The complexities underlying epilepsy in people with glioblastoma

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Seizures are among the most common clinical signs in people with glioblastoma. Advances over the past 5 years, including new clinical trial data, have increased the understanding of why some individuals with glioblastoma are susceptible to seizures, how seizures manifest clinically, and what implications seizures have for patient management. The pathophysiology of epilepsy in people with glioblastoma relates to a combination of intrinsic epileptogenicity of tumour tissue, alterations in the tumour and peritumoural microenvironment, and the physical and functional disturbance of adjacent brain structures. Successful management of epilepsy in people with glioblastoma remains challenging; factors such as drug–drug interactions between cancer therapies and antiseizure medications, and medication side-effects, can affect seizure outcomes and quality of life. Advances in novel therapies provide some promise for people with glioblastoma; however, the effects of these therapies on seizures are yet to be fully determined. Looking forward, insights into electrical activity as a driver of tumour cell growth and the intrinsic hyperexcitability of tumour tissue might represent useful targets for treatment and disease modification. There is a pressing need for large randomised clinical trials in this field.

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Introduction

The interplay between seizures, brain tumours, and ultimately epilepsy in people with glioblastoma is multifactorial and complex.[1–3] Seizures are frequently the presenting symptom in people with glioblastoma, but they could occur at any point in the course of this malignant disease.[1–5] The varying causes of glioblastomas, their growth dynamics, specific location within the CNS, and molecular and cellular pathophysiology can have an effect on the type and severity of tumour-associated seizures.[1–3] Epilepsy could result from primary or metastatic brain tumours, as an unwanted consequence of tumour surgery, or as an adverse response to a specific anticancer treatment.[1–6] Undoubtedly, epilepsy in people with glioblastoma is detrimental to an individual's psychological, psychiatric, and physical wellbeing, with a major negative effect on quality of life. Optimal management of epilepsy in people with glioblastoma currently considers all these factors in a tailored approach to the individual; however, management of epilepsy is not well standardised.[1,2] Emerging data suggest that the management of epilepsy in people with glioblastoma with particular antiseizure medications not only might help improve seizure frequency but also could potentiate antitumour effects.[7–12]

Advances in genetics since 2018, biomarker research, and immunotherapies, and the lack of international consensus on the medical management of epilepsy in people with glioblastoma, underpin the need for a comprehensive review of the area.[1–3] In this Review, we focus primarily on advances in the field of epilepsy in people with glioblastoma and developments that have occurred over the past 5 years. We consider the epidemiology, medical management, and prognosis of seizures related specifically to glioblastoma in the context of tumour biology and underlying pathophysiology. We also address novel insights into cancer therapies and associations with seizures. Surgical management is not included in the scope of this Review.

Epidemiology

The worldwide morbidity and mortality attributed to CNS malignancy is high, and the incidence of brain tumours increased between 1990 and 2016, with China, India, and the USA reporting the highest incidence rates, probably in part due to high ascertainment.[13] The Central Brain Tumor Registry of the United States reported the incidence of primary malignant and non-malignant brain and other CNS tumours in the USA between 2013 and 2017 to be 24·23 cases per 100 000 people, for a total count of 431 773 cases, with a slightly higher overall incidence in woman than in men.[14] Additionally, approximately 93 470 new cases of brain tumour were anticipated to be diagnosed in the USA in 2022.[15]

Glioblastoma is the most common and malignant primary brain tumour in adults,[16] with a reported median overall survival of approximately 15 months.[17] In one study, an even shorter survival was reported in people analysed between 2001 and 2017, with a median observed survival of 8 months, which is the lowest survival rate for all primary malignant CNS tumours and the worst 5-year survival rate for all cancers.[16] Most glioblastomas are primary tumours that occur in the absence of previous malignancy. Primary glioblastomas are most common in older individuals and are usually diffuse and infiltrative. Secondary glioblastomas arise from astrocytomas of a lower grade, are most likely to occur in younger patients, are often frontal in location, and usually confer a better prognosis than that of primary glioblastomas in other brain regions.

More than 10% of people with focal brain tumours have epilepsy related to their tumour.[2] In general, gliomas, glioneuronal tumours, and neuronal tumours are the most common types of CNS tumour associated with seizures. An estimated 80% of patients with gliomas will have one or more seizure episode during their disease course.[2] In this Review, we focus on epilepsy in people with glioblastoma primarily because management guidance in this area, especially with

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respect to anti-epileptic prophylaxis, is lacking in consensus. Gaining a clear understanding of the precise incidence and prevalence of epilepsy in people with glioblastoma is difficult, partly because of variability in histological subtypes of glioblastoma and the varying location of these tumours within the CNS.[5,18] The frequency of seizures varies depending on tumour histology and the heterogeneity of underlying pathophysiological mechanisms of epileptogenesis.[3,19] Notably, in patients with glioblastoma with a high tumour cell proliferation and growth rate, rates of epilepsy appear to be slightly lower (30–50%) than in patients with lower-grade malignancies, such as in oligodendroglioma and astrocytoma.[5] Anaplastic astrocytomas (ie, CNS WHO grade 3) and oligodendrogliomas are also more likely to be associated with generalised seizures than are glioblastomas, supporting the notion that more aggressive and fast-growing tumours might be less epileptogenic.[3,20] In some patients with glioblastoma, epilepsy might not occur due to rapid lesion growth outstripping epileptogenesis, rapid disease progression, and short patient survival.[5,20] When seizures are seen as the presenting symptom of glioblastoma, a longer survival time might be predicted, particularly in patients younger than 60 years old, although a younger age at time of diagnosis might create a bias in favour of improved outcomes in this context.[21]

In general, cortical lesions are more frequently associated with seizures than are subcortical lesions.[22] The innate epileptogenicity of mesial temporal structures, specifically the hippocampus, is well described,[22] and patients with temporal lobe lesions frequently have refractory tumour-related epilepsy.[19,22] Peritumoral oedema is one of the most substantial risk factors for seizures in patients with brain tumours, along with older age, male sex, and non-skull base tumour location.[23]

