Trends in Cancer

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Review

Malignant glioma remodeling of neuronal circuits: therapeutic opportunities and repurposing of antiepileptic drugs

Cesar Nava Gonzales[1,3], Mikias B. Negussie[1,3], Saritha Krishna[1,2,3], Vardhaan S. Ambati[1], and Shawn L. Hervey-Jumper[1,2,*]

Tumor-associated epilepsy is the most common presenting symptom in patients diagnosed with diffuse gliomas. Recent evidence illustrates the requirement of synaptic activity to drive glioma proliferation and invasion. Class 1, 2, and 3 evidence is limited regarding the use of antiepileptic drugs (AEDs) as antitumor therapy in combination with chemotherapy. Furthermore, no central mechanism has emerged as the most targetable. The optimal timing of AED regimen remains unknown. Targeting aberrant neuronal activity is a promising avenue for glioma treatment. Clinical biomarkers may aid in identifying patients most likely to benefit from AEDs. Quality evidence is needed to guide treatment decisions.

Highlights

Malignant gliomas cause tumor-intrinsic and peritumoral neuronal hyperexcitability and hypersynchrony through paracrine-medicated factors and direct electrochemical synapses, subsequently driving malignant cell proliferation.

The requirement of synaptic activity for malignant glioma proliferation and invasion supports pharmacological targeting of aberrant neuronal activity as a promising avenue for glioma treatment.

Preclinical evidence suggests the FDA-approved antiepileptic drugs, gabapentin, talampanel, and valproic acid, may show promising antitumor activity.

No specific drug mechanism appears to provide a consistent survival benefit for glioma patients in a clinical setting, and the optimal timing of pharmacological therapy targeting activity-dependent malignant glioma proliferation remains unknown.

Epileptogenesis and oncogenesis

In the US population, three million adults are living with epilepsy (annual incidence of 67 per 100 000). Tumors are the leading cause, representing 17.5 cases of epilepsy per 100 000 per year [1]. In glioblastoma (GBM), the most common malignant tumor in the adult brain, seizures are the presenting symptom in two-thirds of cases, and 90% of patients experience seizures requiring medical management [2,3]. Close to half of GBM-induced epilepsy is resistant to first-line therapy, and medication-refractory seizures have a strong negative impact on cognition, quality of life, and survival. Compared with GBM, low- and high-grade astrocytomas harboring the isocitrate dehydrogenase (IDH) 1 or 2 mutations suffer from disproportionally high rates of epileptic seizures, imposing a substantial impact on quality of life and ability to work. There has been a litany of poorly performing or failed clinical trials of molecular therapies for glioma-associated epilepsy, and the only multi-institutional randomized studies of new epilepsy treatments over the past 5 years demonstrated a seizure freedom rate of only 35% [4].

A multitude of studies investigating the pathophysiology of epilepsy in glioma patients have demonstrated overlapping shared mechanistic pathways between tumor burden and epileptogenesis. At the molecular level, the epileptogenic-related process includes: (i) an imbalance of excitatory and inhibitory synaptic signals due to glutamate and GABA dysregulation; (ii) aberrant activity of voltage-gated sodium and calcium channels; and (iii) IDH mutation status – all shared relevant mechanisms in glioma development. In this regard, it is possible that drugs with antiepileptic properties could also affect the interlinked oncogenic pathways; therefore, representing a presently available treatment that could be repurposed to control both seizures and tumor growth and progression (Figure 1, Key figure). Here, we describe preclinical *in vitro* and *in vivo* data and clinical evidence regarding the antiproliferative potential of FDA approved AEDs currently prescribed for adult glioma patients, focusing on glioblastoma.

[1]Department of Neurological Surgery, University of California, San Francisco, CA, USA
[2]Weill Institute of Neurosciences, University of California, San Francisco, CA, USA
[3]These authors contributed equally.

*Correspondence: Shawn.hervey-jumper@ucsf.edu (S.L. Hervey-Jumper).

