition, and increases the overall survival [7, 28, 40]. However, surgery and a history of preoperative seizures may increase the risk of BTRE in the postoperative period [28].

A number of authors have demonstrated a correlation between the tumor epileptogenic potential and its growth rate [39]. The BTRE/GRE recurrence in the postoperative period or after first-line anti-tumor therapy may be attributed to tumor progression [30, 41]. Thus, the occurrence of seizures within 30 days post-surgery is a predictor of unfavorable outcome in GBM patients [42].

TREATMENT OF BRAIN TUMOR-RELATED EPILEPSY

The occurrence of BTRE in MBG patients requires the use of AEDs for seizure control, management, and secondary prevention [29, 39]. Patients with untreated BTRE tend to have a lower overall survival [14, 39]. Typically, a single AED is sufficient for the treatment of BTRE. However, in approximately 30% of cases, the administration of two or more AEDs is necessary, which increases the risk of adverse drug reactions, drug interactions, and, in some cases, BTRE resistance to treatment, thereby further reducing the quality of life [14, 22, 39]. The elevated risk of epilepsy relapse often requires the prolonged use

of AEDs in BTRE patients [39]. The choice of AEDs for each BTRE patient is individualized, based on a comprehensive assessment of efficacy, tolerability, dose regimen and titration, pharmacokinetics, comorbidities, and the potential for drug interactions [43].

The potential for drug interactions between AEDs and chemotherapeutics represents a significant concern, particularly in light of the potential for decreased efficacy of anti-tumor therapy and/or increased toxicity [44]. The preferred AEDs are those that have no significant drug interactions, do not affect the liver monooxygenase system (MOS) activity, and do not have hematotoxic or immunosuppressive effects [26, 39]. The use of AEDs for the treatment of BTRE should be accompanied by a low risk of neurotoxicity, since the majority of MBG patients present with some degree of cognitive disorders [39, 45].

Valproic acid (VPA), phenytoin (PHT), carbamazepine (CBZ), and levetiracetam (LEV) are commonly used to treat BTRE [26, 39, 46]. However, VPA is known to be associated with hepato- and neurotoxicity, the risk of bleeding, suppression of hematopoiesis in the bone marrow, hormonal imbalance, and liver MOS activity inhibition, which increases the risk of drug interaction [8, 43, 47]. PHT and CBZ have been demonstrated to induce liver MOS activity and cause a number of endocrine disorders, alter vitamin D metabolism, contributing to osteopenia, and are known to be engaged in significant drug interactions [8, 43, 47]. Both drugs are sodium channel blockers that have been associated with cardiotoxicity, rhythm disturbances, and QRS prolongation [32, 47]. Similarly to PHT, CBZ has a hepatotoxic potential, increases the risk of bleeding, and may cause urinary tract disorders. The use of PHT is associated with the risk of aesthetic defects [32, 39, 47].

In recent years, LEV and PER have been used for the treatment of BTRE, and their anti-tumor activity has been demonstrated [48]. However, the use of LEV is limited due to adverse drug reactions such as behavioral and thinking disorders, hostility, aggression, irritability, and psychotic disorders [49–51].

Glutamate and AMPA receptor activation play an important role in the BTRE occurrence, mediating both seizure activity and tumor progression [12, 13, 52]. In this regard, great interest is focused on PER, a third-generation AED, a selective non-competitive AMPA receptor antagonist [53–55].

PERAMPANEL IN EPILEPSY TREATMENT

PER inhibits glutamatergic transmission, reduces intracellular Ca^{2+}, and suppresses abnormal brain pulsations in epileptogenic foci [13, 32, 39]. Administered once daily, PER has linear pharmacokinetics, high bioavailability (100%), and long half-life (105–130 h) [39]. At therapeutic doses, PER does not affect liver MOS activity, and at high doses it is a weak inducer of CYP2B6 and CYP3A4/5 [10, 43].

The lack of significant effects on liver MOS, uridine diphosphate-glucuronosyltransferases and P-glycoprotein activities contributes to the low risk of PER drug interaction [8]. PER is used for the treatment of focal and generalized epilepsy [56], including in combination therapy of drug-resistant epilepsy [21, 46, 57]. A pooled analysis of three large, placebo-controlled, phase III studies involving 1480 patients with drug-resistant epilepsy treated with AEDs that induce liver MOS activity [58, 59] showed that the addition of PER (at 4–12 mg) provided a two-fold reduction in seizures [60]. These findings suggest that AEDs, which induce liver MOS activity, reduce PER blood levels without altering its antiepileptic activity [61].

Sagar et al. [57] performed a retrospective multicenter study involving 387 patients with drug-resistant epilepsy. A ⩾50% reduction in seizure frequency was observed in 41.3% of patients, while 14.7% of patients exhibited complete seizure freedom. The side effects included neuropsychiatric disorders (18.86%) followed by dizziness (13.7%) and drowsiness (5.68%).

The efficacy of PER often allows for the withdrawal of other AEDs, which improves patient's cognitive functions and quality of life [54, 62]. An analysis of 9 studies including 241 epileptic patients demonstrated that PER has a neutral cognitive profile [63]. At doses <4 mg/day or ⩾8 mg/day, PER did not affect or slightly decreased the psychomotor speed, respectively [10]. In contrast to most AEDs, PER does not affect intracardiac conduction and does not cause ataxia, tremor, diplopia, or nystagmus [32, 39, 47].

The most common adverse drug reactions associated with PER administration are dizziness and drowsiness; less common ones include irritability and anger [54, 62, 64]. Adverse drug reactions caused by PER are dose-dependent, which requires the initiation of therapy with low doses with a gradual dose increase until the clinical effect is achieved [64].

EXPERIMENTAL STUDIES OF PERAMPANEL EFFICACY IN EPILEPSY TREATMENT

The efficacy of PER for BTRE was first reported in 2016, when Cunningham et al. [65] showed that the addition of PER reduces interictal activity in peritumoral slices *ex vivo* [65]. In 2019, PER was revealed to suppress voltage-dependent Na^+ currents in U87 glioma cells, which may contribute to the anticonvulsant effect of PER [66]. A number of studies have shown that AMPA receptor inhibition increases the tumor cell response to

chemotherapy in lung cancer, astrocytoma, neuroblastoma, and rhabdomyosarcoma [12, 13]. This suggested that AEDs (AMPA receptor antagonists) might have anti-tumor effects [12, 13].

A study of the anti-tumor activity of LEV, VPA, CBZ, and PER on 4 low-passage GBM cell lines and 3 brain metastasis cell lines showed that only PER inhibited cell proliferation [67]. This was accompanied by a decrease in glucose uptake, extracellular glutamate levels, and an increase in both GLUL (glutamine synthetase/glutamate-ammonia ligase) activity and *GLUL* gene expression [67]. The findings led to the conclusion that PER has both anti-convulsant and anti-tumor activity [67].

Analysis of the effect of PER and its combination with temozolomide on the growth of human U87, A172, U138 GBM cell lines showed that PER exerted an anti-proliferative effect in all investigated cell lines by enhancing apoptosis processes, and also increased the expression of GluR2/3 subunits in U87 and U138 cell lines. In combination with temozolomide, however, a synergistic effect was found in U87 and A172 cell lines [68].

Tatsuoka et al. [48] studied the effect of PER on proliferation of 6 malignant glioma cell lines (A-172, AM-38, T-98G, U-138MG, U-251MG, and YH-13). The observed dose-dependent inhibitory effect of PER on the cell line viability was also attributed to the induction of apoptosis, which was enhanced in combination with temozolomide. In contrast, U-138MG cells with high levels of PAI-1 (plasminogen activator inhibitor1) expression were resistant to PER. PAI-1 is known to play an important role in the angiogenesis processes in tumor tissue and tumor progression. When tiplaxtinin, a PAI1 inhibitor, was combined with PER, the U138MG cell viability was reduced [48].

In 2022, Yagi et al. [37] studied the anti-tumor activity of PER, CBZ, VPA, and LEV on 6 malignant glioma cell lines (A-172, AM-38, T-98G, U-138MG, U-251MG and YH13) at doses used for BTRE treatment [37]. PER, VPA, CBZ and LEV were found to suppress cell proliferation in 6, 4, 3, and 2 cell lines, respectively. A study of the effects of AEDs in combination with temozolomide on T-98G and U-251MG cell lines revealed that PER inhibited tumor growth and migration in both cell lines, LEV inhibited tumor growth and migration in T-98G cells, and CBZ and VPA had no effect [37]. PER has been shown to decrease the expression of Rac1 and RhoA, which constitute the cytoskeleton that enables cell motility. The authors found decreased expression of N-cadherin, a mesenchymal marker, which is involved in cell migration. This was accompanied by decreased expression of matrix metalloproteinase2 and increased expression of E-cadherin, which enhances intercellular adhesion and reduces cell motility. This may explain the PER-induced suppression of tumor cell migration. The findings suggest that PER may have a positive effect on MBG outcomes [37].

