Seizures in brain tumors: pathogenesis, risk factors and management (Review)

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Received December 6, 2024; Accepted March 5, 2025

DOI: 10.3892/ijmm.2025.5523

Abstract. Seizures in the context of brain tumors are a relatively common symptom, with higher occurrence rates observed in glioneuronal tumors and gliomas. It is a serious burden that can have a significant impact on the quality of life (QoL) of patients and influence the disease's prognosis. Brain tumor-related epilepsy (BTRE) is a challenging entity because the pathophysiological mechanisms are not fully understood yet. Nonetheless, neuroinflammation is considered to play a pivotal role. Next to neuroinflammation, findings on the pathogenesis of BTRE have established that certain genetic mutations are involved, of which the most known would be IDH mutations in gliomas. Others discussed more thoroughly in the present review include genes such as PTEN, TP53, IGSF3, and these findings all provide fresh and fascinating insights into the pathogenesis of BTRE. Treatment for BTRE presents unique challenges, mainly related to burdens of polytherapy, debated necessity of anti-epileptic prophylaxis, and overall impact on the QoL. In fact, there are no established anti-seizure medications (ASMs) of choice for BTRE, nor is there any protocol to guide the use of these medications at every step of disease progression. Treatment strategies aimed at the tumor, that is surgical procedures, radio- and chemotherapy appear to influence seizure control. Conversely, some ASMs have also shown antitumor properties. The present review summarizes and retrospectively analyzes the literature on the pathogenesis and management of BTRE to provide an updated comprehensive understanding. Furthermore, the challenges and opportunities for developing future therapies aimed at BTRE are discussed.

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Key words: seizures, epilepsy, anti-seizures medication, neuroinflammation, brain metastases, glioma, meningioma, epilepto-genesis, risk factors

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1. Introduction

Annually, >300,000 brain tumor cases are diagnosed globally, making them the fifth most prevalent type of cancer. Meningiomas represent the most prevalent primary benign tumors of the central nervous system (CNS). Recent figures indicate that 40.8% of all CNS tumors in the USA are meningiomas, constituting 56.2% of all benign tumors, whereas gliomas account for 26.3% of all tumors and 50.9% of all malignant tumors (1). Brain metastases (BM) constitute a distinct category and are the most prevalent form of brain tumor, with an incidence ~5-fold greater than that of primary brain tumors (2). Lung cancers, breast cancers and melanomas are the most likely to metastasize to the brain (2). The incidence of seizures varies significantly among different types of brain tumors, ranging from 10% to over 80%, contingent upon the tumor type (3,4). This is a significant side effect that should not be underestimated due to its potential impact on the patients' quality of life (QoL). Numerous studies conducted throughout the years have endeavored to elucidate the pathophysiological mechanisms of brain tumor-related epilepsy (BTRE), yielding various degrees of results. It is generally acknowledged that mutations in the isocitrate dehydrogenase type 1 (IDH1) and type 2 genes contribute to the development of BTRE in gliomas at the molecular level (5,6). In general, various mechanisms, including mechanical (compression), vascular (imbalance in vascularization), chemical (neurotransmitter dysregulation), and inflammatory processes, have been identified in the pathophysiology of BTRE (7). Neurosurgeons frequently prescribe anti-seizure medications (ASMs) during the perioperative period, particularly post-operatively, despite

the absence of studies demonstrating the advantages of this practice for seizure-naïve patients. Current research on BTRE has predominantly focused on gliomas and glioneuronal tumors, while other tumor forms, including meningiomas and BM, have received far less attention. The present review examines the pathophysiology of BTRE, encompassing molecular mechanisms and genetic implications. Risk factors, the correlation between epileptogenesis and tumorigenesis, and the influence of ASMs on tumor progression were also discussed. Finally, some insight was provided into anti-epileptogenesis, which aims to cure epilepsy. The progress made so far and the challenges associated with developing novel therapies are discussed; and the potential solutions that may be advantageous for epilepsy broadly and BTRE specifically are delineated.

2. Pathophysiology of BTRE

The role of neuroinflammation. Inflammation has always played a role in epilepsy, as evidenced by the existence of febrile seizures. This indicates a mechanism through which inflammation induces a hyper-excitable state in brain tissue. Numerous studies have sought to elucidate this mechanism, and while the findings remain partially unsatisfactory, the principal pathophysiological agents have been identified. In neuroinflammation, the microglia and astrocytes secrete pro-inflammatory cytokines (PICs) such as interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), among others. The overload of PICs in the CNS leads to the blood-brain barrier (BBB) breakdown, resulting in further recruitment of PICs from the systemic circulation (8,9). This review focuses on the role of IL-1β, TNF-α, toll-like receptor 4 (TLR4) and High-mobility group box 1 (HMGB1) in BTRE pathophysiology.