Key figure

AEDs target glioma activity

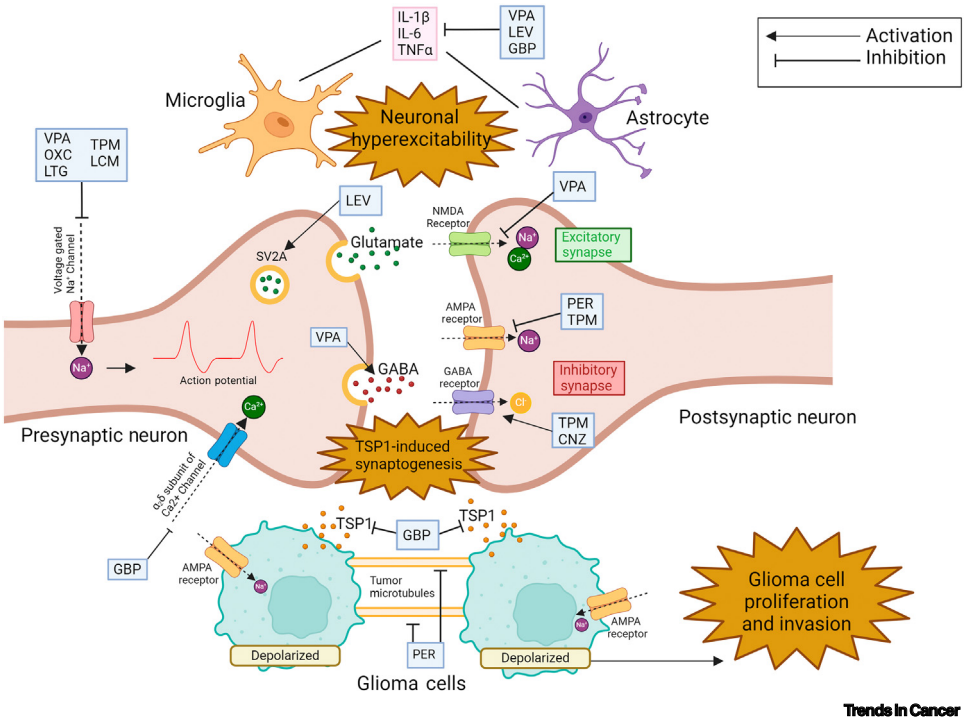

Figure 1. This figure illustrates the shared pathogenic mechanisms underlying the antitumor effects of AEDs. Neuronal hyperexcitability in the tumor microenvironment drives glioma progression via multiple mechanisms. As shown, various AEDs, such as VPA, OXC, LTG, TPM, and LCM target neuronal hyperexcitability by inhibiting the abnormal activity of voltage-gated sodium channels. Glutamate released from presynaptic terminals binds to AMPA and NMDA receptors expressed on the postsynaptic neuron and glioma cells to promote depolarization. PER and TPM, two noncompetitive AMPAR inhibitors, reduce the AMPA-mediated postsynaptic currents and hyperexcitability in both neurons and cancer cells, decreasing tumor cell proliferation and invasion. PER also contributes to reduced tumor growth by decreasing tumor microtube formation. Besides increasing the GABAergic activity, VPA blocks aberrant activation of NMDA receptors to decrease neuronal hyperexcitability and glioma cell proliferation. In response to exaggerated neuronal activity, glioma cells can produce the synaptogenic factor TSP-1. TSP-1-induced neuronal synaptogenesis is inhibited by GBP, which decreases neuronal hyperactivity and glioma cell proliferation. The synaptic release of glutamate into the tumor microenvironment also activates glial cells, namely microglia and astrocytes, to release pro-inflammatory cytokines, such as IL-1β, IL-6, and TNFα, inducing a proinflammatory state. AEDs such as VPA, LEV, and GBP further mediate neuronal hyperexcitability by inhibiting proinflammatory cytokines. Besides glutamatergic dysregulation, the reduction of GABAergic inhibitory activity also contributes to brain tumor-related epilepsy and glioma progression. $GABA_A$ receptor modulators, such as TPM and CNZ, target GABA-mediated chloride influx into the neurons to decrease neuronal excitability and subsequent glioma cell proliferation. Abbreviations: AED, antiepileptic drug; AMP, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNZ, clonazepam; GAB, γ-aminobutyric acid; GBP, gabapentin; IL, interleukin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; NMDA, N-methyl-D-aspartic acid; OXC, oxcarbazepine; PER, perampanel; SV2A, synaptic vesicle glycoprotein 2A; TNFα, tumor necrosis factor-α, TPM, topiramate; TSP1, thrombospondin-1; VPA, valproic acid. Figure created with BioRender.