Moreover, Lange et al. [69] experimentally established that PER, when added to chemoradiation therapy, can protect healthy peritumoral tissues by preserving the activity of their glutamatergic network.

In 2020, Mayer et al. [52], who studied the anti-convulsant and anti-tumor effects of PER *in vitro*, found that PER reduced glucose uptake without affecting the level of extracellular glutamate. To study the effects of PER *in vivo*, they created a GRE model: C6 glioma cells were orthotopically injected into the neocortex of Wistar rats. It was shown that PER eliminated abnormal electrical activity in the GRE rat model, while no effect of PER on tumor size or animal survival was found.

CLINICAL USE OF PERAMPANEL FOR EPILEPSY TREATMENT

In 2015, PER was used in combination therapy for partial seizures in a patient with GBM multiforme without IDH1 mutation and O6-methylguanine-DNA methyltransferase (MGMT) methylation [70]. The median overall survival in patients with this disease is 6.5 months. The administration of PER increased the median overall survival in the GBM patient by approximately one year, seizures did not recur, and the toxicity of temozolomide did not increase [70].

The use of PER in 12 patients with low- and high-grade MBG and drug-resistant epilepsy provided a response to therapy in 9 patients (75%), a 50% reduction in seizure frequency in 3 patients (25%), and seizure freedom in 6 patients (50%) [11]. In 6 patients (50%), the authors found improvement in cognitive functions, which may be attributed to a decrease in the number of AEDs used in combination with PER [11].

According to Izumoto et al. [71], PER provided seizure control in 10 patients (100%) with glioma and drug-resistant epilepsy, of whom 6 (60%) had complete seizure freedom. Magnetic resonance imaging revealed suppression of tumor growth and reduction of peritumoral edema, which correlated with plasma PER concentration.

Dunn-Pirio et al. [72] showed the efficacy of PER as an additional AED for focal seizure control in 6 (75%) of 8 BTRE patients, with 3 (37.5%) showing a seizure reduction and the other 3 (37.5%) showing an improved seizure control. The authors noted that 5 patients had tumors with IDH1 mutation and 2 had wild-type IDH1 tumors, and all patients had MGMT hypermethylation.

A retrospective analysis of data from 11 patients with glioma and epilepsy who received PER for 12 months as adjunctive therapy revealed a response to therapy in 9 patients (81.8%), with 5 patients (45.5%) experiencing complete seizure freedom, 4 patients (36.4%) experiencing a ⩾50% reduction in seizures, and only 2 patients (18.2%) experiencing no change in seizure frequency [73].

Later, in 2020, Maschio et al. [74] studied the efficacy of PER (at a mean daily dose of 6.6 mg/day) in 26 BTRE patients, of whom 16 received chemotherapy and 11 received radiation therapy. The use of PER resulted in complete absence of seizures in 8 patients (30.8%) and a ⩾ 50% reduction in seizures in 15 patients (57.7%). However, 4 patients (15.4%) reported adverse drug reactions, which required PER dose reduction in 2 patients and drug withdrawal in 2 patients. No neuropsychological changes were detected. The authors found no significant differences in seizure control in patients with or without IDH1 mutations and with or without MGMT methylation [74].

Chonan et al. [46] showed that the addition of low-dose PER (2–4 mg) to LEV (500–3,000 mg) in 18 GBM patients with uncontrolled seizures provided complete seizure freedom in 17 patients (94.4%).

According to the PERADET prospective observational study, which included 36 BTRE patients with uncontrolled focal seizures, the efficacy of PER (at 2–12 mg/day) was 90.4% (34 patients), with complete absence of seizures observed in 33.3% (12 patients) [15].

In 2021, Heugenhauser et al. [6] showed the efficacy of PER in 5 patients with refractory BTRE, 2 of whom had SMART (Stroke-like migraine attacks after radiation therapy) syndrome. The response rate was 80%, and 2 patients with SMART syndrome showed a ⩾50% reduction in seizure frequency. Rossi et al. [55] analyzed 13 studies with a sample size ranging from 8 to 36 patients who received additional PER (at 4–7 mg/day) for BTRE. At 6–12-month follow-up, 75%–95% of patients showed seizure freedom or a ⩾50% reduction in seizure frequency. However, 11%–52% of patients experienced dizziness, pruritus, anxiety, or irritability, and only 12.5% of patients had to discontinue PER due to adverse drug reactions. According to the authors, PER is an effective and safe drug for BTRE treatment [55].

POTENTIAL MECHANISMS OF PERAMPANEL EFFICACY IN EPILEPSY TREATMENT

A comprehensive study of BTRE pathogenesis allows identifying new treatment targets with a lower risk of adverse drug reactions and drug interactions, improving the efficacy of therapy and the quality of life [13]. The oncogenesis and epileptogenesis are complex, multifactorial, and interrelated processes [8, 75]. Glutamate and its effects on ion-metabotropic receptors, such as AMPA, kainate, and NMDA receptors (N-methyl-D-aspartate) play an important role in epileptogenesis and progression of tumor growth in GBM [12, 13, 76]. AMPA receptors, which provide rapid excitatory transmission in the central nervous system, were found in GBM cells [77–79]. Increased glutamate secretion in MBG is known to promote tumor progression, the onset of epilepsy, neurodegeneration, and cognitive disorders [80]. Thus, the increase in glutamate secretion in MBG is accompanied by an increase in the expression and activation of AMPA receptors, enhancing seizure activity and neuronal excitotoxicity [15, 21, 80]. AMPA receptor activation increases the release of brain-derived neurotrophic factor (BDNF) and the number of synapses between peritumoral neurons and glioma cells, which contributes to tumor progression [12, 13, 80]. The latter is associated with activation of neuroligin 3 (NLGN3), which increases β3 integrin expression and GBM cell sensitivity to chemotherapy-induced apoptosis [22]. The expression of epidermal growth factor receptor (EGFR), fibroblast growth factor (FGFR), and vascular endothelial growth factor (VEGFR) increases, which is accompanied by the progression of tumor growth and invasiveness [10, 22]. The formation of AMPA-receptor-dependent neuron-glioma synapses leads to their electrochemical interaction and the formation of single neural circuits, contributing to the progression of tumor growth [79]. This is confirmed by intraoperative electrocorticography demonstrating increased excitability of the glioma-infiltrated cerebral cortex [79]. *In vitro* and *in vivo* studies have shown that AMPA receptor inhibition and/or mutations provide epilepsy control, suppress calcium-related tumor invasion and GBM growth [22, 78, 80].

Of note, glutamate is released by GBM cells via the cystine/glutamate transporter, solute carrier family 7 member 11 (SLC7A11, or xCT) [21, 75, 81], the expression of which is often increased in GBM cells [82, 83]. High levels of xCT correlate with a high frequency of epi-seizures in GBM patients [45, 75, 80]. Glutamate, by reducing cystine uptake via xCT, decreases the production of endogenous antioxidants, exacerbating the damaging effects of reactive oxygen species [13, 21]. High levels of glutamate, affecting depolarization processes, lead to an abnormal increase in intracellular calcium and consequently exacerbate excitotoxicity [12, 21, 75].

The astrocytic enzyme GLUL is known to convert glutamate to glutamine, reducing the glutamate level in the cell, which is accompanied by a decrease in seizure activity [84]. GLUL deficiency leads to glutamate accumulation and the onset of seizures, as evidenced by lower GLUL levels in GRE patients compared to GBM patients without epilepsy [22, 85]. A GLUL expression pattern has been shown to correlate with survival rates in GBM patients [22, 85].

The increase of Cl^- ions in glioma cells and in peritumoral tissue is important in MBG-related epileptogenesis [45, 86]. Injection of GABA into peritumoral tissues after glioma removal is accompanied by a >140% increase in the expression of Na-K2Cl-cotransporter type 1 (NKCC1), which mediates the penetration of Cl^- ions into neurons [45, 86]. Increased GABA levels around glioma cells may activate excitation rather than inhibition processes with increased epileptic activity in the peritumoral zone

[45, 86]. Increased Cl^- levels in glioma cells, oxidative stress, hypoxia, and acidosis contribute to tumor progression [21, 45, 72]. Given the important role of glutamate in tumor invasion and epileptogenesis in BTRE, PER, which inhibits AMPA receptors, is of particular interest [13, 47, 55]. It was shown that PER, by inhibiting the intracellular penetration of Na^+ and K^+ ions and preventing depolarization of neurons and glioma cells, can not only effectively control seizures in BTRE, but also suppress tumor progression [12, 13, 54]. PER also decreases glucose uptake, glutamate levels, and increases *GLUL* gene expression and activity [53, 67, 79].