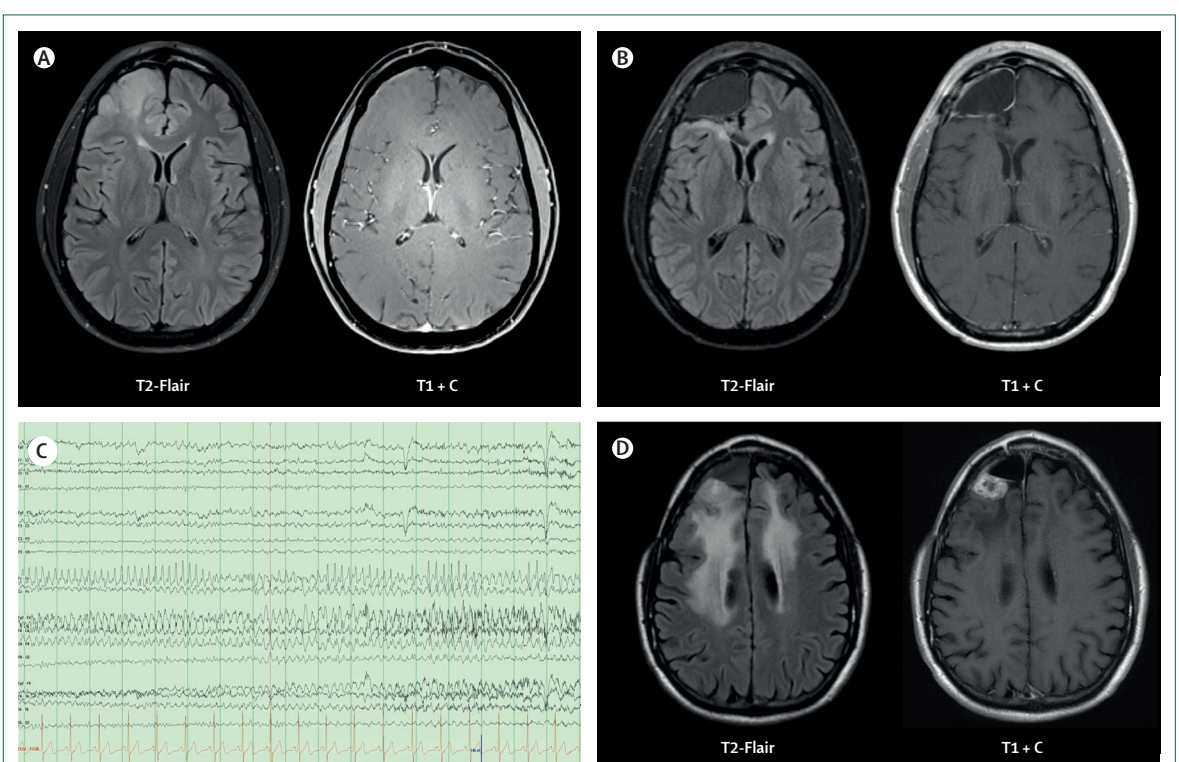

Figure 1: **Case of a patient with right frontal glioblastoma and challenging secondary seizure disorder**
A 47-year-old man presented to hospital after a generalised seizure. (A) T1 + C showed a non-enhancing right frontal mass, while T2-weighted images showed cortical and subcortical T2-FLAIR hyperintensity with mass effect. Treatment with levetiracetam (500 mg twice daily) was initiated immediately to manage seizures, but because of the rapid onset of anxiety and depression after several days, levetiracetam was stopped and carbamazepine (target dose 300 mg twice daily) was substituted. The patient continued to have focal unaware seizures and focal-to-bilateral seizures before surgery so a second antiseizure medication, lacosamide (target dose 150 mg twice daily), was added to his regimen. (B) After tumour resection, a diagnosis was made of *IDH*-wildtype, *MGMT*-methylated anaplastic astrocytoma. Subsequently, *EGFR* amplification was identified and the integrated diagnosis was updated to diffuse astrocytic glioma, *IDH*-wildtype, with molecular features of glioblastoma, WHO grade 4.[20] Tumour therapy included radiation therapy (60 Gy), followed by six cycles of adjuvant temozolomide. Over the next 1–2 years, the patient developed fatigue with memory impairment, poor cognitive initiation, and reduced motivation, along with worsening bifrontal T2-FLAIR hyperintensities, which were presumed secondary to radiation effects. Although no definitive tumour progression was noted for more than 3 years, seizures continued at a frequency of 1–2 per month. (C) A seizure captured on EEG shows focal rhythmic activity from the right anterior quadrant followed by secondary generalisation and profound post-ictal slowing. Lamotrigine (target dose 200 mg twice daily) was added as third agent, but the patient's baseline fatigue worsened. (D) Tumour progression was confirmed 4 years after initial presentation, with a new area of nodular enhancement posterior to the previous resection cavity. FLAIR=fluid-attenuated inversion recovery. T1 + C=T1-weighted with gadolinium contrast.

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Clinical manifestations

Seizures are the initial presentation of glioblastoma in approximately 25–30% of individuals with this malignant disease (figure 1).[24] Seizures in people with glioblastoma can also result from tumour-directed treatments, including surgical injury and radiation-induced tissue injury.[25] Signs and symptoms of epilepsy in people with glioblastoma are highly variable depending not only on tumour location but also on the cortical structures involved in the epileptic network. Tumour size and growth rate also affect presentation.[1–3]

Characterisation of seizure semiology with respect to current guidelines is important for choosing the best possible medical management. Seizure type and semiology can be classified according to the 2017 International League Against Epilepsy guidelines.[26] Seizure semiology typically reflects the underlying location of the lesion; however, in some patients, particularly when non-eloquent cortical structures are involved, seizure semiology is driven predominantly by seizure spread.[22] Seizure semiology could change after surgical resection, because there could be disruption of local or more distant networks due to scar tissue formation and cerebral oedema in the first instance.[27]

Pathophysiological mechanisms

The pathophysiology of epilepsy in people with glioblastoma most likely relates to a combination of the intrinsic epileptogenicity of tumour tissue, alterations in the tumoural and peritumoural microenvironment, and physical and functional disturbance of adjacent brain structures. Tumour site, the molecular biology of the tumour, histopathology, the predisposition and subsequent susceptibility of peritumoural tissue to epileptogenicity, and blood–brain barrier integrity have all been implicated in epilepsy in people with glioblastoma.[1–3,22,23] Several molecular markers and genetic alterations are pertinent not only to glioblastoma but also to epilepsy in people with glioblastoma (panel 1), indicating a role for microRNAs and ion channels in both seizures and tumour biology.

Proinflammatory molecules, such as interleukins and specific cytokines in the tumour microenvironment, also have been shown to have a role in epileptogenecity.[52–56] This notion has been supported by emerging data from the use of chimeric antigen receptor T (CAR-T) cell therapies, with their high rate of associated neurological complications in patients without CNS disease for whom an elevated seizure risk is driven by endothelial damage and cytokine release.[57,58]

Distinct molecular alterations in tumour tissue might have crucial implications for both tumour biology and seizure risk. The PI3K–mTOR pathway has a role in modulating cellular mechanisms, including cell growth, proliferation, longevity, neuronal morphology, and migration. It is emerging as a pivotal pathway in tumorigenesis.[59–63] This pathway interacts with the metabolite of *IDH1* mutant activity, 2-hydroxyglutarate, which might potentiate tumour growth and enhance cellular excitation and has been associated with epilepsy.[64,65] Overactivation of the mTOR pathway in the peritumoral environment can lead to seizures resulting from disrupted regulation of synaptic transmission and ion channel expression.[60] Therefore, novel insights into the mTOR pathway have indicated new therapeutic approaches for both epilepsy and brain tumours.[59,60,66] Moreover, loss of mTOR signalling and expression of *Trp53* are considered essential in determining the diversity and electrical activity of *BRAF*^{V600E}-induced tumours in the developing brain.[60] Inhibition of the mTOR pathway in *IDH*-mutant glioma can improve mean survival and slow tumour growth and, perhaps not coincidentally, could subsequently reduce seizure burden

***Panel 1:* Glioblastoma characteristics and factors associated with epilepsy**

Clinical presentation

- Median age at diagnosis, 68–70 years
- Symptoms include vomiting, headaches, and seizures
- Tumours are typically located extratemporally

Molecular markers

- PI3K–mTOR[28]
- *IDH1* and *IDH2*
- *BRAF*^{V600E} (ie, Val600Glu)
- RAF–MEK[29–36]
- 2-hydroxyglutarate
- MicroRNAs[37–40]
- KCC2[41–45]
- Glutamate[46–48]
- EGFR[49]
- PTEN[38]
- *CDKN2A*[50,51]
- Loss of heterozygosity in chromosome 10q[50,51]

Factors associated with epilepsy

- Tumour recurrence or progression
- Preoperative seizure history and treatment with multiple antiseizure medications
- MGMT promoter status
- *BRAF*^{V600E}
- miR-21-5p
- miR-128
- Reduced expression of KCC2
- Glutamate
- *IDH1* mutation
- Low OLIG2
- Hypoxia–HIF1α–STAT5b signalling pathway

Factors associated with improvements in seizures

- Located in the temporal lobe
- Total resection
- *BRAF* and *MEK* inhibition
- *REST* inhibition

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(ie, frequency and severity).[62] The mTOR inhibitor everolimus is licensed for treatment of tuberous sclerosis-associated subependymal astrocytoma, and this drug has shown promising results in other gliomas.[62,63]

Novel data suggest a unique role of glial cell involvement and glia–tumour cell interactions in tumour-driven epileptogenesis. Increasing cellular excitability and subsequent seizure onset is associated with neurosynaptogenesis that might arise due to the expansion of pathological glial cells within the tumour. Epilepsy-associated genes were shown to be expressed on some of these pathological glial cells and provide support for a potentially erroneous synaptic mechanism contributing to seizure generation in patients with glioma.[67]

Genetics

Genetic alterations in glioblastoma, which have been evidenced in the past 5–10 years, indicate potential actionable targets for both diagnosis and treatment of seizures related to glioblastoma, and they outline core biological pathways relevant to tumorigenesis and tumour behaviour. Findings of a multiomics study[68] in 2021 suggest that a combination of biomarkers is needed to provide a holistic and well rounded approach to diagnosis and classification of glioblastoma subtypes, with subsequent implications for prognosis and management. Heterogeneity within glioblastoma is a key factor in its poor prognosis.[69,70] Most primary glioblastomas contain an alteration in either *EGFR*, *PTEN*, or *CDKN2A*, or loss of heterozygosity in chromosome 10q,[71] whereas in secondary glioblastoma, *Trp53* and *IDH1* mutations are more prolific. Variability in genetic alterations is also highly relevant because mutations can predict the aggressiveness of tumour subtypes.[67] The function of some *EGFR* missense mutations has been described;[49] however, further insights into how tumour phenotype is affected and the subsequent clinical implications, including the effect on seizure burden, are needed. The tyrosine kinase–RAS–PI3K pathway and the tumour-suppressive *Trp53* and retinoblastoma pathways are also crucial in glioblastoma.[49] However, gene alteration within these pathways has not been successful because of the involvement of complex regulatory networks.[49]