Physiology and pharmacology of glioblastoma-related epilepsy

GBM, the most common and aggressive primary brain tumor, remains universally fatal, with a median overall survival (OS) of ~15 months [5]. While the standard of care, including maximal tumor resection followed by radiation and temozolomide (TMZ), demonstrates proven benefits, all

patients experience progression [6]. Structural and functional integration of malignant cells into neuronal circuits is critical to GBM treatment resistance [7]. Evidence from preclinical animal studies studying GBM-associated neuronal hyperexcitability demonstrated intratumoral and peritumoral mechanisms, including AMPA receptor-dependent neuron–glioma synaptic transmission [7,8]. Neuronal hyperexcitability results in the activity-regulated release of neuroligin-3 and brain-derived neurotrophic factor (BDNF), which are required for glioma progression and invasion. Neuroligin-3, in return, induces the expression of numerous synaptic genes within glioblastoma, which engage in synaptic communication [9]. It was subsequently discovered that the activity-dependent transmembrane potassium depolarizations between neurons and glioma cells are propagated throughout GBM by gap junctions between malignant cells, which form a network of tumor microtubes [10]. Depolarization of glioma membranes assessed by *in vivo* optogenetics promoted proliferation, shortening mouse survival [9]. In IDH mutant gliomas, neuronal hyperexcitability is associated with the activation of NMDA receptors via the accumulation of the d-2-hydroxyglutarate (2HG), a molecule structurally similar to the excitatory neurotransmitter glutamate [11]. Therefore, the hyperexcitability and hypersynchrony of tumor-intrinsic and peritumoral neurons and resulting neuronal activity-dependent GBM proliferation reported by *in vitro* and *in vivo* preclinical studies are critical processes worthy of therapeutic targeting in glioma patients.

Tumor-associated epilepsy is a hallmark of GBM, impacting patient morbidity and quality of life. Approximately one-third of patients experience inadequate seizure control [12].

Recently, an enhanced understanding of the role of synaptic drivers of malignant growth, together with the prognostic implications of GBM-related epilepsy, has prompted re-evaluation of the FDA-approved AED therapies targeting tumor growth. AEDs, such as levetiracetam (LEV) and valproic acid (VPA), have demonstrated synergy with alkylating chemotherapeutic agents without inducing cytochrome P450 enzymes while enzyme-inducing antiepileptic drugs (EIAEDs) contribute to drug–drug interactions that may interfere with chemotherapy metabolism [6,7].

Mechanisms of action and survival data

Given the diverse mechanisms of action of AEDs, understanding which AEDs may prove effective at inhibiting GBM progression may be essential to future care. Later, we synthesize current literature focused on the mechanisms of action and estimated survival benefit of commonly used AEDs as antitumor therapy for adult GBM patients (Table 1 and see the supplemental information online).

Levetiracetam

LEV selectively inhibits synchronized epileptiform activity through binding to synaptic vesicle protein 2A, regulating action-potential-dependent neurotransmitter release from excitatory presynaptic neurons [13] (Figure 1). The antineoplastic effect of LEV has primarily been attributed to its inhibitory action on the O6-methylguanine-DNA methyltransferase (MGMT) promoter, thereby sensitizing GBM cells to TMZ by activating apoptotic pathways. Moreover, LEV has diverse molecular targets involving calcium homeostasis, GABAergic signaling, and AMPA receptors, which could also contribute to the antitumor properties of LEV. A preclinical study found that LEV reduces GABAergic postsynaptic currents in diffuse intrinsic pontine glioma (DIPG) cells and attenuates glioma proliferation in patient-derived DIPG xenografts [14]. Furthermore, this study showed a tumor subtype-specific effect of LEV with the drug. Still, it showed no significant impact on the growth rate of hemispheric high-grade glioma patient-derived xenograft models [14]. However, in a recent study, *in vitro* treatment of neurons with LEV can impair neuronal activation and reduce the immunosuppressive M2 polarization of microglial cells [15]. A similar phenotype