The activation of apoptosis in malignant glioma cell lines, the ability to inhibit tumor cell migration, and the protective effect on healthy peritumoral tissues during chemoradiation are important aspects of the PER efficacy [37, 48, 69].

CONCLUSION

The experimental studies demonstrate that PER has the anti-tumor potential, does not reduce the efficacy of anti-tumor drugs and is even able to exhibit adjuvant properties in radiochemotherapy, which increases its importance in the treatment of BTRE patients [48, 67, 69].

Clinical trials, despite their small number and limited samples, indicate the potential efficacy of PER either alone or as an adjuvant AED in the treatment of BTRE patients [15, 71, 74].

Different studies have shown that the number of BTRE patients who responded to PER therapy ranged from 75% to 100%, with complete absence of seizures observed in 33.3%–94.4% and a ⩾50% reduction in seizure frequency in 12.5%–57% of patients [11, 46, 72].

The efficacy of PER in BTRE patients with IDH mutations/MGMT methylation remains inconclusive based on the available clinical data. Further studies are necessary to elucidate the potential benefits of PER in this patient population [13].

Data from most clinical studies indicate good tolerability of PER in BTRE patients, and the described adverse drug reactions are mild and do not require drug withdrawal [87, 88]. In BTRE patients, PER may cause adverse drug reactions such as increased irritability or hostility; therefore, it is not used at all or used with caution in patients with serious mental conditions [87, 88]. Aggression predictors include high doses of PER (8 mg/day or higher), psychotic/depressive symptoms, and variations in glutamate levels in the amygdala, hypothalamus, and periaqueductal gray matter [64, 89]. Finally, aggression and anger, and a number of symptoms (headache, dizziness, and anxiety) may be attributed to the tumor and its progression [43, 64]. It is essential to consider the time to the symptom onset and a PER dose administered [53, 88].

AED tolerance in BTRE patients may be influenced by chemoradiation, often exacerbating/provoking adverse drug reactions to AEDs [64].

The data available to date suggest that PER is an effective and safe drug that may be used as a new adjunctive treatment for controlling epi-seizures in BTRE patients, including those with refractory BTRE, and in patients with SMART syndrome.

Considering the significance of BTRE treatment, clinical efficacy and good tolerability of PER in BTRE patients, revealed anti-tumor effect, good compatibility with temozolomide, radioprotective effect on peritumoral tissues, further controlled studies involving a larger number of patients are needed to study in depth the mechanisms of the anti-convulsant and anti-tumor efficacy of PER in the treatment of BTRE patients.

ADDITIONAL INFO

Authors' contributions. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: Y. Wang, N.A. Mufazalova, L.F. Mufazalova, N.V. Ilyasova, R.R. Muradova, I.E. Kiyomov, L.Sh. Davurova, A.V. Samorodov — analysis of the obtained data, literature review, final correction; concept and design of the study, collection and processing of materials, fundraising.

Funding source. The study was carried out with the financial support of a grant from the Russian Science Foundation (project No. 23-25-00144 "Creation of a means for correcting depression in violation of cerebral circulation", Bashkir State Medical University of the Ministry of Health of Russia, RB).

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Личный вклад каждого автора: Юи Ванг, Н.А. Муфазалова, Л.Ф. Муфазалова, Н.В. Ильясова, Р.Р. Мурадова, И.Э. Киёмов, Л.Ш. Давурова, А.В. Самородов — анализ полученных данных, обзор литературы, внесение окончательной правки; концепция и дизайн исследования, сбор и обработка материалов, привлечение финансирования.

Источник финансирования. Исследование выполнено при финансовой поддержке гранта Российского научного фонда (проект № 23-25-00144 «Создание средства для коррекции депрессии при нарушении мозгового кровообращения», ФГБОУ ВО «Башкирский государственный медицинский университет» Минздрава России).

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

REFERENCES

1. Ostrom QT, Patil N, Cioffi G, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the united states in 2013–2017. *Neuro Oncol*. 2020;22(S1):iv1–iv96. doi: 10.1093/neuonc/noaa200

2. Shabanov PD, Fisher EL, Urakov AL. Hydrogen peroxide formulations and methods of their use for blood oxygen saturation. *J Med Pharm Allied Sci*. 2022;11:5489–5493. doi: 10.55522/jmpas.V11I6.4604

3. Hey G, Rao R, Carter A, et al. Ligand-gated ion channels: Prognostic and therapeutic implications for gliomas. *J Pers Med*. 2023;13(5):853. doi: 10.3390/jpm13050853

4. Gretskikh KV, Tokarev AS. High-grade gliomas: a literature review. Part 1. Epidemiology, classification and approaches to combination treatment. *Russian journal of neurosurgery*. 2021;23(1):124–134. EDN: UDKRQA doi: 10.17650/1683-3295-2021-23-1-124-134

5. Jahangir M, Nicholas GA, Mohtashem S., editors. *Epidemiology of brain and spinal tumors. 1st ed*. Academic Press; 2021. P. 129–145.

6. Heugenhauser J, Iglseder S, Muigg A, et al. Perampanel in brain tumor and SMART-syndrome related epilepsy — A single institutional experience. *J Neurol Sci*. 2021;423:117386. doi: 10.1016/j.jns.2021.117386

7. Ius T, Pauletto G, Tomasino B, et al. Predictors of postoperative seizure outcome in low grade glioma: from volumetric analysis to molecular stratification. *Cancers (Basel)*. 2020;12(2):397. doi: 10.3390/cancers12020397

8. Rudà R, Mo F, Pellerino A. Epilepsy in brain metastasis: an emerging entity. *Curr Treat Options Neurol*. 2020;22(2):6 doi: 10.1007/s11940-020-0613-y

9. Urakov AL, Shabanov PD. Opioid, cannabinoid, cocaine, and methamphetamine epidemics: History, risk factors associated with them, and characteristics of drug action. *Psychopharmacology and biological narcology*. 2023;14(4):251–262. EDN: RSBFCF doi: 10.17816/phbn568586

10. Sánchez-Villalobos JM, Aledo-Serrano Á, Villegas-Martínez I, et al. Epilepsy treatment in neuro-oncology: A rationale for drug choice in common clinical scenarios. *Front Pharmacol*. 2022;13:991244. doi: 10.3389/fphar.2022.991244

11. Vecht C, Duran-Peña A, Houillier C, et al. Seizure response to perampanel in drug-resistant epilepsy with gliomas: Early observations. *J Neurooncol*. 2017;133:603–607. doi: 10.1007/s11060-017-2473-1

12. Wirsching H-G, Weller M. Does neuronal activity promote glioma progression? *Trends Cancer*. 2020;6(1):1–3. doi: 10.1016/j.trecan.2019.11.002

13. Tabaee Damavandi P, Pasini F, Fanella G, et al. Perampanel in brain tumor-related epilepsy: A systematic review. *Brain Sci*. 2023;13(2):326. doi: 10.3390/brainsci13020326

14. Cacho-Diaz B, San-Juan D, Salmeron K, et al. Choice of antiepileptic drugs affects the outcome in cancer patients with seizures. *Clin Transl Oncol*. 2018;20(12):1571–1576. doi: 10.1007/s12094-018-1892-6

15. Coppola A, Zarabla A, Maialetti A, et al. Perampanel confirms to be effective and well-tolerated as an add-on treatment in patients with brain tumor-related epilepsy (PERADET study) front. *Neurol*. 2020;11:592. doi: 10.3389/fneur.2020.00592

16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PloS Med*. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097

17. Alifieris C, Trafalis DT. Glioblastoma multiforme: Pathogenesis and treatment. *Pharmacol Ther*. 2015;152:63–82. doi: 10.1016/j.pharmthera.2015.05.005

18. Hu S, Kao H-Y, Yang T, Wang Y. Early and Bi-hemispheric seizure onset in a rat glioblastoma Multiforme model. *Neurosci Lett*. 2022;766:36351. doi: 10.1016/j.neulet.2021.136351

19. Kalyango K, Dyachenko AA, Bogdanov DV, et al. Increment of the incidence of glioblastoma following decrease in the incidence of brain tumors in 2000–2020: a population-based registry study. *Burdenko's Journal of Neurosurgery*. 2022;86(5):2836. EDN: GHQEXS doi: 10.17116/neiro20228605128

20. Laghari AA, Ahmed SI, Qadeer N, Shamim MS. Choice of therapeutic anti-seizure medication in patients with brain tumour. *J Pak Med Assoc*. 2019;69:442–444.