IDH1 mutations are a hallmark mutation in individuals with secondary high-grade gliomas,[65,71] and they are associated with a high incidence of preoperative seizures in people with low-grade glioma.[72] Gene expression imaging can be used to identify regional variability in people with glioblastoma. For example, significantly lower expression of *OLIG2* was recorded using this method in people with glioblastoma with seizures compared with those without seizures.[28] Mesenchymal gene expression has also been linked with epilepsy in people with glioblastoma, and modulation of transcription factors (eg, NF-κB, STAT, and CEBP-β) has been shown to be relevant in this patient population. For example, downregulation of the hypoxia–HIF1α–STAT5b signalling pathway is associated with epilepsy in people with glioblastoma.[73]

Some genetic mutations have multiple effects on tumour biology and seizure risk. For example, the $BRAF^{V600E}$ mutation—which is more frequent in women than in men—is an emerging molecular marker of tumour epileptogenicity (primarily in cells of neuronal lineage) and is a potential target for treatment.[74–79] In a case study, however, inhibition of *BRAF* and *MEK* was not effective for control of epilepsy in people with glioblastoma.[74] Although treatments targeting $BRAF^{V600E}$ are emerging as a strategy in lesions such as gangliogliomas, little evidence is available to suggest this approach will be effective in glioblastoma.[76] Next-generation kinase inhibitors, including RAF and MEK inhibitors, are being developed as pharmacological agents for treatment of $BRAF^{V600E}$ mutation-driven primary brain tumours, particularly those that might be difficult to access surgically.[74–79] The $BRAF^{V600E}$ somatic mutation has been identified as an important cause of refractory epilepsy in developing neurons in murine models. RNA sequencing of brain tissue with the mutation showed that $BRAF^{V600E}$-induced epileptogenesis is modulated by REST—a regulator of ion channels and neurotransmitter receptors associated with epilepsy. Koh and colleagues[79] showed that seizures in these preclinical models were significantly reduced in terms of frequency and severity by vemurafenib, a $BRAF^{V600E}$ inhibitor, and by some genetic inhibitions of REST, indicating the potential for future targeting of these genetic biomarkers.

Mutations in *MGMT* are frequently reported in people with glioblastoma and other astrocytic tumours.[80] NF-κB helps to regulate the transcription of *MGMT*, and this transcription factor is also thought to have a role in seizure risk by modulating T cells and proinflammatory cytokines in the peritumoural environment.[81] Resistance to chemotherapeutic agents such as temozolomide has been reported in some gliomas with mutations in *MGMT*. Levetiracetam plus interferon alfa has shown some promise against temozolomide resistance in *MGMT*-positive glioma.[81]

MicroRNAs—which consist of non-coding RNA—are considered novel biomarkers for many neurological disorders, including refractory epilepsy.[29,30] Epigenetic modifications of microRNAs affect gene expression at the post-translational level, potentially affecting hundreds of genes at a time. They could serve as diagnostic markers because of noted variations in expression in the CSF of both healthy people and those with glioblastoma. A close relation has been reported between some microRNAs and the mTOR pathway. For example, increased concentrations of miR-21-5p cause upregulation of the mTOR pathway and subsequent epileptogenesis.[29] The microRNA miRNA-128 has been identified as a possible silencing target in people with glioma who have

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seizures.[64] Therapies that target microRNA, such as RGLS5579 (an anti-miR-10), have shown some promise in people with glioblastoma and epilepsy.[31]

A definitive feature of glioblastoma is tumour cell invasion into normal brain parenchyma, and this process could be facilitated by ion channels.[35] These proteins have a pivotal role in some epilepsy disorders and they might contribute to epileptogenesis in people with glioblastoma.[32–34] Ion channels are promising pharmaceutical targets for the management of seizures.[35] Study findings have shown that potassium homoeostasis that is modulated by specific potassium channels (eg, Kir4.1) in the peritumoural microenvironment can affect seizure risk.[82] Kir4.1 is expressed on glial cells and is thought to maintain cellular potassium homoeostasis and buffering. Neuronal potassium homoeostasis is pivotal to the hyperexcitability of the cell and, therefore, mutations or variation in expression of Kir4.1 could have a crucial role in epileptogenesis and in tumorigenesis.[82] The potassium chloride transporter KCC2—a neuron-specific membrane protein with notable expression in the brainstem, hippocampus, and hypothalamus—regulates GABA activity and actively maintains the chloride gradient across neuronal networks.[32,33,35,36] Neuronal excitability is enhanced by glutamate, whereas GABAergic interneurons are inhibitory. GABAergic inhibition is largely mediated via the KCC2 cotransporter. A reduction in KCC2 expression has been reported in the peritumoral microenvironment of glioma in rodent models, and in patients with glioma after surgery in whom the amount of KCC2 expression was inversely correlated with increased seizure burden.[32,33,36] Downregulation or loss of inhibitory neuronal signalling modulated by GABA and decreased KCC2 expression has been described in preclinical glioma models.[36] The predicted result of these changes would be a hyperexcitable peritumoral environment and a predisposition to seizures. Astrocytes are key modulators of extracellular glutamate concentrations. They express two high-affinity glutamate transporters—GLT-1 and GLAST—that eliminate glutamate from the extracellular space. Astrocytes form scars in the peritumoural microenvironment and, with their usual function impaired, glutamate concentrations rise leading to hyperexcitability and seizures.[83] Complexes can form between AQP-4—a widely expressed cerebral water channel in astrocytic end-feet—and both chloride and potassium channels, which might have a downstream modulatory effect on membrane excitability through the regulation of potassium and glutamate.[84] AQP-4 is also integral to mechanisms that lead to cerebral oedema in the context of brain injury, including tumour-related injury. Glutamate can modulate the expression of AQP-4 via mGluR5, identifying these potential targets in oedema control and, subsequently, seizures related to brain injury.[84,85]

The complex interplay between glutamate, AMPA, NMDA, and GABA probably contributes to the origin of seizures in people with glioblastoma. Upregulation of glutamate, AMPA, and NMDA receptors, and downregulation or impaired function of GABA receptors, enhances the excitability of the peritumoural and tumoural environment and increases the likelihood of seizures.[37] Phosphorylation changes in the extrasynaptic NMDA receptor in murine peritumoural tissues have been shown to result in neuronal hyperexcitation.[38] Moreover, glutamate is secreted in high quantities in glioblastoma and can have a toxic effect on local brain parenchyma, enabling tumour growth and epileptogenesis. High concentrations of glutamate are associated with an increased propensity to seizures in glioblastoma.[38,85] The MRI modality glutamate-weighted chemical exchange saturation transfer at 7T (7T GluCEST) can be used to non-invasively identify and quantify glutamate expression. 7T GluCEST studies have shown that, in the setting of glioma, glutamate is a potential biomarker of both local epileptogenicity and survival.[39]

Management

The management of epilepsy in people with glioblastoma can vary considerably; it is not prescriptive and should be tailored to the individual, requiring a multidisciplinary strategy. Factors including sex, BMI, underlying comorbidities, and adjunct therapy should be considered when planning the treatment of epilepsy in people with glioblastoma.[42–45,86–88] Tumour resection followed by radiotherapy plus temozolomide chemotherapy is the current standard of care (panel 2).[91] Figure 2 suggests a basic initial management plan for epilepsy in people with glioblastoma based on current best practice.[45,88,91] In 2019, a group from China proposed a guideline for the management of glioma-related epilepsy;[45] however, worldwide practice remains varied, and there is currently no national or international consensus on specific guidelines and protocols. A multifaceted epilepsy evaluation, including video EEG, nuclear medicine scans (ie, ictal and interictal SPECT and PET), and anatomical and functional MRI, can be used.[2]

Antiseizure medications

Antiseizure medications are the most widely used and effective approach for seizure control. Nonetheless, they do not provide complete relief from seizures for approximately 20% of people with glioblastoma (figure 1).[92–94] Antiseizure medications should be administered immediately after a definite epileptic seizure and at the lowest dose required to control seizures, to minimise side-effects and drug–drug interactions.[44,45,74] Broadly, the standard approach to management of focal epilepsies (unrelated to a brain tumour) can be used for management of seizures in people with glioblastoma.