Table 1. Summary of AEDs with clinical data targeting glioma proliferation

Drug	Mechanism of action	Related study	Study finding[a]	Evidence class[b]
Levetiracetam (LEV)	Selectively inhibits synchronized epileptiform activity through binding to synaptic vesicle protein 2A [9].	Rigamonti *et al*. [16]	No survival benefit	Class 3
		Ryu *et al*. [17]	Survival benefit	Class 3
		Kim *et al*. [18]	Survival benefit	Class 3
Lamotrigine (LTG)	Believed to inhibit voltage-gated sodium channels, stabilizes presynaptic neuronal membranes, and inhibits presynaptic glutamate and aspartate release [12].	Rigamonti *et al*. [16]	No survival benefit	Class 3
		van Opijnen *et al*. [22]	No survival benefit	Class 3
		Anastasaki *et al*. [23]	Reduces optic glioma (NF1) growth rate	Preclinical (mice)
Topiramate (TPM)	Encompasses blocking voltage gated sodium and calcium channels, inhibiting glutamate receptors, inhibiting mitochondrial carbonic anhydrase, and enhancing GABA activity [16].	Ryu *et al*. [17]	No survival benefit	Class 3
Valproic acid (VPA)	Voltage gated sodium channel blocker and t-type calcium channel blocker. May serve as a HDAC inhibitor, potentially synergizing with traditional chemotherapeutic agents. [17]	Rigamonti *et al*. [16]	No survival benefit	Class 3
		Yuan *et al*. [31]	Survival benefit	Class 1
		Guthrie *et al*. [37]	Survival Benefit	Class 3
Clonazepam (CNZ)	Long-acting and potent benzodiazepine, which acts on GABA-A receptors to increase the frequency of chloride channel opening, hyperpolarizing neurons and reducing neuronal firing. Also increases serotonin production.	Rigamonti *et al*. [16]	No survival benefit	Class 3
		Pallud *et al*. [29]	Possibly harmful due to chloride dysregulation in GBM	Preclinical (human tissue)
Talampanel	Noncompetitive antagonist of the AMPA receptor.	Grossman *et al*. [49]	Survival benefit	Class 2, 3
		Iwamoto *et al*. [50]	No survival benefit	Class 4
Gabapentin (GBP)/ pregabalin	α-2-δ ligands that were initially designed as GABA analogs but were found to have no activity on GABA receptors. New evidence suggests it serves as inhibitor thrombospondin-1 (α-2-δ-1 is one of the many neuronal receptors of thrombospondin-1). [3,23,24]	Rigamonti *et al*. [16]	No survival benefit	Class 3
		Krishna *et al*. [7]	Inhibits TSP-1 mediated remodeling human neuronal circuits by GBM	Preclinical (mice, human tissue, mice-human xenograft)
Oxcarbazepine (OXC)	Blockades of voltage-sensitive sodium channels. [57]	Knudsen-Baas *et al*. [38]	No survival benefit	Class 2, 3
		Dao Trong *et al*. [59]	Reduces proliferation of IDH mutant glioma cells	Preclinical (human tissue)

[a]Study findings are summarized and abridged. For detailed methods and findings, please refer to each individual study's manuscript.
[b]Classifications based on the 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence (verified by two authors). Preclinical studies were not classified based on evidence level.

was also observed *in vivo*. LEV treatment reversed the neuronal activity-mediated microglial M2 polarization and prevented GBM growth and progression in mice bearing glioma stem cells [15]. This discrepancy in the results on the antitumor effect of LEV on GBM between the two studies suggests a differential effect of the drug on the regulation of neuronal activity on stem-like glioma cells versus more differentiated GBM cells.