21. Lange F, Hörnschemeyer J, Kirschstein T. Glutamatergic mechanisms in glioblastoma and tumor-associated epilepsy. *Cells*. 2021;10(5):1226. doi: 10.3390/cells10051226

22. Shabanov PD, Nozdrachev AD, Lebedev AA, Lebedev VA. Neurochemical organization of the brain reinforcing systems. *Russian Journal of Physiology*. 2000;86(8):935–945.

23. Schaff LR, Mellinghoff IK. Glioblastoma and other primary brain malignancies in adults: A review. *JAMA*. 2023;329(7):574–587. doi: 10.1001/jama.2023.0023

24. Solomons MR, Jaunmuktane Z, Weil RS, et al. Seizure outcomes and survival in adult low-grade glioma over 11 years: living longer and better. *Neurooncol Pract*. 2020;7(2):196–201. doi: 10.1093/nop/npz056

25. van der Meer PB, Taphoorn MJB, Koekkoek JAF. Management of epilepsy in brain tumor patients. *Curr Opin Oncol*. 2022;34(6): 685–690. doi: 10.1097/CCO.0000000000000876

26. Seidel S, Wehner T, Miller D, et al. Brain tumor related epilepsy: pathophysiological approaches and rational management of antiseizure medication. *Neurol Res Pract*. 2022;4(1):45. doi: 10.1186/s42466-022-00205-9

27. Englot DJ, Berger MS, Chang EF, Garcia PA. Characteristics and treatment of seizures in patients with high-grade glioma: a review. *Neurosurg Clin N Am*. 2012;23(2):227–235. doi: 10.1016/j.nec.2012.01.009

28. Youngerman BE, Joiner EF, Wang X, et al. Patterns of seizure prophylaxis after oncologic neurosurgery. *J Neurooncol*. 2020;146(1):171–180. doi: 10.1007/s11060-019-03362-1

29. Maialetti A, Maschio M, Zarabla A, et al. Multimodal pathway for brain tumor-related epilepsy patients: Observational study. *Acta Neurol Scand*. 2020;141(6):450–462. doi: 10.1111/ane.13228

30. Hills KE, Kostarelos K, Wykes RC. Converging mechanisms of epileptogenesis and their insight in glioblastoma. *Front Mol Neurosci*. 2022;15:903115. doi: 10.3389/fnmol.2022.903115

31. Airapetov MI, Eresko SO, Lebedev AA. Expression of the growth hormone secretagogue receptor 1a (GHS-R1a) in the brain. *Physiol Rep*. 2021;9(21):e15113. doi 10.14814/phy2.15113

32. Stella M, Baiardi G, Pasquariello S, et al. Antitumor potential of antiepileptic drugs in human glioblastoma: pharmacological targets and clinical benefits. *Biomedicines*. 2023;11(2):582. doi: 10.3390/biomedicines11020582

33. Liang S, Fan X, Zhao M, et al. Clinical practice guidelines for the diagnosis and treatment of adult diffuse glioma-related epilepsy. *Cancer Med*. 2019;8(10):4527–4535. doi: 10.1002/cam4.2362
34. Ryu JY, Min KL, Chang MJ. Effect of anti-epileptic drugs on the survival of patients with glioblastoma multiforme: A retrospective, single-center study. *PLoS ONE*. 2019;14:0225599. doi: 10.1371/journal.pone.0225599
35. Chen DY, Chen CC, Crawford JR, Wang SG. Tumor-related epilepsy: epidemiology, pathogenesis and management. *J Neurooncol*. 2018;139:13–21. doi: 10.1007/s11060-018-2862-0
36. Dührsen L, Sauvigny T, Ricklefs FL, et al. Seizures as presenting symptom in patients with glioblastoma. *Epilepsia*. 2019;60(1): 149–154. doi: 10.1111/epi.14615
37. Yagi C, Tatsuoka J, Sano E, et al. Antitumor effects of antiepileptic drugs in malignant glioma cells. *Oncol Rep*. 2022;48(6):216. doi: 10.3892/or.2022.8431
38. Ahmadipour Y, Rauschenbach L, Santos A, et al. Preoperative and early postoperative seizures in patients with glioblastoma — two sides of the same coin? *Neurooncol Adv*. 2020;3(1):vdaa158. doi: 10.1093/noajnl/vdaa158
39. de Bruin ME, van der Meer PB, Dirven L, et al. Efficacy of antiepileptic drugs in glioma patients with epilepsy: a systematic review. *Neurooncol Pract*. 2021;8(5):501–517. doi: 10.1093/nop/npab030
40. Wach J, Güresir Á, Hamed M, et al. Impact of levetiracetam treatment on 5-aminolevulinic acid fluorescence expression in IDH1 wild-type glioblastoma. *Cancers (Basel)*. 2022;14(9):2134. doi: 10.3390/cancers14092134
41. Sachdev B, Rees J. Incidentalomas to glioblastoma multiforme. *Oxf Med Case Rep*. 2014;2014(5):96–97. doi: 10.1093/omcr/omu036
42. Zheng Y, Yang Y, Ng MH, et al. Effect of perioperative seizures on mortality and recurrence in patients with brain metastases. *Front Oncol*. 2022;12:1048304. doi: 10.3389/fonc.2022.1048304
43. Armstrong TS, Grant R, Gilbert MR, et al. Epilepsy in glioma patients: Mechanisms, management, and impact of anticonvulsant therapy. *Neuro-Oncology*. 2016;18(6):779–789. doi: 10.1093/neuonc/nov269
44. Cucchiara F, Ferraro S, Luci G, Bocci G. Relevant pharmacological interactions between alkylating agents and antiepileptic drugs: Preclinical and clinical data. *Pharmacol Res*. 2022;175:105976. doi: 10.1016/j.phrs.2021.105976
45. Lebedeva AV, Burd SG, Vlasov PN, et al. Treatment of epilepsy associated with primary and metastatic brain tumors. *Epilepsy and paroxysmal conditions*. 2021;13(3):286–304. EDN: ZQEZOA doi: 10.17749/2077-8333/epi.par.con.2021.099
46. Chonan M, Saito R, Kanamori M, et al. Experience of low dose perampanel to add-on in glioma patients with levetiracetam-uncontrollable epilepsy. *Neurol Med Chir*. 2020;60(1):37–44. doi: 10.2176/nmc.oa.2018-0245
47. Mufazalova NA, Valeeva LA, Mufazalova LF, Batrakova KV. *Undesirable drug reactions. Drug interactions*. Antiepileptic drugs. Ufa: Print+; 2021. (In Russ.)
48. Tatsuoka J, Sano E, Hanashima Y, et al. Anti-tumor effects of perampanel in malignant glioma cells. *Oncol Lett*. 2022;24(6):421. doi: 10.3892/ol.2022.13541
49. Ogunsakin O, Tumenta T, Louis-Jean S, et al. Levetiracetam induced behavioral abnormalities in a patient with seizure disorder: a diagnostic challenge. *Case Rep Psychiatry*. 2020;2020:8883802. doi: 10.1155/2020/8883802
50. Chen J-S, Clarke R, Haddad AF, et al. The effect of levetiracetam treatment on survival in patients with glioblastoma: a systematic review and meta-analysis. *J Neurooncol*. 2022;156(2):257–267. doi: 10.1007/s11060-021-03940-2
51. Kanner AM, Bicchi MM. Antiseizure medications for adults with epilepsy: A review. *JAMA*. 2022;327(13):1269–1281. doi: 10.1001/jama.2022.3880
52. Mayer J, Kirschstein T, Resch T, et al. Perampanel attenuates epileptiform phenotype in C6 glioma. *Neurosci Lett*. 2020;715:134629. doi: 10.1016/j.neulet.2019.134629
53. Piña-Garza JE, Rosenfeld W, Saeki K, et al. Efficacy and safety of adjunctive perampanel in adolescent patients with epilepsy: Post hoc analysis of six randomized studies. *Epilepsy Behav*. 2020;104:106876. doi: 10.1016/j.yebeh.2019.106876
54. Lavu A, Aboulatta L, Abou-Setta AM, et al. Efficacy and safety of perampanel in epilepsy: A systematic review and meta-analysis of randomised controlled trials. *Seizure*. 2022;102:54–60. doi: 10.1016/j.seizure.2022.09.020
55. Rossi J, Cavallieri F, Bassi MC, et al. Efficacy and tolerability of perampanel in brain tumor-related epilepsy: A systematic review. *Biomedicines*. 2023;11(3):651. doi: 10.3390/biomedicines11030651
56. Steinhoff BJ, Klein P, Klitgaard H, et al. Behavioral adverse events with brivaracetam, levetiracetam, perampanel, and topiramate: A systematic review. *Epilepsy Behav*. 2021;118:107939. doi: 10.1016/j.yebeh.2021.107939
57. Sagar P, Wawryk O, Vogrin S, et al. Efficacy and tolerability of adjuvant perampanel: an Australian multicenter real-world observational study in refractory focal and generalized epilepsy syndromes. *Epilepsy Behav*. 2021;119:107935. doi: 10.1016/j.yebeh.2021.107935
58. French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia*. 2013;54(1): 117–125. doi: 10.1111/j.1528-1167.2012.03638.x
59. Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology*. 2012;78(18):1408–1415. doi: 10.1212/WNL.0b013e318254473a
60. Kwan P, Brodie MJ, Laurenza A, et al. Analysis of pooled phase III trials of adjunctive perampanel for epilepsy: Impact of mechanism of action and pharmacokinetics on clinical outcomes. *Epilepsy Res*. 2015;117:117–124. doi: 10.1016/j.eplepsyres.2015.09.002
61. Gidal BE, Ferry J, Majid O, Hussein Z. Concentration-effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures. *Epilepsia*. 2013;54(8):1490–1497. doi: 10.1111/epi.12240
62. Lattanzi S, Cagnetti C, Foschi N, et al. Adjunctive perampanel in older patients with epilepsy: A multicenter study of clinical practice. *Drugs Aging*. 2021;38(7):603–610. doi: 10.1007/s40266-021-00865-3
63. Witt JA, Helmstaedter C. The impact of perampanel on cognition: A systematic review of studies employing standardized tests in patients with epilepsy. *Seizure*. 2022;94:107–111. doi: 10.1016/j.seizure.2021.12.001
64. Akyüz E, Köklü B, Ozenen C, et al. Elucidating the potential side effects of current anti-seizure drugs for epilepsy. *Curr Neuropharmacol*. 2021;19(11):1865–1883. doi: 10.2174/1570159X19666210826125341
65. Cunningham M. Targeting elevated glutamate in brain tumour related epilepsy. *Epilepsia*. 2016;57(S2):226. doi: 10.1111/epi.13610