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Panel 2: **Medical management of glioblastoma and associated epilepsy**

- Tumour resection plus radiotherapy plus temozolomide chemotherapy are the current standard of care[4,24,37]
- MRI should be done 24–72 h after tumour resection
- Postoperative radiotherapy should be initiated at an early stage after surgery[2]
- Chemotherapy (ie, procarbazine–lomustine–vincristine or temozolomide) has been associated with improved seizure outcomes[89]
- Levetiracetam has been linked to improved survival after a definite epileptic seizure, at the lowest dose for control of seizures[90]
- The amounts of antiseizure medications in blood should be monitored[2]
- A next-line antiseizure agent at the minimum effective dose should be added if seizures persist[40] (figure 2)
- Enzyme-inducing antiseizure medications should be avoided in patients on chemotherapy,[40] and doctors should be mindful of drug–drug interactions
- In patients with newly diagnosed brain tumours, and in perioperative patients who remain seizure free, antiseizure medications are not currently indicated, but the doctor and patient should discuss risks and whether to use these drugs[40]

The choice of antiseizure medication for people with glioblastoma depends on seizure classification and interactions with concomitant drug therapies (table).[45,91,93,94] Co-administration of chemotherapeutic agents and antiseizure medications is common, and potential interactions and additive toxicities need to be carefully considered. Although practice varies by region, levetiracetam is typically the first-line choice for treatment of epilepsy in people with glioblastoma.[44,91] Advantages of levetiracetam include the availability of an intravenous preparation for situations in which the patient is unable to take tablets and that few drug–drug interactions have been reported. In contrast, many antiseizure medications, such as carbamazepine and its derivatives, are potent enzyme inducers. Valproic acid, which is also available as an intravenous preparation, is a broad-spectrum enzyme inhibitor that might interact with some antitumour treatments. Valproate, lamotrigine, and lacosamide are common second-line choices. Lamotrigine requires a titration repeated over multiple weeks to achieve an effective plasma concentration to minimise the risk of Stevens-Johnson syndrome. If seizures persist despite the administration of one of these antiseizure medications at the maximum tolerated dose then others can be added.[40–45,86–88,91] Antiseizure medications developed over the past three decades (eg, lamotrigine, lacosamide, zonisamide, brivaracetam, levetiracetam, and perampanel) might be better tolerated than older agents (eg, phenobarbital and phenytoin). Valproate in combination with a newer antiepileptic drug, such as levetiracetam, can be effective for patients with refractory seizures.[92,93]

The difficulty of effectively treating glioblastoma is partly due to glioma stem cells, which can rapidly repopulate the tumour after the initial treatment. Several studies have shown that perampanel increases apoptosis of tumour cells and reduces extracellular glutamate in vitro.[46,86] In one 2018 study,[86] perampanel was shown not only to reduce seizure frequency and severity in patients with glioma but also to have radiographically detectable inhibitory effects on tumour growth. The results of this study might have been confounded by the use of chemotherapeutic agents, and the overall study was limited by the small cohort of 12 patients.[86] Further studies are needed to investigate and delineate the possible antitumour effects of perampanel in glioblastoma.

Many antiseizure medications are metabolised via cytochrome P450, as are several chemotherapeutic agents used to treat brain tumours, raising concerns about drug–drug interactions—eg, possible heightened drug clearance, associated toxicity, and higher doses needed for efficacy.[41] Some antiseizure medications can either inhibit or induce specific cytochrome isoenzymes, subsequently impeding or potentiating the metabolism of other drugs. Potent enzyme-inducing antiseizure medications include phenytoin, phenobarbital, carbamazepine, and topiramate, which are generally not suitable for use in conjunction with several conventional chemotherapies, notably temozolomide, due to pharmacological interactions.[80] These antiseizure medications will also enhance the clearance of several other chemotherapeutic agents (eg, vinca alkaloids, anthracyclines, taxanes, nitrogen mustards, epipodophyllotoxins, and alkylating agents) and corticosteroids.[41] Conversely, chemotherapeutic agents can also affect the pharmacodynamics of antiseizure medications, thereby affecting seizure risk. Combining antiseizure medications with chemotherapy, tyrosine kinase inhibitors, or steroids increases the risk of side-effects and drug interactions. Ensuring the therapeutic ranges of antiseizure medications are achieved, and toxicity is identified early by clinical assessment and plasma monitoring, is recommended.[16]

Prophylaxis

The role of prophylactic antiseizure medications in patients with a brain tumour without a history of seizures remains controversial, partly because of study design and bias with underpowering and inadequate blinding.[92,93] In 2021, the American Academy of Neurology updated guidance to state that, in patients with newly diagnosed brain tumours who are seizure free, clinicians should not routinely prescribe antiseizure medications to minimise the risk of seizure.[91] These recommendations were made despite acknowledgment that newer antiepileptics might have fewer side-effects and potential

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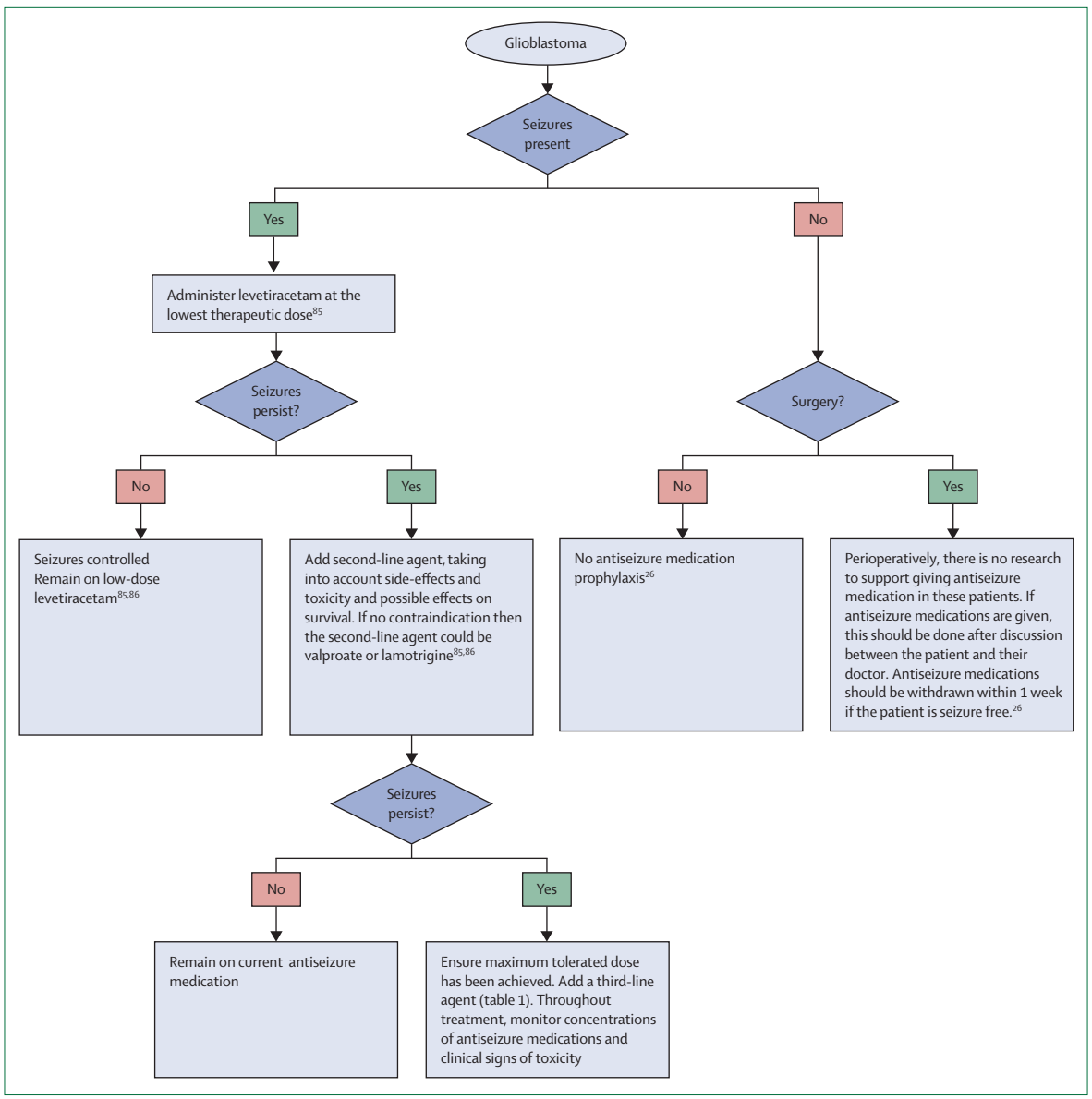