Despite emerging preclinical evidence, clinical observations on the survival benefit of LEV use are limited, and mixed results have been reported. Rigamonti *et al*. performed a retrospective study of 285 patients with newly diagnosed adult GBM. The study reported a nonsignificant increase in

OS among patients taking LEV compared with other AEDs (13 vs. 10.9 months, $P = 0.250$) [16]. Furthermore, no difference was found in OS between patients taking AEDs and those not taking AEDs (12.2 vs. 11.1 months, $P = 0.925$) [16]. However, a subsequent study by Ryu *et al*. reported prolonged OS in a cohort of patients treated with LEV (21 months) versus no LEV (16 months, $P < 0.001$) [17]. This study also reported a survival benefit of LEV in MGMT promoter methylated patients [$P = 0.006$; hazard ratio (HR), 0.174; 95% confidence interval (CI): 0.050–0.608], while no significant difference was observed in MGMT promoter unmethylated patients ($P = 0.623$; HR, 0.810; 95% CI: 0.351–1.874) [17]. Kim *et al*. also identified prolonged OS associated with patients taking LEV combined with chemotherapy (25.7 vs. 16.7 months, $P = 0.027$) [18]. It is worth noting that most of the clinical data showing survival differences of LEV in glioma patients are from retrospective analyses. Prospective clinical studies failed to show a survival benefit [19,20]. Therefore, the association between LEV and survival outcome remains questionable, and prospective randomized controlled trials are needed to address the efficacy of LEV in glioma patients.

Lamotrigine (LTG)

Although the mechanism of action of LTG is not completely understood, current understanding indicates LTG inhibits voltage-gated sodium channels, stabilizes presynaptic neuronal membranes, and inhibits presynaptic glutamate and aspartate release [21].

van Opijnen *et al*. performed a retrospective study of 139 patients with grade 2–4 gliomas; 44% were given LTG and 56% lacosamide (LCM) [22]. At the 12-month follow-up, there was no significant difference between the two drugs and no association with AED use and death (HR, 1.63; 95% CI: 0.51–5.26) [22]. Recent evidence suggests that LTG targets glioma-induced hyperexcitability and reduces the growth rate of optic pathway glioma in a preclinical model of neurofibromatosis 1 [23]. LTG-mediated targeting of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, a member of the voltage-gated cation channel family, could reverse the reduced channel activity-regulated neuronal hyperexcitability and decrease optic nerve proliferation and optic glioma progression *in vivo* [23]. HCN channels are overexpressed in breast cancer cells, and pharmacological modulation of HCN channels using LTG has been shown to exert strong antitumor activity on breast cancer [21,24]. Thus, LTG may represent a promising therapeutic option for achieving epileptic seizure control and more prolonged survival in patients with breast-to-brain metastasis.

Topiramate (TPM)

The mechanism of TPM action is broad and encompasses blocking voltage-gated sodium and calcium channels, inhibiting glutamate AMPA receptors, reducing mitochondrial carbonic anhydrase, and increasing inhibitory GABA activity [25]. Although the clinical efficacy of TPM has been well established in multiple epilepsy subtypes, the usage of this drug is not recommended in patients with high-grade gliomas because of its potential side effects, such as metabolic acidosis and blood toxicity [26,27]. A retrospective study examined 418 patients treated with surgery, radiotherapy, and chemotherapy with TMZ and AEDs. TPM showed no significant benefit in patient OS [17]. Recent mechanistic studies suggest that GBM can transition the neuronal hyperpolarizing inhibitory effect of GABA into excitatory action potentials because of dysregulated chloride transport [28,29]. In GBM, perineuronal neurons develop elevated intracellular chloride, rendering GABAergic input excitatory, as GABA activation leads to chloride efflux. Published studies to date have not stratified between GBM and IDH mutant World Health Organization (WHO) grade 4 astrocytomas. The nonsignificant patient survival result following the use of TPM could be attributed to heterogeneity in how GBM and peritumoral neurons utilize GABA for excitatory signaling or incomplete tumor molecular subclassification.