66. Lai M-C, Tzeng R-C, Huang C-W, Wu S-N. The novel direct modulatory effects of perampanel, an antagonist of AMPA receptors, on voltage-gated sodium and M-type potassium currents. *Biomolecules*. 2019;9(10):638. doi: 10.3390/biom9100638
67. Lange F, Weßlau K, Porath K, et al. AMPA receptor antagonist perampanel affects glioblastoma cell growth and glutamate release *in vitro*. *PLoS ONE*. 2019;14:0211644. doi: 10.1371/journal.pone.0211644
68. Salmaggi A, Corno C, Maschio M, et al. Synergistic effect of perampanel and temozolomide in human glioma cell lines. *J Pers Med*. 2021;11:390. doi: 10.3390/jpm11050390
69. Lange F, Hartung J, Liebelt C, et al. Perampanel add-on to standard radiochemotherapy *in vivo* promotes neuroprotection in a Rodent F98 glioma model. *Front Neurosci*. 2020;14:598266. doi: 10.3389/fnins.2020.598266
70. Rösche J, Piek J, Hildebrandt G, et al. Perampanel in the treatment of a patient with glioblastoma multiforme without IDH1 mutation and without MGMT promotor methylation. *Neurol Psychiatr*. 2015;83(5):286–289. doi: 10.1055/s-0034-1399459
71. Izumoto S, Miyauchi M, Tasaki T, et al. Seizures and tumor progression in glioma patients with uncontrollable epilepsy treated with perampanel. *Anticancer Res*. 2018;38(7):4361–4366. doi: 10.21873/anticanres.12737
72. Dunn-Pirio AM, Woodring S, Lipp E, et al. Adjunctive perampanel for glioma-associated epilepsy. *Epilepsy Behav Case Rep*. 2018;10:114–117. doi: 10.1016/j.ebcr.2018.09.003
73. Maschio M, Pauletto G, Zarabla A, et al. Perampanel in patients with brain tumor-related epilepsy in real-life clinical practice: A retrospective analysis. *Int J Neurosci*. 2019;129(6):593–597. doi: 10.1080/00207454.2018.1555160
74. Maschio M, Zarabla A, Maialetti A, et al. Perampanel in brain tumor-related epilepsy: Observational pilot study. *Brain Behav*. 2020;10(6):01612. doi: 10.1002/brb3.1612
75. Prokudin MYu, Martynov BV, Yakovenko AI, et al. The role of glutamine synthetase expression and cystine/glutamate transporter (SLC7A11, XCT) in epilepsy pathogenesis of patients with supratentorial brain gliomas. *Epilepsy and paroxysmal conditions*. 2022;14(2):204–213. EDN: ZITPYJ doi: 10.17749/2077-8333/epi.par.con.2022.118
76. Müller-Längle A, Lutz H, Hehlgans S, et al. NMDA receptor-mediated signaling pathways enhance radiation resistance, survival and migration in glioblastoma cells — a potential target for adjuvant radiotherapy. *Cancers*. 2019;11(4):503. doi: 10.3390/cancers11040503
77. Brocke KS, Staufner C, Luksch H, et al. Glutamate receptors in pediatric tumors of the central nervous system. *Cancer Biol Ther*. 2010;9(6):455–468. doi: 10.4161/cbt.9.6.10898
78. Venkataramani V, Tanev DI, Strahle C, et al. Glutamatergic synaptic input to glioma cells drives brain tumour progression. *Nature*. 2019;573(7775):532–538. doi: 10.1038/s41586-019-1564-x
79. Venkatesh HS, Morishita W, Geraghty AC, et al. Electrical and synaptic integration of glioma into neural circuits. *Nature*. 2019;573(7775):539–545. doi: 10.1038/s41586-019-1563-y
80. Radin DP, Tsirka SE. Interactions between tumor cells, neurons, and microglia in the glioma microenvironment. *Int J Mol Sci*. 2020;21(22):8476. doi: 10.3390/ijms21228476
81. Lo M, Wang Y-Z, Gout PW. The x(c)-cystine/glutamate antiporter: A potential target for therapy of cancer and other diseases. *J Cell Physiol*. 2008;215(3):593–602. doi: 10.1002/jcp.21366
82. Takeuchi S, Wada K, Toyooka T, et al. Increased xCT expression correlates with tumor invasion and outcome in patients with glioblastomas. *Neurosurgery*. 2013;72(1):33–41. doi: 10.1227/NEU.0b013e318276b2de
83. Long Y, Tao H, Karachi A, Grippin AJ, et al. Dysregulation of glutamate transport enhances TREG function that promotes VEGF blockade resistance in glioblastoma. *Cancer Res*. 2020;80(3):499–509. doi: 10.1158/0008-5472.CAN-19-1577
84. Xuan DTM, Wu C-C, Wang W-J, et al. Glutamine synthetase regulates the immune microenvironment and cancer development through the inflammatory pathway. *Int J Med Sci*. 2023;20(1):35–49. doi: 10.7150/ijms.75625
85. Rosati A, Poliani PL, Todeschini A, et al. Glutamine synthetase expression as a valuable marker of epilepsy and longer survival in newly diagnosed glioblastoma multiforme. *Neuro Oncol*. 2013;15(5):618–625. doi: 10.1093/neuonc/nos338
86. Pallud J, Le Van Quyen M, Bielle F, et al. Cortical GABAergic excitation contributes to epileptic activities around human glioma. *Sci Transl Med*. 2014;6(244):244–289. doi: 10.1126/scitranslmed.3008065
87. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol*. 2018;75(3):279–286. doi: 10.1001/jamaneurol.2017.3949
88. Löscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: From bromide salts to cenobamate and beyond. *CNS Drugs*. 2021;35(9):935–963. doi: 10.1007/s40263-021-00827-8.
89. Lee S-A, Jeon JY, Kim H-W. Effect of perampanel on aggression in patients with refractory focal epilepsy: A 6-month longitudinal study. *Epilepsy Behav*. 2020;102:106658. doi: 10.1016/j.yebeh.2019.106658