Figure 2: **Proposed initial management algorithm for epilepsy in patients with glioblastoma**
This model should be used as a guide. The importance of the discussion between patient and doctor, and patient-specific care, cannot be underestimated and always has the primary role in decision making.[44,45,88,91]

antitumour effects. Importantly, in the perioperative setting, no definitive evidence is available to recommend prescription of antiseizure medications in patients undergoing surgery or, indeed, with the aim to improve overall survival.[88,93] Despite this absence of evidence, many neurosurgeons still prescribe antiseizure medications to patients undergoing tumour resection.[94] Ultimately, treatment decisions regarding prophylactic antiseizure medications rest with the treating clinician, taking into account the patient's choice and factors such as the location and type of tumour, the burden of comorbidities, and the risk of toxicity.[93,94] Evidence is inadequate to address the question of whether and when to discontinue antiseizure medications in the postoperative setting. However, withdrawal of antiseizure medication can be considered in selected patients.[47,48]

Antitumour effects of antiseizure medications

Some antiseizure medications have shown promising additional antitumour effects.[7,8,10–12] Valproate, a histone deacetylase inhibitor, is the best-studied antiseizure medication regarding its effect on survival in patients with glioblastoma with seizures.[7] Histone deacetylase inhibitors have a role in both gene expression and epigenetic modulation, and they have also been used as anticancer agents.[16] In several studies, valproate has

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	Mechanism of action	Side-effects	Adverse effects	Drug interactions	Suggested approach
Levetiracetam	Modulates SV2A, a synaptic vesicle glycoprotein, and inhibits presynaptic calcium channels	Mood disturbance, depression, and anxiety	..	..	First-line therapy
Valproate	Probable upregulation of GABA	Postural tremor, increased weight, alopecia, nausea, and vomiting	Thrombocytopenia, pancreatitis, and hepatotoxicity	Clinically significant drug–drug interactions possible with lamotrigine and temozolomide; close monitoring required	First-line or second-line therapy
Lamotrigine	Modulates voltage-gated sodium channels	Insomnia and hyperhidrosis	Haemophagoctytic lymphohistiocytosis and rash	..	Commonly used add-on therapy in glioblastoma-related epilepsy
Topiramate	Modulates voltage-gated sodium channels and calcium channels; targets GABA-A and AMPA or kainate receptors and inhibits carbonic anhydrase	Psychosis, weight loss, speech disturbance, and paraesthesia	Glaucoma and renal stones	Potential for serious interaction with mTOR inhibitors, requiring regular monitoring	Commonly used add-on therapy in glioblastoma-related epilepsy
Oxcarbazepine	Sodium channel blocker and glutamate modulator	Hyponatraemia	..	Potential for serious interaction with mTOR inhibitors; diminishes the effect of tyrosine kinase inhibitors; dose increments might be required alongside close monitoring	Commonly used add-on therapy in glioblastoma-related epilepsy
Lacosamide	Modulates voltage-gated sodium channels	Arrhythmias, heart block, dizziness, and syncope	..	..	Commonly used add-on therapy in glioblastoma-related epilepsy
Perampanel	Negative allosteric AMPA-receptor antagonist	Weight gain and mood fluctuation	Suicidal ideation	..	Commonly used add-on therapy in glioblastoma-related epilepsy
Zonisamide	A weak carbonic anhydrase inhibitor; modulates voltage-gated sodium channels and calcium channels	Weight loss and photosensitivity	Glaucoma, rash, and renal stones	..	Add-on therapy
Brivaracetam	Increases cerebral GABA concentrations	Depression and anxiety	..	..	Add-on therapy
Pregabalin	Calcium channel inhibitor	Weight gain, peripheral oedema, and poor efficacy	..	..	Add-on therapy
Eslicarbazepine	Modulates voltage-gated sodium channels	Hyponatraemia	..	Diminishes the effect of tyrosine kinase inhibitors; dose increments might be required alongside close monitoring	Add-on therapy
Gabapentin	Modulates voltage-dependent calcium channels	Weight gain and peripheral oedema	..	..	Add-on therapy
Epidiolex	Anticonvulsant properties of unclear cause	Labile mood, psychosis, and weight gain	..	..	Use only if all other options exhausted
Carbamazepine	Modulates voltage-gated sodium channels	Hyponatraemia	Stevens-Johnson syndrome, bone marrow suppression, hepatotoxicity, and rash	Lowers the effects of tyrosine kinase inhibitors; dose increments might be required alongside close monitoring	Not recommended if alternatives are available
Phenobarbital	Allosteric modulator of chloride channels	Osteopenia, osteoporosis, low mood, and haematological toxicity	Stevens-Johnson syndrome, hepatotoxicity, and aplastic anaemia	..	Not recommended if alternatives are available
Phenytoin	Modulates voltage-gated sodium channels	Impaired glucose control, gingival hypertrophy, hirsutism, osteopenia, and osteoporosis	Stevens-Johnson syndrome, hepatotoxicity, and aplastic anaemia	..	Not recommended if alternatives are available
Vigabatrin	GABA aminotransferase inhibition	Retinal toxicity, fatigue, and tremor	..	..	No current evidence in glioblastoma-related epilepsy

Medications are listed with the medicines that are most commonly used and best tolerated listed first.

Table: **Antiseizure medication options in for people with glioblastoma and epilepsy[95]**

been shown to improve survival; however, it has been associated with worse outcomes in grade 2 and 3 glioma.[96] Valproate and levetiracetam can interact with MGMT and might elicit antitumour effects through this mechanism.[80] A few studies have linked valproate to improved survival in patients with newly diagnosed glioblastoma.[12] However, Happold and colleagues[97] did a combined survival analysis of antiseizure medications in this patient group and concluded that valproate and levetiracetam could only be used for seizure control, and neither drug was associated with outcome of glioblastoma. In another study, Wnt–β-catenin

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signalling was affected by valproate-induced methylation changes, with subsequent effects on the function of this pathway, reducing the proliferation and motility of glioma stem cells.[11] Redjal and colleagues[98] linked valproate treatment with improved survival in patients with high-grade glioma and glioblastoma in a dose-dependent manner. When used in conjunction with temozolomide and radiation, prolonged survival in people with glioblastoma was also described.[12,80] Valproate has been shown to potentiate carboplatin cytotoxicity in vitro and is being considered as an adjuvant therapy in diffuse intrinsic pontine glioma.[7] A promising therapeutic strategy involves the modulation of histone deacetylase activity and 2-deoxy-D-glucose analogues by utilising inhibitors, such as valproate, which can mediate cytotoxic effects in glioblastoma cells.[48] Currently, no prospective clinical trial data are available to show the possible antitumour effects of valproate or levetiracetam in patients with glioblastoma. A retrospective study found longer overall survival in patients treated with levetiracetam alone or with other antiseizure medications compared with patients who did not receive levetiracetam.[12] The effect was most notable in patients with the methylated MGMT promoter.[13] Levetiracetam in conjunction with standard chemoradiation possibly improved overall survival of patients with IDH-wild-type glioblastoma.[90]

Antiseizure effects of glioblastoma treatments

Some alkylating agents, alone or in addition to radiotherapy, might be helpful in reducing the frequency of seizures.[99] Temozolomide was reviewed regarding its effect on seizures in older patients with glioblastoma and was not shown to be efficacious in this regard, although this study was underpowered.[89]

Prognosis

Clinical factors have been identified that might be associated with improved prognosis for people with glioblastoma who have had surgery and are receiving radiotherapy and adjuvant temzolomide. These factors include young age at diagnosis (ie, <65 years), higher functional performance, frontal location of the tumour, and greater resection margins with complete tumour resection.[24,100] Seizures as the presenting symptom in people with glioblastoma might also predict prolonged survival. Findings of a comprehensive meta-analysis in 2018 showed that a history of seizures at the initial presentation of glioblastoma was significantly associated with improved survival compared with people who present with no seizure history.[24]

Although epilepsy in people with glioblastoma negatively affects quality of life, it does seem to confer overall improved prognosis.[2,24,100] No biological basis for this effect is clear, although several factors could be involved. First, apparent prolonged survival might reflect the fact that tumours are often diagnosed earlier in people who present with seizures (ie, lead-time bias). Second, seizures tend to arise from cortical rather than subcortical lesions, which are more readily amenable to surgical resection.[101] Third, people who present with a history of seizures often have smaller tumours with less oedema at diagnosis than do those who present with other symptoms.[102] Finally, seizures are typically associated with lesions of less deleterious histological subtypes, which are associated with slow tumour growth.