Valproic acid

In addition to blocking NMDA receptors, voltage-gated sodium channels, and t-type calcium channels, VPA inhibits histone deacetylase (HDAC) activity, potentially synergizing with traditional chemotherapeutic agents [30,31]. VPA can also enhance both serotonergic and dopaminergic transmission [32,33]. In general, both serotonin and dopamine have been linked to seizure pathogenesis, and increased extracellular levels of monoamines are reported to reduce seizure frequency [33,34]. Conversely, several studies have identified serotonergic and dopaminergic signaling as critical players in gliomagenesis and highlighted the ability of monoamines to interact with canonical growth factors, such as mitogen-activated protein kinase (MAPK) and AKT signaling pathways [35]. Therefore, although the monoaminergic modulation of VPA could further boost its antiepileptic action, a drug-induced increase in synaptic monoamine levels in the tumor microenvironment could exert an opposite effect on antitumor activity and survival outcomes of glioma patients. Thus, data on survival outcomes associated with VPA use in glioma patients are inconsistent, with some studies reporting prolonged survival in GBM patients [36,37].

By contrast, others show no association with survival [16,20,38]. Guthrie *et al*. retrospectively analyzed the survival of 236 patients with newly diagnosed GBM at a single institution [37]. In their cohort, 138 patients received no AED, 24 were prescribed VPA, 19 carbamazepine, 20 phenytoin, and nine another AED. All patients in the study received standard therapy, including surgery, radiation, and chemotherapy. AED choice was made based on the preference of each patient's treating physician, and Kaplan–Meier survival analyses were performed retrospectively. The study demonstrated that the AED-treated cohort had improved survival compared with patients not taking AEDs (Mantel–Cox log-rank χ^2 test 19.617, $P < 0.001$) [37]. Patients who were prescribed VPA had more prolonged survival than patients prescribed other AEDs ($P < 0.02$). Patients with GBM were 2.7 times more likely to die if they were not treated with VPA (Mantel–Cox log-rank χ^2 test 17.506, $P < 0.001$) [37]. The survival benefit associated with VPA is controversial because Rigamonti *et al*. subsequently found no survival benefit [16]. The study compared survival for patients receiving non-enzyme-inducing AEDs [NEIAEDs, e.g., VPA, LTG, clonazepam (CNZ), ethosuximide, and gabapentin (GBP)] over EIAEDs, (phenobarbitone, phenytoin, and carbamazepine) with a nonsignificant trend towards the superiority of NEIAEDs [16]. There are several preclinical reports of accelerated tumor development after VPA use in mammary and prostate cancer models [39,40]. Hence, a thorough examination of the tumor burden in the non-benefited cohort of glioma patients should be conducted to assess if the absence of survival outcome difference is linked to any adverse tumorigenic effects of VPA.

Clonazepam

CNZ is a long-acting and potent benzodiazepine. Benzodiazepines bind GABA-A receptors to increase the frequency of neuronal chloride channel opening, hyperpolarizing neurons and reducing neuronal firing [41]. In addition to its GABA-A agonism, CNZ acts to increase serotonin production. Recent evidence suggests that chloride dysregulation in GBM results in a paradoxical and harmful effect of benzodiazepines on GBM growth, although this topic warrants further study.

Perampanel (PER)

PER is an FDA-approved, noncompetitive AMPA-receptor inhibitor with blood–brain and tumor barrier penetrance. The drug has a terminal half-life of 48 h when given alone, which is pharmacokinetically favorable [42]. As an antiepileptic medication, PER reduces seizure frequency in 75–90% of patients (defined as the percentage of patients achieving seizure freedom or reduction of at least 50% of seizure frequency). Across published reports, 11–52% of patients experience drug intolerability, resulting in a drug retention rate of 56–83%. Several preclinical

studies have investigated the antineoplastic activity of PER in preclinical models. *In vitro* work using human glioma cell lines suggests several mechanisms, including reduced glucose uptake, reduced glutamate release, and increased apoptosis of glioma cells [43,44]. In *in vivo* experiments, two separate xenograft studies using rat C6 and F98 glioma cell lines reported similar results, where PER administration as a monotherapy [45] or in combination with chemoradiation [43] blocked tumor-associated epileptic events but failed to show a positive result on tumor burden and survival of GBM-bearing rats. By contrast, recent studies using murine models showed significant antiproliferative activity and survival benefits after treatment of glioma-xenografted mice with PER [46,47]. Furthermore, PER treatment suppressed tumor invasion *in vivo* by reducing neuronal-activity-driven increased branching and length of tumor microtubes [47]. These findings imply the shared mechanism of AMPA activation connecting seizure activity and glioma growth and further underscore the importance of AMPA-receptor-mediated glutamatergic neuron–glioma synaptic signaling in tumor progression. Clinical data on the potential antitumor activity of PER are limited. Clinical trials are underway to determine the clinical efficacy and tolerability of PER toward reducing tumor proliferation and tumor-associated synapses and improving progression-free survival for patients with recurrent GBM [48].