СПИСОК ЛИТЕРАТУРЫ

1. Ostrom Q.T., Patil N., Cioffi G., et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the united states in 2013–2017 // Neuro Oncol. 2020. Vol. 22, N S1. P. iv1–iv96. doi: 10.1093/neuonc/noaa200
2. Shabanov P.D., Fisher E.L., Urakov A.L. Hydrogen peroxide formulations and methods of their use for blood oxygen saturation // J Med Pharm Allied Sci. 2022. Vol. 11. P. 5489–5493. doi: 10.55522/jmpas.V11I6.4604
3. Hey G., Rao R., Carter A., et al. Ligand-gated ion channels: Prognostic and therapeutic implications for gliomas // J Pers Med. 2023. Vol. 13, N 5. ID 853. doi: 10.3390/jpm13050853
4. Грецких К.В., Токарев А.С. Глиомы высокой степени злокачественности: обзор литературы. Часть 1. Эпидемиология, классификация и подходы к комбинированному лечению // Нейрохирургия. 2021. Т. 23, № 1. С. 124–134. EDN: UDKRQA doi: 10.17650/1683-3295-2021-23-1-124-134
5. Jahangir M., Nicholas G.A., Mohtashem S. Epidemiology of brain and spinal tumors. 1st ed. / M. Jahangir, G.A. Nicholas, S. Mohtashem, editors. Academic Press, 2021. P. 129–145.
6. Heugenhauser J., Iglseder S., Muigg A., et al. Perampanel in brain tumor and SMART-syndrome related epilepsy — A single

institutional experience // J Neurol Sci. 2021. Vol. 423. ID 117386. doi: 10.1016/j.jns.2021.117386

7. Ius T., Pauletto G., Tomasino B., et al. Predictors of postoperative seizure outcome in low grade glioma: from volumetric analysis to molecular stratification // Cancers (Basel). 2020. Vol. 12, N 2. ID 397. doi: 10.3390/cancers12020397

8. Rudà R., Mo F., Pellerino A. Epilepsy in brain metastasis: an emerging entity // Curr Treat Options Neurol. 2020. Vol. 22, N 2. ID 6. doi: 10.1007/s11940-020-0613-y

9. Ураков А.Л., Шабанов П.Д. Опиоидная, каннабиноидная, кокаиновая и метамфетаминовая эпидемии. История, факторы риска, связанные с ними, и особенности действия наркотиков // Психофармакология и биологическая наркология. 2023. Т. 14, № 4. С. 251–262. EDN: RSBFCF doi: 10.17816/phbn568586

10. Sánchez-Villalobos J.M., Aledo-Serrano Á., Villegas-Martínez I., et al. Epilepsy treatment in neuro-oncology: A rationale for drug choice in common clinical scenarios // Front Pharmacol. 2022. Vol. 13. ID 991244. doi: 10.3389/fphar.2022.991244

11. Vecht C., Duran-Peña A., Houillier C., et al. Seizure response to perampanel in drug-resistant epilepsy with gliomas: Early observations // J Neurooncol. 2017. Vol. 133. P. 603–607. doi: 10.1007/s11060-017-2473-1

12. Wirsching H.-G., Weller M. Does neuronal activity promote glioma progression? // Trends Cancer. 2020. Vol. 6, N 1. P. 1–3. doi: 10.1016/j.trecan.2019.11.002

13. Tabaee Damavandi P., Pasini F., Fanella G., et al. Perampanel in brain tumor-related epilepsy: A systematic review // Brain Sci. 2023. Vol. 13, N 2. ID 326. doi: 10.3390/brainsci13020326

14. Cacho-Diaz B., San-Juan D., Salmeron K., et al. Choice of antiepileptic drugs affects the outcome in cancer patients with seizures // Clin Transl Oncol. 2018. Vol. 20, N 12. P. 1571–1576. doi: 10.1007/s12094-018-1892-6

15. Coppola A., Zarabla A., Maialetti A., et al. Perampanel confirms to be effective and well-tolerated as an add-on treatment in patients with brain tumor-related epilepsy (PERADET study) front // Neurol. 2020. Vol. 11. ID 592. doi: 10.3389/fneur.2020.00592

16. Moher D., Liberati A., Tetzlaff J., et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement // PloS Med. 2009. Vol. 6, N 7. ID e1000097. doi: 10.1371/journal.pmed.1000097

17. Alifieris C., Trafalis D.T. Glioblastoma multiforme: Pathogenesis and treatment // Pharmacol Ther. 2015. Vol. 152. P. 63–82. doi: 10.1016/j.pharmthera.2015.05.005

18. Hu S., Kao H.-Y., Yang T., Wang Y. Early and Bi-hemispheric seizure onset in a rat glioblastoma Multiforme model // Neurosci Lett. 2022. Vol. 766. ID 136351. doi: 10.1016/j.neulet.2021.136351

19. Кальянго К., Дяченко А.А., Богданов Д.В., и др. Рост заболеваемости глиобластомой на фоне уменьшения частоты опухолей головного мозга в 2000–2020 гг.: популяционное регистровое исследование // Вопросы нейрохирургии им. Н.Н. Бурденко. 2022. Т. 86, № 5. С. 2836. EDN: GHQEXS doi: 10.17116/neiro20228605128

20. Laghari A.A., Ahmed S.I., Qadeer N., Shamim M.S. Choice of therapeutic anti-seizure medication in patients with brain tumour // J Pak Med Assoc. 2019. Vol. 69. P. 442–444.

21. Lange F., Hörnschemeyer J., Kirschstein T. Glutamatergic mechanisms in glioblastoma and tumor-associated epilepsy // Cells. 2021. Vol. 10, N 5. ID 1226. doi: 10.3390/cells10051226

22. Shabanov P.D., Nozdrachev A.D., Lebedev A.A., Lebedev V.A. Neurochemical organization of the brain reinforcing systems // Russian Journal of Physiology. 2000. Vol. 86, N 8. P. 935–945.

23. Schaff L.R., Mellinghoff I.K. Glioblastoma and other primary brain malignancies in adults: A review // JAMA. 2023. Vol. 329, N 7. P. 574–587. doi: 10.1001/jama.2023.0023

24. Solomons M.R., Jaunmuktane Z., Weil R.S., et al. Seizure outcomes and survival in adult low-grade glioma over 11 years: living longer and better // Neurooncol Pract. 2020. Vol. 7, N 2. P. 196–201. doi: 10.1093/nop/npz056

25. van der Meer P.B., Taphoorn M.J.B., Koekkoek J.A.F. Management of epilepsy in brain tumor patients // Curr Opin Oncol. 2022. Vol. 34, N 6. P. 685–690. doi: 10.1097/CCO.0000000000000876

26. Seidel S., Wehner T., Miller D., et al. Brain tumor related epilepsy: pathophysiological approaches and rational management of antiseizure medication // Neurol Res Pract. 2022. Vol. 4, N 1. ID 45. doi: 10.1186/s42466-022-00205-9

27. Englot D.J., Berger M.S., Chang E.F., Garcia P.A. Characteristics and treatment of seizures in patients with high-grade glioma: a review // Neurosurg Clin N Am. 2012. Vol. 23, N 2. P. 227–235. doi: 10.1016/j.nec.2012.01.009

28. Youngerman B.E., Joiner E.F., Wang X., et al. Patterns of seizure prophylaxis after oncologic neurosurgery // J Neurooncol. 2020. Vol. 146, N 1. P. 171–180. doi: 10.1007/s11060-019-03362-1

29. Maialetti A., Maschio M., Zarabla A., et al. Multimodal pathway for brain tumor-related epilepsy patients: Observational study // Acta Neurol Scand. 2020. Vol. 141, N 6. P. 450–462. doi: 10.1111/ane.13228

30. Hills K.E., Kostarelos K., Wykes R.C. Converging mechanisms of epileptogenesis and their insight in glioblastoma // Front Mol Neurosci. 2022. Vol. 15. ID 903115. doi: 10.3389/fnmol.2022.903115

31. Airapetov M.I., Eresko S.O., Lebedev A.A. Expression of the growth hormone secretagogue receptor 1a (GHS-R1a) in the brain // Physiol Rep. 2021. Vol. 9, N 21. ID e15113. doi 10.14814/phy2.15113

32. Stella M., Baiardi G., Pasquariello S., et al. Antitumor potential of antiepileptic drugs in human glioblastoma: pharmacological targets and clinical benefits // Biomedicines. 2023. Vol. 11, N 2. ID 582. doi: 10.3390/biomedicines11020582

33. Liang S., Fan X., Zhao M., et al. Clinical practice guidelines for the diagnosis and treatment of adult diffuse glioma-related epilepsy // Cancer Med. 2019. Vol. 8, N 10. P. 4527–4535. doi: 10.1002/cam4.2362

34. Ryu J.Y., Min K.L., Chang M.J. Effect of anti-epileptic drugs on the survival of patients with glioblastoma multiforme: A retrospective, single-center study // PLoS ONE. 2019. Vol. 14. ID 0225599. doi: 10.1371/journal.pone.0225599

35. Chen D.Y., Chen C.C., Crawford J.R., Wang S.G. Tumor-related epilepsy: epidemiology, pathogenesis and management // J Neurooncol. 2018. Vol. 139. P. 13–21. doi: 10.1007/s11060-018-2862-0

36. Dührsen L., Sauvigny T., Ricklefs F.L., et al. Seizures as presenting symptom in patients with glioblastoma // Epilepsia. 2019. Vol. 60, N 1. P. 149–154. doi: 10.1111/epi.14615