Il-1β can induce hyperexcitability via several mechanisms and possesses various receptors, with IL-1R1 being the most involved in epileptogenesis. Upon binding of Il-1β to IL-1R1, ceramide is generated through the activation of neutral sphingomyelinase (N-SMase). Ceramide stimulates phosphorylation of the NR2B subunit of N-methyl-D-aspartate receptors (NMDAR), leading to an increased influx of Ca^{2+} in neuron cells and, subsequently, increased excitability (8). This increase in intracellular calcium (Ca^{2+}) may also stimulate the overproduction of nitric oxide (NO) through nitric oxide synthase. NO induces oxidative stress and cell damage, therefore leading to increased PICs' secretion (10). IL-1β may also induce epilepsy via the synaptic protein synaptophysin (SYN). Using rat models, Xiao *et al* (11) proposed that SYN can regulate neurotransmitter release by acting on Ca^{2+}, and discovered that IL-1β increases SYN expression in the hippocampal neurons via the activation of the PI3K/Akt/mTOR pathway. In another study on temporal lobe epilepsy (TLE), using hippocampal tissues from human subjects, researchers demonstrated that the complex Il-1β/IL-1R1 was responsible for a decrease of up to 30% in GABA-mediated neurotransmission, with protein kinase C also contributing to this phenomenon (12).

TNF-α is secreted by microglial cells and astrocytes under physiological conditions to palliate an eventual decrease of glutamate, thus maintaining an adequate level of neuronal excitability (13). TNF-α has two receptors, TNFR1 and TNFR2, which are considered to have opposing functions in epilepsy (14). TNFR1 serves as the proconvulsive receptor, evidenced by neuroinflammation where excessive TNF-α-TNRF1 binding results in increased glutamate levels through various mechanisms, such as the upregulation of glutaminase in microglia and the upregulation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPAR) (15,16). TNFR1 is also responsible for the neurotoxicity effects of TNF-α due to its possession of a death domain, the TNFR-associated death domain (TADD), which is lacking in TNFR2. TADD facilitates the activation of caspase enzymes (caspases 8 and 10), resulting in cell death. While studies still remain ambiguous on the predominant pathway during TNF-α activation, some discovered that low doses of TNF-α triggered the TNF-α/TNFR1 pathway, while higher doses were required for anticonvulsant effects (TNF-α/TNFR2 pathway) (17,18). While TNF-α enhances the hyperactivity of AMPAR and NMDAR, it conversely induces endocytosis of GABA receptors, increasing GABA absorption and thus resulting in hyperexcitability (19-21).

Another inflammatory mediator with a key role in neuroinflammation would be TLRs. In immunology, TLRs function by binding to specific molecules known as damage-associated molecular patterns. One such molecule is the HMGB1, a DNA-binding protein. In pathological conditions, excess HMGB1 is produced by glial cells and neurons (among others), a reaction that is amplified by cytokines. HMGB1 acts by binding to molecules known as pattern recognition receptors, specifically TLR4 and the receptor for advanced glycated end-products (RAGE). It is considered that TLR4 has a more significant role in epileptogenesis than RAGE (22). Regardless of its binding to RAGE or TLR4, HMGB1 ultimately induces the release and activation of multiple transcription factors (23,24), with nuclear factor kappa B (NF-κB), being a prominent factor in both pathways, crucial in inflammatory and immune gene expression. Activated TLR4 can also enhance calcium influx in neurons through NMDAR, a mechanism that involves N-SMases (8,25). Moreover, HMGB1 is involved in the BBB breakdown, either through binding to RAGE or TLR4 (26), and studies reported decreased seizure activity upon inhibition of the HMGB1-TLR4 pathway (27). HMGB1 protein can also bind to Il-1β, thereby activating it. The latter has similar intracellular domains to TLR4s, and thus is involved in similar metabolic pathways (8). Il-1β and TLR4 can enhance the activation of pro-inflammatory genes through the stimulation of the NF-κB transcription factor. NOD-like receptor protein 3 is among the several activated genes. The latter activates caspase-1 via its inflammasome, which mediates inflammation and is responsible for the production of PICs. The synthesized PICs can then activate the Il-1β/TLR4 pathway, resulting in a cycle of sustained inflammation, and increased seizure risk (28-31).