Talampanel

Talampanel is a noncompetitive antagonist of the AMPA receptor. Grossman *et al*. reviewed Phase 2 compared with Phase 3 European Organization for Research and Treatment of Cancer survival data [49]. Three hundred and sixty-five patients with GBM were given radiation therapy (RT) + TMZ or RT + TMZ + talampanel, poly-ICLC, or cilengitide. This study demonstrated that newly diagnosed patients with GBM had longer median OS with RT + TMZ + talampanel, poly ICLC, or cilengitide compared with RT + TMZ alone (19.6 vs. 14.6 months, $P < 0.0001$) [49]. Another study evaluated the utility of talampanel as a single agent in recurrent malignant glioma and found that the 30 patients tolerated the medication well. However, talampanel had no anti-glioma activity when given as monotherapy [50].

Gabapentin

GBP and pregabalin are α-2-δ ligands initially designed as GABA analogs but have been found to have no activity on GABA receptors [51]. They are utilized as AEDs and analgesics with a broad therapeutic index. GBP exerts its antiepileptic and analgesic actions by blocking thrombospondin (TSP) binding to the neuronal thrombospondin receptor α2δ-1 involved in excitatory synaptic transmission. Besides this known antiseizure activity, prior studies have reported the antiproliferative actions of GBP using human GBM [52] and mouse melanoma [53] cell lines. Recent work from our group also demonstrated the antitumor effects of GBP via inhibition of TSP-1 paracrine signaling of primary patient-derived GBM cells and in GBM xenografted mice [7]. This emerging preclinical evidence on the survival benefits of GBP use established the basis for a new ongoing clinical trial to investigate the potential of repurposing this FDA-approved drug to extend survival in patients [54].

Oxcarbazepine (OXC)

Like VPA, OXC targets HDAC activity and induces apoptosis by inhibiting the downstream PI3K-Akt-mTOR axis. OXC-mediated cell cycle arrest and apoptosis have been demonstrated in several prior studies [55,56]. Besides targeting apoptotic pathways, the antitumor effect of OXC observed in preclinical studies could also be linked to its antiepileptic mechanisms of action via blocking voltage-gated Na^+ channels and subsequent repetitive firing of action potentials in neural circuits. The neuroprotective action of OXC via inhibition of spontaneous neuronal activity and excitability has been demonstrated in several pathological models, including cerebral ischemia [57] and neuropathic pain [58]. Hence, it is conceivable that the anticancer effect of OXC in GBM may be mediated via

neuronal-activity-dependent mechanisms. Despite the preclinical evidence from multiple studies, clinical studies focused on the possible antitumor impact and survival benefits of OXC are scarce. A retrospective cohort study of 1263 patients with GBM diagnosed in Norway between 2004 and 2010 reviewed the utility of OXC in treating glioma patients and did not find a significant effect on OS [38]. OXC can reduce the proliferation of IDH mutant gliomas in preclinical models therefore stratification by IDH status may provide added value [59].

Lacosamide

LCM shares a similar mechanism of action as OXC and has been demonstrated to be an effective AED in brain tumor patients with epilepsy [60]. LCM selectively enhances the slow inactivation of voltage-gated sodium channels, thereby controlling the abnormal neuronal activity associated with epilepsy [61]. The antiepileptic action of LCM has also been linked to its inhibitory action on abnormal axon sprouting, a phenomenon implicated in epilepsy [61]. Specifically, LCM can suppress spontaneous recurrent seizures and reduce hippocampal neuronal loss in an animal model of status epilepticus by inhibiting collapsin response mediator protein 2 (CRMP2); an axon guidance protein involved in neurite outgrowth [62]. The CRMP-2-mediated excessive axon sprouting can lead to abnormal synapse formation and rewiring of neuronal circuits, contributing to epileptic events. Given the recent evidence supporting glioma-associated remodeling of neuronal circuit and tumor progression [7], it raises the intriguing question of whether the protective action of LCM, inhibiting axon sprouting, and synaptic remodeling could synergistically contribute to antineoplastic benefits and confer a survival advantage.