Seizures that occur after craniotomy are relatively common, with reported incidence rates ranging from 3% to 22%.[103–107] *IDH1* mutations in glioma have been associated with an increased risk of developing seizures, but postoperative seizure control of *IDH1*-positive tumours might be better than that for other glioma subtypes.[108] The strongest predictors of freedom from seizure in unifocal glioma is gross total resection of the lesion followed by seizure type and choice of antiseizure medication.

Conclusions and future directions

Successful medical management of epilepsy in people with glioblastoma remains challenging because additional factors—eg, interactions with oncological treatments and side-effects of antiseizure medication—can affect seizure outcomes and quality of life of the patient. Clinical trials are urgently needed to better understand epilepsy in people with glioblastoma and to improve the quality of life for this patient group. Surgical management is an option for some people with epilepsy related to glioblastoma, which we have not discussed in this Review. Personalised oncological treatments benefitting both tumour control and seizures might represent future targets for primary brain tumours that are difficult to resect (eg, if they reside within eloquent cortex), and $BRAF^{V600E}$ mutations targeted by kinase inhibitors provide one such route.[51,60,69,74,] The tumour microenvironment is another potential therapeutic target and is of particular interest in both glioblastoma and seizure risk.[1,2] Ion channels (eg, KCC2) could be useful targets for seizure management in individuals with

Search strategy and selection criteria

We did a comprehensive free-text search of PubMed, Ovid Embase, Cochrane Central Register of Controlled Trials, Cochrane Database, and Google Scholar, including peer-reviewed articles published between approximately 2016 and 2022, using the terms "brain tumor related epilepsy", "glioblastoma", and "seizures", and combination logic including AND/OR criteria. No language restrictions were applied. We also searched the reference lists of relevant articles. Older articles were included as judged necessary by the authors. The final reference list was generated on the basis of relevance to the topics covered in this Review.

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primary brain tumours. Moreover, microRNAs are molecules with high potential for therapeutic intervention, closely interacting with mTOR pathways, and could be used as biomarkers. Novel immunotherapy agents are of great interest. Possible options include immune checkpoint modulators, CAR-T cells, and dendritic cell vaccines.[102,109–111] Advances in novel CAR-T cell therapy are promising for patients with haematological malignancies and, potentially, those with solid tumours of varying causes. However, high-grade neurotoxicity with CAR-T cell therapy manifest as seizures and requires close monitoring.[4,57,58] To understand the close integral relation between glioblastoma and seizures, future work should provide more insights into electrical activity as a driver of tumour growth, and the reciprocal relation.

Contributors

All authors contributed to the drafting of the manuscript, completing a comprehensive literature search, and the review and compilation of the final manuscript.

Declaration of interests

JD is a consultant for Unum Therapeutics and Amgen and has received royalties from Wolters Kluwer. AJC is a consultant for Sage Therapeutics, Biogen, Precisis AG, and has received royalties from Wolters Kluwer. All other authors declare no competing interests.

References

1 Hills KE, Kostarelos K, Wykes RC. Converging mechanisms of epileptogenesis and their insight in glioblastoma. *Front Mol Neurosci* 2022; **15:** 903115.

2 Chen DY, Chen CC, Crawford JR, Wang SG. Tumor-related epilepsy: epidemiology, pathogenesis and management. *J Neurooncol* 2018; **139:** 13–21.

3 Berntsson SG, Merrell RT, Amirian ES, et al. Glioma-related seizures in relation to histopathological subtypes: a report from the glioma international case-control study. *J Neurol* 2018; **265:** 1432–42.

4 Akhavan D, Alizadeh D, Wang D, Weist MR, Shepphird JK, Brown CE. CAR T cells for brain tumors: lessons learned and road ahead. *Immunol Rev* 2019; **290:** 60–84.

5 Toledo M, Sarria-Estrada S, Quintana M, et al. Epileptic features and survival in glioblastomas presenting with seizures. *Epilepsy Res* 2017; **130:** 1–6.

6 Chen H, Judkins J, Thomas C, et al. Mutant *IDH1* and seizures in patients with glioma. *Neurology* 2017; **88:** 1805–13.

7 Killick-Cole CL, Singleton WGB, Bienemann AS, et al. Repurposing the anti-epileptic drug sodium valproate as an adjuvant treatment for diffuse intrinsic pontine glioma. *PLoS One* 2017; **12:** e0176855.

8 Lu VM, Texakalidis P, McDonald KL, Mekary RA, Smith TR. The survival effect of valproic acid in glioblastoma and its current trend: a systematic review and meta-analysis. *Clin Neurol Neurosurg* 2018; **174:** 149–55.

9 Luo D, Fraga-Lauhirat M, Millings J, et al. Phospho-valproic acid (MDC-1112) suppresses glioblastoma growth in preclinical models through the inhibition of STAT3 phosphorylation. *Carcinogenesis* 2019; **40:** 1480–91.

10 Barker CA, Bishop AJ, Chang M, Beal K, Chan TA. Valproic acid use during radiation therapy for glioblastoma associated with improved survival. *Int J Radiat Oncol Biol Phys* 2013; **86:** 504–09.

11 Riva G, Cilibrasi C, Bazzoni R, et al. Valproic acid inhibits proliferation and reduces invasiveness in glioma stem cells through Wnt/β catenin signalling activation. *Genes* 2018; **9:** 522.

12 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:** e0225599.

13 Fang S, Zhou C, Fan X, Jiang T, Wang Y. Epilepsy-related brain network alterations in patients with temporal lobe glioma in the left hemisphere. *Front Neurol* 2020; **11:** 684.

14 Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. *Neuro-oncol* 2020; **22** (suppl 2)**:** iv1–96.

15 Central Brain Tumor Registry of the United States. CBTRUS fact sheet. https://cbtrus.org/cbtrus-fact-sheet-2022/#:~:text=An%20estimated%2093%2C470%20new%20cases,in%20the%20US%20in%202022.&text=This%20includes%20an%20estimated%2026%2C670,brain%20and%20other%20CNS%20tumors (accessed March 19, 2023).

16 Patel AP, Fisher JL, Nichols E, et al. Global, regional, and national burden of brain and other CNS cancer, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18:** 376–93.

17 Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol* 2020; **22:** 1073–113.

18 Beghi E. The epidemiology of epilepsy. *Neuroepidemiology* 2020; **54:** 185–91.

19 Yinyan W, Wei W, Zhenyu L, et al. Predicting the type of tumor-related epilepsy in patients with low-grade gliomas: a radiomics study. *Front Oncol* 2020; **10:** 235.

20 Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 2021; **23:** 1231–51.

21 Tykocki T, Eltayeb M. Ten-year survival in glioblastoma. a systematic review. *J Clin Neurosci* 2018; **54:** 7–13.

22 Venkatesh HS, Morishita W, Geraghty AC, et al. Electrical and synaptic integration of glioma into neural circuits. *Nature* 2019; **573:** 539–45.

23 Huang C, Chi XS, Hu X, et al. Predictors and mechanisms of epilepsy occurrence in cerebral gliomas: what to look for in clinicopathology. *Exp Mol Pathol* 2017; **102:** 115–22.

24 Lu VM, Jue TR, Phan K, McDonald KL. Quantifying the prognostic significance in glioblastoma of seizure history at initial presentation: a systematic review and meta-analysis. *Clin Neurol Neurosurg* 2018; **164:** 75–80.

25 Xue H, Sveinsson O, Bartek J Jr, et al. Long-term control and predictors of seizures in intracranial meningioma surgery: a population-based study. *Acta Neurochir* 2018; **160:** 589–96.

26 International League Against Epilepsy. ILAE Classification of the Epilepsies (2017). https://www.ilae.org/guidelines/definition-and-classification/ilae-classification-of-the-epilepsies-2017 (accessed March 19, 2023).

27 Zoccarato M, Nardetto L, Basile AM, Giometto B, Zagonel V, Lombardi G. Seizures, edema, thrombosis and haemorrhages: an update review on the medical management of gliomas. *Front Oncol* 2021; **11:** 617966.

28 Lee JW, Norden AD, Ligon KL, et al. Tumor associated seizures in glioblastomas are influenced by survival gene expression in a region-specific manner: a gene expression imaging study. *Epilepsy Res* 2014; **108:** 843–52.