37. Yagi C., Tatsuoka J., Sano E., et al. Antitumor effects of antiepileptic drugs in malignant glioma cells // Oncol Rep. 2022. Vol. 48, N 6. ID 216. doi: 10.3892/or.2022.8431

38. Ahmadipour Y., Rauschenbach L., Santos A., et al. Preoperative and early postoperative seizures in patients with glioblastoma —

two sides of the same coin? // Neurooncol Adv. 2020. Vol. 3, N 1. ID vdaa158. doi: 10.1093/noajnl/vdaa158
39. de Bruin M.E., van der Meer P.B., Dirven L., et al. Efficacy of antiepileptic drugs in glioma patients with epilepsy: a systematic review // Neurooncol Pract. 2021. Vol. 8, N 5. P. 501–517. doi: 10.1093/nop/npab030
40. Wach J., Güresir Á., Hamed M., et al. Impact of levetiracetam treatment on 5-aminolevulinic acid fluorescence expression in IDH1 wild-type glioblastoma // Cancers (Basel). 2022. Vol. 14, N 9. ID 2134. doi: 10.3390/cancers14092134
41. Sachdev B., Rees J. Incidentalomas to glioblastoma multiforme // Oxf Med Case Rep. 2014. Vol. 2014, N 5. P. 96–97. doi: 10.1093/omcr/omu036
42. Zheng Y., Yang Y., Ng M.H., et al. Effect of perioperative seizures on mortality and recurrence in patients with brain metastases // Front Oncol. 2022. Vol. 12. ID 1048304. doi: 10.3389/fonc.2022.1048304
43. Armstrong T.S., Grant R., Gilbert M.R., et al. Epilepsy in glioma patients: Mechanisms, management, and impact of anticonvulsant therapy // Neuro-Oncology. 2016. Vol. 18, N 6. P. 779–789. doi: 10.1093/neuonc/nov269
44. Cucchiara F., Ferraro S., Luci G., Bocci G. Relevant pharmacological interactions between alkylating agents and antiepileptic drugs: Preclinical and clinical data // Pharmacol Res. 2022. Vol. 175. ID 105976. doi: 10.1016/j.phrs.2021.105976
45. Лебедева А.В., Бурд С.Г., Власов П.Н., и др. Лечение эпилепсии, ассоциированной с первичными и метастатическими опухолями головного мозга // Эпилепсия и пароксизмальные состояния. 2021. Т. 13, № 3. С. 286–304. EDN: ZQEZOA doi: 10.17749/2077-8333/epi.par.con.2021.099
46. Chonan M., Saito R., Kanamori M., et al. Experience of low dose perampanel to add-on in glioma patients with levetiracetam-uncontrollable epilepsy // Neurol Med Chir. 2020. Vol. 60, N 1. P. 37–44. doi: 10.2176/nmc.oa.2018-0245
47. Муфазалова Н.А., Валеева Л.А., Муфазалова Л.Ф., Батракова К.В. Нежелательные лекарственные реакции. Взаимодействие лекарственных средств. Противоэпилептические препараты. Уфа: Принт+, 2021.
48. Tatsuoka J., Sano E., Hanashima Y., et al. Anti-tumor effects of perampanel in malignant glioma cells // Oncol Lett. 2022. Vol. 24, N 6. ID 421. doi: 10.3892/ol.2022.13541
49. Ogunsakin O., Tumenta T., Louis-Jean S., et al. Levetiracetam induced behavioral abnormalities in a patient with seizure disorder: a diagnostic challenge // Case Rep Psychiatry. 2020. Vol. 2020. ID 8883802. doi: 10.1155/2020/8883802
50. Chen J.-S., Clarke R., Haddad A.F., et al. The effect of levetiracetam treatment on survival in patients with glioblastoma: a systematic review and meta-analysis // J Neurooncol. 2022. Vol. 156, N 2. P. 257–267. doi: 10.1007/s11060-021-03940-2
51. Kanner A.M., Bicchi M.M. Antiseizure medications for adults with epilepsy: A review // JAMA. 2022. Vol. 327, N 13. P. 1269–1281. doi: 10.1001/jama.2022.3880
52. Mayer J., Kirschstein T., Resch T., et al. Perampanel attenuates epileptiform phenotype in C6 glioma // Neurosci Lett. 2020. Vol. 715. ID 134629. doi: 10.1016/j.neulet.2019.134629
53. Piña-Garza J.E., Rosenfeld W., Saeki K., et al. Efficacy and safety of adjunctive perampanel in adolescent patients with epilepsy: Post hoc analysis of six randomized studies // Epilepsy Behav. 2020. Vol. 104. ID 106876. doi: 10.1016/j.yebeh.2019.106876
54. Lavu A., Aboulatta L., Abou-Setta A.M., et al. Efficacy and safety of perampanel in epilepsy: A systematic review and meta-analysis of randomised controlled trials // Seizure. 2022. Vol. 102. P. 54–60. doi: 10.1016/j.seizure.2022.09.020
55. Rossi J., Cavallieri F., Bassi M.C., et al. Efficacy and tolerability of perampanel in brain tumor-related epilepsy: A systematic review // Biomedicines. 2023. Vol. 11, N 3. ID 651. doi: 10.3390/biomedicines11030651
56. Steinhoff B.J., Klein P., Klitgaard H., et al. Behavioral adverse events with brivaracetam, levetiracetam, perampanel, and topiramate: A systematic review // Epilepsy Behav. 2021. Vol. 118. ID 107939. doi: 10.1016/j.yebeh.2021.107939
57. Sagar P., Wawryk O., Vogrin S., et al. Efficacy and tolerability of adjuvant perampanel: an Australian multicenter real-world observational study in refractory focal and generalized epilepsy syndromes // Epilepsy Behav. 2021. Vol. 119. ID 107935. doi: 10.1016/j.yebeh.2021.107935
58. French J.A., Krauss G.L., Steinhoff B.J., et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305 // Epilepsia. 2013. Vol. 54, N 1. P. 117–125. doi: 10.1111/j.1528-1167.2012.03638.x
59. Krauss G.L., Serratosa J.M., Villanueva V., et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures // Neurology. 2012. Vol. 78, N 18. P. 1408–1415. doi: 10.1212/WNL.0b013e318254473a
60. Kwan P., Brodie M.J., Laurenza A., et al. Analysis of pooled phase III trials of adjunctive perampanel for epilepsy: Impact of mechanism of action and pharmacokinetics on clinical outcomes // Epilepsy Res. 2015. Vol. 117. P. 117–124. doi: 10.1016/j.eplepsyres.2015.09.002
61. Gidal B.E., Ferry J., Majid O., Hussein Z. Concentration-effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures // Epilepsia. 2013. Vol. 54, N 8. P. 1490–1497. doi: 10.1111/epi.12240
62. Lattanzi S., Cagnetti C., Foschi N., et al. Adjunctive perampanel in older patients with epilepsy: A multicenter study of clinical practice // Drugs Aging. 2021. Vol. 38, N 7. P. 603–610. doi: 10.1007/s40266-021-00865-3
63. Witt J.A., Helmstaedter C. The impact of perampanel on cognition: A systematic review of studies employing standardized tests in patients with epilepsy // Seizure. 2022. Vol. 94. P. 107–111. doi: 10.1016/j.seizure.2021.12.001
64. Akyüz E., Köklü B., Ozenen C., et al. Elucidating the potential side effects of current anti-seizure drugs for epilepsy // Curr Neuropharmacol. 2021. Vol. 19, N 11. P. 1865–1883. doi: 10.2174/1570159X19666210826125341
65. Cunningham M. Targeting elevated glutamate in brain tumour related epilepsy // Epilepsia. 2016. Vol. 57, N S2. P. 226. doi: 10.1111/epi.13610
66. Lai M.-C., Tzeng R.-C., Huang C.-W., Wu S.-N. The novel direct modulatory effects of perampanel, an antagonist of AMPA receptors, on voltage-gated sodium and M-type potassium currents // Biomolecules. 2019. Vol. 9, N 10. ID 638. doi: 10.3390/biom9100638
67. Lange F., Weßlau K., Porath K., et al. AMPA receptor antagonist perampanel affects glioblastoma cell growth and glutamate release *in vitro* // PLoS ONE. 2019. Vol. 14. ID 0211644. doi: 10.1371/journal.pone.0211644
68. Salmaggi A., Corno C., Maschio M., et al. Synergistic effect of perampanel and temozolomide in human glioma cell lines // J Pers Med. 2021. Vol. 11. ID 390. doi: 10.3390/jpm11050390
69. Lange F., Hartung J., Liebelt C., et al. Perampanel add-on to standard radiochemotherapy *in vivo* promotes neuroprotection in