Immunomodulating properties of antiepileptic drugs

In addition to glutamatergic and GABAergic signal dysregulation, increased inflammatory responses characterized by robust activation of innate and adaptive immune systems can contribute to neuronal excitability and pro-epileptogenic inflammatory processes [63]. Excess glutamate release into the peritumoral microenvironment activates astrocytes and microglia, resulting in elevated concentrations of proinflammatory cytokines, such as interleukin (IL-1β, tumor necrosis factor (TNF)-α, and IL-6); all of which promote tumor growth, invasion, and seizure susceptibility [64] (Figure 1). Experimental evidence from several *in vitro* and *in vivo* preclinical studies has demonstrated the ability of AEDs such as LEV, VPA, and GBP to promote an anti-inflammatory state, accompanied by decreased neuronal activity and epileptic seizure occurrence [30,42,52,65,66]. In this regard, it is conceivable that glioma patients are more likely to benefit from treatment with AEDs that possess immunomodulating properties.

Concluding remarks

The requirement for neuronal activity to drive malignant glioma proliferation and invasion is an area of active basic and translational investigations. Many questions remain, such as the heterogeneity of activity-dependent growth within and between patients (see Outstanding questions). Furthermore, few biomarkers exist to identify patients with tumors that may be most prone to proliferate via neuronally driven mechanisms. These unanswered questions may explain some of the conflicting findings in the current body of evidence regarding the use of AEDs beyond the treatment of tumor-associated epilepsy to inhibit tumor growth. Tumors that proliferate via neuronally driven mechanisms incorporate into neuronal circuits and induce neuronal hyperexcitability. Clinically available drugs used to treat epilepsy may rescue neuronal hyperexcitability. Given neuronal excitability fuels glioma progression, the hope is that medicines that lower neuronal hyperexcitability will reduce glioma progression.

Recently published preclinical data supports the advancement of therapeutic clinical trials focused on using antiepileptics as tumor-directed therapies. However, it remains an open

Outstanding questions

Are all malignant gliomas equally dependent on activity-dependent mechanisms for proliferation and invasion? If not, what are the optimal biomarkers to identify vulnerable tumors?

Given that malignant gliomas promote neuronal hyperexcitability and hypersynchrony, does the frequency of clinical seizures in patients correlate with tumor growth and patient survival?

Knowing that synaptic activity driving malignant proliferation increases at the point of GBM recurrence, what would be the optimal timing of AED therapy?

How can we enhance emerging mechanistic insights uncovered by glioma neuroscience to develop promising new neuroactive drugs that may be advanced to therapeutic clinical trials?

question why the antitumorigenic effects of AEDs observed in animal models could not be translated into successful clinical trials to date. The risk of drug–drug interactions between antiepileptic and chemotherapeutic drugs is high, and the concurrent use of both drugs can complicate therapeutic management. There are several known mechanisms underlying the antiepileptic and antitumor effects of AEDs. Each drug can have a different outcome based on its targeting mechanism, and the positive therapeutic influences of certain AEDs could exceed those of others. For example, the acute inhibition of glutamatergic AMPA receptors by PER can directly influence excitatory neuronal signaling. In light of the emerging evidence of increased neuronal activity promoting tumor progression, the reduced neuronal activity exerted by PER could profoundly affect glioma cell proliferation and tumor progression. By contrast, extra caution should be taken when choosing AEDs, such as VPA, LEV, and TPM, that exert their antiseizure effect via enhanced GABAergic signaling. Emerging evidence points to a depolarizing excitatory action of GABA in glioma, which in turn could promote tumor growth, resulting in increased adverse events and mortality of patients with GBM. Therefore, clinicians should pay particular attention to the AED choice, and a thorough mechanistic understanding and focused evaluation of the therapeutic outcomes is warranted when prescribing AEDs to patients with glioma.

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Declaration of interests

The authors declare no competing interests.

Supplemental information

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