29 Tang C, Gu Y, Wang H, et al. Targeting of microRNA-21-5p protects against seizure damage in a kainic acid-induced status epilepticus model via PTEN-mTOR. *Epilepsy Res* 2018; **144:** 34–42.

30 Tiwari D, Peariso K, Gross C. MicroRNA-induced silencing in epilepsy: opportunities and challenges for clinical application. *Dev Dyn* 2018; **247:** 94–110.

31 Hanna J, Hossain GS, Kocerha J. The potential for mRNA therapeutics and clinical research. *Front Genet* 2019; **10:** 478.

32 Chen L, Wan L, Wu Z, et al. KCC2 downregulation facilitates epileptic seizures. *Sci Rep* 2017; **7:** 156.

33 Takayasu T, Kurisu K, Esquenazi Y, Ballester LY. Ion channels and their role in the pathophysiology of gliomas. *Mol Cancer Ther* 2020; **19:** 1959–69.

34 Tang BL. The expanding therapeutic potential of neuronal KCC2. *Cells* 2020; **9:** 240.

35 Noh W, Pak S, Choi G, Yang S, Yang S. Transient potassium channels: therapeutic targets for brain disorders. *Front Cell Neurosci* 2019; **13:** 265.

36 Moore YE, Deeb TZ, Chadchankar H, Brandon NJ, Moss SJ. Potentiating KCC2 activity is sufficient to limit the onset and severity of seizures. *Proc Natl Acad Sci USA* 2018; **115:** 10166–71.

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37 MacKenzie G, O'Toole KK, Moss SJ, Maguire J. Compromised GABAergic inhibition contributes to tumor-associated epilepsy. *Epilepsy Res* 2016; **126:** 185–96.

38 Gao X, Wang H, Pollok KE, Chen J, Cohen-Gadol AA. Activation of death-associated protein kinase in human peritumoral tissue: a potential therapeutic target. *J Clin Neurosci* 2015; **22:** 1655–60.

39 Neal A, Moffat BA, Stein JM, et al. Glutamate weighted imaging contrast in gliomas with 7 Tesla magnetic resonance imaging. *Neuroimage Clin* 2019; **22:** 101694.

40 Vecht C, Royer-Perron L, Houillier C, Huberfeld G. Seizures and anticonvulsants in brain tumours: frequency, mechanisms and anti-epileptic management. *Curr Pharm Des* 2017; **23:** 6464–87.

41 Tatum WO, Quinones-Hinojosa A. Onco-epilepsy: more than tumor and seizures. *Mayo Clin Proc* 2018; **93:** 1181–84.

42 Maschio M, Dinapoli L, Zarabla A, et al. Zonisamide in brain tumor-related epilepsy: an observational pilot study. *Clin Neuropharmacol* 2017; **40:** 113–19.

43 Maschio M, Maialetti A, Mocellini C, et al. Effect of brivaracetam on efficacy and tolerability in patients with brain tumor-related epilepsy: a retrospective multicenter study. *Front Neurol* 2020; **11:** 813.

44 Van Der Meer P, Dirven L, Fiocco M, Taphoorn M, Koekkoek J. First-line antiepileptic drug treatment in glioma patients with epilepsy: levetiracetam vs valproic acid. *Epilepsia* 2021; **62:** 1119–29.

45 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:** 4527–35.

46 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:** e0211644.

47 Kerkhof M, Koekkoek JAF, Vos MJ, et al. Withdrawal of antiepileptic drugs in patients with low grade and anaplastic glioma after long-term seizure freedom: a prospective observational study. *J Neurooncol* 2019; **142:** 463–70.

48 Pająk B, Siwiak-Niedbalska E, Jaśkiewicz A, et al. Synergistic anticancer effect of glycolysis and histone deacetylases inhibitors in a glioblastoma model. *Biomedicines* 2021; **9:** 1749.

49 Lee JC, Vivanco I, Beroukhim R, et al. Epidermal growth factor receptor activation in glioblastoma through novel missense mutations in the extracellular domain. *PLoS Med* 2006; **3:** e485.

50 Mustansir F, Mushtaq N, Darbar A. Dabrafenib in *BRAF*^{V600E} mutant pilocytic astrocytoma in a pediatric patient. *Childs Nerv Syst* 2020; **36:** 203–07.

51 Yau WH, Ameratunga M. Combination of *BRAF* and *MEK* inhibition in *BRAF*^{V600E} mutant low-grade ganglioglioma. *J Clin Pharm Ther* 2020; **45:** 1172–74.

52 Duffau H. Brain connectomics applied to oncological neuroscience: from a traditional surgical strategy focusing on glioma topography to a meta-network approach. *Acta Neurochir* 2021; **163:** 905–17.

53 Mostofa AGM, Punganuru SR, Madala HR, Al-Obaide M, Srivenugopal KS. The process and regulatory components of inflammation in brain oncogenesis. *Biomolecules* 2017; **7:** 34.

54 Blumcke I, Spreafico R, Haaker G, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. *N Engl J Med* 2017; **377:** 1648–56.

55 Mikkelsen VE, Solheim O, Salvesen Ø, Torp SH. The histological representativeness of glioblastoma tissue samples. *Acta Neurochir* 2021; **163:** 1911–20.

56 McCullough BJ, Ader V, Aguedan B, et al. Preoperative relative cerebral blood volume analysis in gliomas predicts survival and mitigates risk of biopsy sampling error. *J Neurooncol* 2018; **136:** 181–88.

57 Gust J, Hay KA, Hanafi L-A, et al. Endothelial activation and blood–brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov* 2017; **7:** 1404–19.

58 Karschnia P, Jordan JT, Forst DA, et al. Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells. *Blood* 2019; **133:** 2212–21.

59 Yuan Y, Xiang W, Yanhui L, et al. Activation of the mTOR signaling pathway in peritumoral tissues can cause glioma-associated seizures. *Neurol Sci* 2017; **38:** 61–66.

60 Cases-Cunillera S, van Loo KMJ, Pitsch J, et al. Heterogeneity and excitability of *BRAF*^{V600E}-induced tumors is determined by Akt/mTOR-signaling state and *Trp53*-loss. *Neuro-oncol* 2022; **24:** 741–54.

61 Wahl M, Chang SM, Phillips JJ, et al. Probing the phosphatidylinositol 3-kinase/mammalian target of rapamycin pathway in gliomas: a phase 2 study of everolimus for recurrent adult low-grade gliomas. *Cancer* 2017; **123:** 4631–39.

62 Schubert-Bast S, Rosenow F, Klein KM, Reif PS, Kieslich M, Strzelczyk A. The role of mTOR inhibitors in preventing epileptogenesis in patients with TSC: current evidence and future perspectives. *Epilepsy Behav* 2019; **91:** 94–98.

63 Cacchione A, Lodi M, Carai A, et al. Upfront treatment with mTOR inhibitor everolimus in pediatric low-grade gliomas: a single-center experience. *Int J Cancer* 2020; **148:** 2522–34.

64 Gutt-Will M, Murek M, Schwarz C, et al. Frequent diagnostic under-grading in isocitrate dehydrogenase wild-type gliomas due to small pathological tissue samples. *Neurosurgery* 2019; **85:** 689–94.

65 Li Y, Shan X, Wu Z, Wang Y, Ling M, Fan X. IDH1 mutation is associated with a higher preoperative seizure incidence in low-grade glioma: a systematic review and meta-analysis. *Seizure* 2018; **55:** 76–82.

66 Batsios G, Viswanath P, Subramani E, et al. PI3K/mTOR inhibition of IDH1 mutant glioma leads to reduced 2HG production that is associated with increased survival. *Sci Rep* 2019; **9:** 10521.

67 Li X, Strasser B, Jafari-Khouzani K, et al. Super-resolution whole-brain 3D MR spectroscopic imaging for mapping d-2-hydroxyglutarate and tumor metabolism in isocitrate dehydrogenase 1-mutated human gliomas. *Radiology* 2020; **294:** 589–97.

68 Herrera-Oropeza GE, Angulo-Rojo C, Gástelum-López SA, Varela-Echavarría A, Hernández-Rosales M, Aviña-Padilla K. Glioblastoma multiforme: a multi-omics analysis of driver genes and tumour heterogeneity. *Interface Focus* 2021; **11:** 20200072.

69 Mansouri A, Karamchandani J, Das S. Molecular genetics of secondary glioblastoma. In: De Vleeschouwer S, ed. Glioblastoma. Brisbane: Codon Publications, 2017: 27–42.