a Rodent F98 glioma model // Front Neurosci. 2020. Vol. 14. ID 598266. doi: 10.3389/fnins.2020.598266
70. Rösche J., Piek J., Hildebrandt G., et al. Perampanel in the treatment of a patient with glioblastoma multiforme without IDH1 mutation and without MGMT promotor methylation // Neurol Psychiatr. 2015. Vol. 83, N 5. P. 286–289. doi: 10.1055/s-0034-1399459
71. Izumoto S., Miyauchi M., Tasaki T., et al. Seizures and tumor progression in glioma patients with uncontrollable epilepsy treated with perampanel // Anticancer Res. 2018. Vol. 38, N 7. P. 4361–4366. doi: 10.21873/anticanres.12737
72. Dunn-Pirio A.M., Woodring S., Lipp E., et al. Adjunctive perampanel for glioma-associated epilepsy // Epilepsy Behav Case Rep. 2018. Vol. 10. P. 114–117. doi: 10.1016/j.ebcr.2018.09.003
73. Maschio M., Pauletto G., Zarabla A., et al. Perampanel in patients with brain tumor-related epilepsy in real-life clinical practice: A retrospective analysis // Int J Neurosci. 2019. Vol. 129, N 6. P. 593–597. doi: 10.1080/00207454.2018.1555160
74. Maschio M., Zarabla A., Maialetti A., et al. Perampanel in brain tumor-related epilepsy: Observational pilot study // Brain Behav. 2020. Vol. 10, N 6. ID 01612. doi: 10.1002/brb3.1612
75. Прокудин М.Ю., Мартынов Б.В., Яковенко А.И., и др. Роль экспрессии глутамин-синтетазы и транспортера цистин/глутамата (SLC7A11, xCT) в патогенезе развития эпилепсии у пациентов с супратенториальными глиомами головного мозга // Эпилепсия и пароксизмальные состояния. 2022. Т. 14, № 2. С. 204–213. EDN: ZITPYJ doi: 10.17749/2077-8333/epi.par.con.2022.118
76. Müller-Längle A., Lutz H., Hehlgans S., et al. NMDA receptor-mediated signaling pathways enhance radiation resistance, survival and migration in glioblastoma cells — a potential target for adjuvant radiotherapy // Cancers. 2019. Vol. 11, N 4. ID 503. doi: 10.3390/cancers11040503
77. Brocke K.S., Staufner C., Luksch H., et al. Glutamate receptors in pediatric tumors of the central nervous system // Cancer Biol Ther. 2010. Vol. 9, N 6. P. 455–468. doi: 10.4161/cbt.9.6.10898
78. Venkataramani V., Tanev D.I., Strahle C., et al. Glutamatergic synaptic input to glioma cells drives brain tumour progression // Nature. 2019. Vol. 573, N 7775. P. 532–538. doi: 10.1038/s41586-019-1564-x
79. Venkatesh H.S., Morishita W., Geraghty A.C., et al. Electrical and synaptic integration of glioma into neural circuits // Nature. 2019. Vol. 573, N 7775. P. 539–545. doi: 10.1038/s41586-019-1563-y
80. Radin D.P., Tsirka S.E. Interactions between tumor cells, neurons, and microglia in the glioma microenvironment // Int J Mol Sci. 2020. Vol. 21, N 22. ID 8476. doi: 10.3390/ijms21228476
81. Lo M., Wang Y.-Z., Gout P.W. The x(c)-cystine/glutamate antiporter: A potential target for therapy of cancer and other diseases // J Cell Physiol. 2008. Vol. 215, N 3. P. 593–602. doi: 10.1002/jcp.21366
82. Takeuchi S., Wada K., Toyooka T., et al. Increased xCT expression correlates with tumor invasion and outcome in patients with glioblastomas // Neurosurgery. 2013. Vol. 72, N 1. P. 33–41. doi: 10.1227/NEU.0b013e318276b2de
83. Long Y., Tao H., Karachi A., Grippin A.J., et al. Dysregulation of glutamate transport enhances TREG function that promotes VEGF blockade resistance in glioblastoma // Cancer Res. 2020. Vol. 80, N 3. P. 499–509. doi: 10.1158/0008-5472.CAN-19-1577
84. Xuan D.T.M., Wu C.-C., Wang W.-J., et al. Glutamine synthetase regulates the immune microenvironment and cancer development through the inflammatory pathway // Int J Med Sci. 2023. Vol. 20, N 1. P. 35–49. doi: 10.7150/ijms.75625
85. Rosati A., Poliani P.L., Todeschini A., et al. Glutamine synthetase expression as a valuable marker of epilepsy and longer survival in newly diagnosed glioblastoma multiforme // Neuro Oncol. 2013. Vol. 15, N 5 P. 618–625. doi: 10.1093/neuonc/nos338
86. Pallud J., Le Van Quyen M., Bielle F., et al. Cortical GABAergic excitation contributes to epileptic activities around human glioma // Sci Transl Med. 2014. Vol. 6, N 244. P. 244–289. doi: 10.1126/scitranslmed.3008065
87. Chen Z., Brodie M.J., Liew D., Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study // JAMA Neurol. 2018. Vol. 75, N 3. P. 279–286. doi: 10.1001/jamaneurol.2017.3949
88. Löscher W., Klein P. The pharmacology and clinical efficacy of antiseizure medications: From bromide salts to cenobamate and beyond // CNS Drugs. 2021. Vol. 35, N 9 P. 935–963. doi: 10.1007/s40263-021-00827-8.
89. Lee S.-A., Jeon J.Y., Kim H.-W. Effect of perampanel on aggression in patients with refractory focal epilepsy: A 6-month longitudinal study // Epilepsy Behav. 2020. Vol. 102. ID 106658. doi: 10.1016/j.yebeh.2019.106658

AUTHORS' INFO

Yi Wang, PhD, Professor; ORCID: 0000-0001-9048-0092; e-mail: makval81@rambler.ru
Natalya A. Mufazalova, Dr. Sci. (Medicine), Professor; ORCID: 0000-0002-0656-3459; eLibrary SPIN: 4053-2051; e-mail: mufazalovanatalya@yandex.ru
Lyaysan F. Mufazalova, MD, Cand. Sci. (Medicine), Assistant Professor; ORCID: 0000-0001-8129-9320; eLibrary SPIN: 1542-2210; e-mail: lya-mufazalova@yandex.ru
Nailya V. Ilyasova; ORCID: 0009-0008-1774-9831; eLibrary SPIN: 4459-6602; e-mail: Na1lyasova@yandex.ru

ОБ АВТОРАХ

Юи Ванг, профессор; ORCID: 0000-0001-9048-0092; e-mail: makval81@rambler.ru
Наталья Альбертовна Муфазалова, д-р мед. наук, профессор; ORCID: 0000-0002-0656-3459; eLibrary SPIN: 4053-2051; e-mail: mufazalovanatalya@yandex.ru
Ляйсан Фагимовна Муфазалова, канд. мед. наук, доцент; ORCID: 0000-0001-8129-9320; eLibrary SPIN: 1542-2210; e-mail: lya-mufazalova@yandex.ru
Наиля Варисовна Ильясова; ORCID: 0009-0008-1774-9831; eLibrary SPIN: 4459-6602; e-mail: Na1lyasova@yandex.ru

AUTHORS' INFO

Railya R. Muradova; ORCID: 0000-0001-9202-0479;
e-mail: ismagilovaln@rambler.ru
Ikhtier E. Kiyomov; ORCID: 0009-0004-7387-7740;
e-mail: lukmanova.gulnur@mail.ru
Laylo Sh. Davurova; ORCID: 0009-0009-1396-1744;
e-mail: anikolaev1957@rambler.ru

***Aleksandr V. Samorodov,** MD, Dr. Sci. (Medicine), Assistant Professor; address: 3 Lenina st., Ufa, 450008, Russia;
ORCID: 0000-0001-9302-499X; eLibrary SPIN: 2396-1934;
e-mail: avsamorodov@gmail.com

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

Раиля Рустамовна Мурадова; ORCID: 0000-0001-9202-0479;
e-mail: ismagilovaln@rambler.ru
Ихтиёр Эргашович Киёмов; ORCID: 0009-0004-7387-7740;
e-mail: lukmanova.gulnur@mail.ru
Лайло Шокир кизи Давурова; ORCID: 0009-0009-1396-1744;
e-mail: anikolaev1957@rambler.ru

***Александр Владимирович Самородов,** д-р мед. наук, доцент; адрес: Россия, 450008, Уфа, ул. Ленина, д. 3;
ORCID: 0000-0001-9302-499X; eLibrary SPIN: 2396-1934;
e-mail: avsamorodov@gmail.com