70 John Lin CC, Yu K, Hatcher A, et al. Identification of diverse astrocyte populations and their malignant analogs. *Nat Neurosci* 2017; **20:** 396–405.

71 Huang LE. Friend or foe—IDH1 mutations in glioma 10 years on. *Carcinogenesis* 2019; **40:** 1299–307.

72 Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 2009; **360:** 765–73.

73 Berendsen S, Spliet WGM, Geurts M, et al. Epilepsy associates with decreased HIF-1alpha/STAT5b signalling in glioblastoma. *Cancers* 2019; **11:** 41.

74 Smith-Cohn M, Davidson C, Colman H, Cohen AL. Challenges of targeting *BRAF*^{V600E} mutations in adult primary brain tumor patients: a report of two cases. *CNS Oncol* 2019; **8:** CNS48.

75 Stone TJ, Keeley A, Virasami A, et al. Comprehensive molecular characterisation of epilepsy-associated glioneuronal tumours. *Acta Neuropathol* 2018; **135:** 115–29.

76 Behling F, Schittenhelm J. Oncogenic *BRAF* alterations and their role in brain tumors. *Cancers* 2019; **11:** 794.

77 Zhang Y-X, Shen C-H, Guo Y, et al. *BRAF*^{V600E} mutation in epilepsy-associated glioneuronal tumors: prevalence and correlation with clinical features in a Chinese population. *Seizure* 2017; **45:** 102–06.

78 Kaley T, Touat M, Subbiah V, et al. *BRAF* inhibition in *BRAF*^{V600}-mutant gliomas: results from the VE-BASKET study. *J Clin Oncol* 2018; **36:** 3477–84.

79 Koh HY, Kim SH, Jang J, et al. *BRAF* somatic mutation contributes to intrinsic epileptogenicity in pediatric brain tumors. *Nat Med* 2018; **24:** 1662–68.

80 Ni X-R, Guo C-C, Yu Y-J, et al. Combination of levetiracetam and IFN-α increased temozolomide efficacy in MGMT-positive glioma. *Cancer Chemother Pharmacol* 2020; **86:** 773–82.

81 Hatcher A, Yu K, Meyer J, Aiba I, Deneen B, Noebels JL. Pathogenesis of peritumoral hyperexcitability in an immunocompetent CRISPR-based glioblastoma model. *J Clin Invest* 2020; **130:** 2286–300.

82 Madadi A, Wolfart J, Lange F, et al. Correlation between Kir4.1 expression and barium-sensitive currents in rat and human glioma cell lines. *Neurosci Lett* 2021; **741:** 135481.

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83 Mola MG, Sparaneo A, Gargano CD, et al. The speed of swelling kinetics modulates cell volume regulation and calcium signaling in astrocytes: a different point of view on the role of aquaporins. *Glia* 2016; **64:** 139–54.

84 Campbell SC, Muñoz-Ballester C, Chaunsali L, et al. Potassium and glutamate transport is impaired in scar-forming tumor-associated astrocytes. *Neurochem Int* 2020; **133:** 104628.

85 Shi Z, Zhang W, Lu Y, et al. Aquaporin 4-mediated glutamate-induced astrocyte swelling is partially mediated through metabotropic glutamate receptor 5 activation. *Front Cell Neurosci* 2017; **11:** 116.

86 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:** 4361–66.

87 Youngerman BE, Joiner EF, Wang X, et al. Patterns of seizure prophylaxis after oncologic neurosurgery. *J Neurooncol* 2020; **146:** 171–80.

88 Stocksdale B, Nagpal S, Hixson JD, et al. *Neuro-Oncology Practice* Clinical Debate: long-term antiepileptic drug prophylaxis in patients with glioma. *Neurooncol Pract* 2020; **7:** 583–88.

89 Climans SA, Brandes AA, Cairncross JG, et al. Temozolomide and seizure outcomes in a randomized clinical trial of elderly glioblastoma patients. *J Neurooncol* 2020; **149:** 65–71.

90 Pallud J, Huberfeld G, Dezamis E, et al. Effect of levetiracetam use duration on overall survival of isocitrate dehydrogenase wild-type glioblastoma in adults: an observational study. *Neurology* 2022; **98:** e125–40.

91 Walbert T, Harrison RA, Schiff D, et al. SNO and EANO practice guideline update: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. *Neuro-oncol* 2021; **23:** 1835–44.

92 Guery D, Rheims S. Is the mechanism of action of antiseizure drugs a key element in the choice of treatment? *Fundam Clin Pharmacol* 2020; **35:** 552–63.

93 Greenhalgh J, Weston J, Dundar Y, Nevitt SJ, Marson AG. Antiepileptic drugs as prophylaxis for postcraniotomy seizures. *Cochrane Database Syst Rev* 2018; **5:** CD007286.

94 Spena G, Schucht P, Seidel K, et al. Brain tumors in eloquent areas: a European multicenter survey of intraoperative mapping techniques, intraoperative seizures occurrence, and antiepileptic drug prophylaxis. *Neurosurg Rev* 2017; **40:** 287–98.

95 de Bruin ME, van der Meer PB, Dirven L, Taphoorn MJB, Koekkoek JAF. Efficacy of antiepileptic drugs in glioma patients with epilepsy: a systematic review. *Neurooncol Pract* 2021; **8:** 501–17.

96 Sachkova A, Sperling S, Mielke D, Schatlo B, Rohde V, Ninkovic M. Combined applications of repurposed drugs and their detrimental effects on glioblastoma cells. *Anticancer Res* 2019; **39:** 207–14.

97 Happold C, Gorlia T, Chinot O, et al. Does valproic acid or levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma. *J Clin Oncol* 2016; **34:** 731–39.

98 Redjal N, Reinshagen C, Le A, et al. Valproic acid, compared to other antiepileptic drugs, is associated with improved overall and progression-free survival in glioblastoma but worse outcome in grade II/III gliomas treated with temozolomide. *J Neurooncol* 2016; **127:** 505–14.

99 Haggiagi A, Avila EK. Seizure response to temozolomide chemotherapy in patients with WHO grade II oligodendroglioma: a single-institution descriptive study. *Neurooncol Pract* 2019; **6:** 203–08.

100 Dobran M, Nasi D, Chiriatti S, et al. prognostic factors in glioblastoma: is there a role for epilepsy? *Neurol Med Chir* 2018; **58:** 110–15.

101 Still MEH, Roux A, Huberfeld G, et al. Extent of resection and residual tumor thresholds for postoperative total seizure freedom in epileptic adult patients harboring a supratentorial diffuse low-grade glioma. *Neurosurgery* 2019; **85:** E332–40.

102 Datsi A, Sorg RV. Dendritic cell vaccination of glioblastoma: road to success or dead end. *Front Immunol* 2021; **12:** 770390.

103 Dührsen L, Sauvigny T, Ricklefs FL, et al. Seizures as presenting symptom in patients with glioblastoma. *Epilepsia* 2019; **60:** 149–54.

104 Lamberink HJ, Otte WM, Blümcke I, et al. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. *Lancet Neurol* 2020; **19:** 748–57.

105 Santos-Pinheiro F, Park M, Liu D, et al. Seizure burden pre- and postresection of low-grade gliomas as a predictor of tumor progression in low-grade gliomas. *Neurooncol Pract* 2019; **6:** 209–17.

106 Bonney PA, Boettcher LB, Burks JD, et al. Rates of seizure freedom after surgical resection of diffuse low-grade gliomas. *World Neurosurg* 2017; **106:** 750–56.

107 Al-Dorzi HM, Alruwaita AA, Marae BO, et al. Incidence, risk factors and outcomes of seizures occurring after craniotomy for primary brain tumor resection. *Neurosciences* 2017; **22:** 107–13.

108 Li Y, Shan X, Wu Z, Wang Y, Ling M, Fan X. IDH1 mutation is associated with a higher preoperative seizure incidence in low-grade glioma: a systematic review and meta-analysis. *Seizure* 2018; **55:** 76–82.

109 Abramson JS, Gordon LI, Palomba ML, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. *Proc Am Soc Clin Oncol* 2018; **36:** 7505.

110 Karschnia P, Teske N, Thon N, et al. Chimeric antigen receptor T cells for glioblastoma: current concepts, challenges, and future perspectives. *Neurology* 2021; **97:** 218–30.

111 Frigault MJ, Nikiforow S, Mansour MK, et al. Tocilizumab not associated with increased infection risk after CAR T-cell therapy: implications for COVID-19? *Blood* 2020; **136:** 137–39.

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