Neurotransmitter disbalances. Alternative mechanisms can lead to an excessive release of glutamate or inadequate levels of GABA. The Xc-Cystine glutamate antiporter system in the brain imports cystine into the cell and in exchange, glutamate is released. Glioma cells not only express Xc-Cystine channels but due to mechanical compression and oxidative stress on adjacent tissues, there is overexpression of these channels on normal cells in an attempt to supply adequate cystine

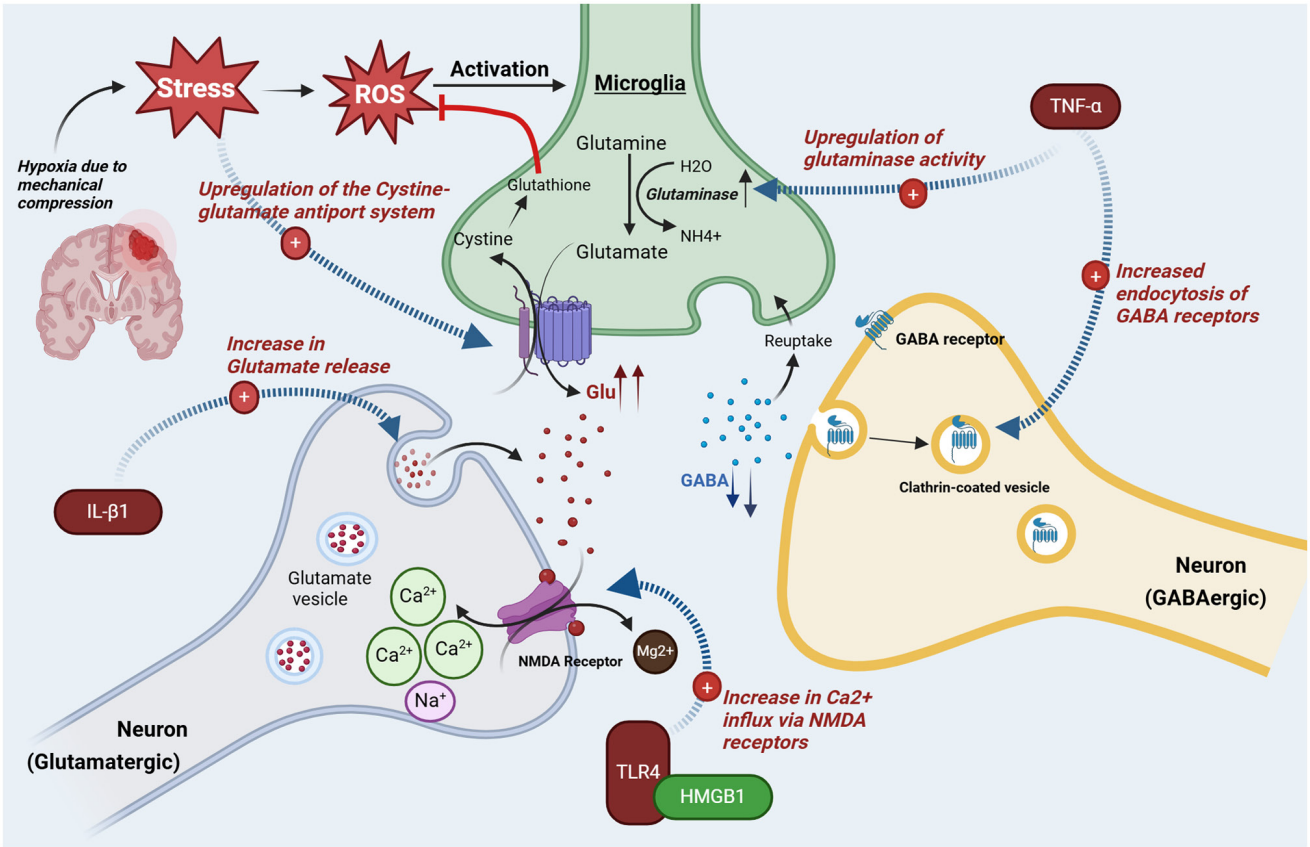

Figure 1. Neurotransmitters imbalance following neuroinflammation. Illustration of how neuroinflammation ultimately leads to high levels of Glu and low levels of GABA in the synaptic cleft. On one hand, the stress induced by the tumor on surrounding tissues triggers a feedback mechanism, activating the Xc-Cystine antiport system in an attempt to produce sufficient glutathione to fight against ROS. TNF-α ensures an adequate supply of Glu for this antiport system by facilitating Glu synthesis via increased activity of glutaminase. Additionally, IL-β1 can directly upregulate Glu release at synapses, while the complex TLR4-HMGB1 promotes excess influx of calcium and sodium ions, leading to increased release of Glu. On the other hand, TNF-α also acts on GABAergic neurons by promoting the endocytosis of GABA receptors. With no receptors to attach to, there is then a reuptake of the 'stranded' GABA neurotransmitters in the synaptic space. This imbalance between Glu and GABA at the synapse tips the balance towards hyperexcitability. Created with BioRender.com. GABA, gamma-aminobutyric acid; TLR4, toll-like receptor 4; HMGB1, High-mobility group box 1; ROS, reactive oxygen species.

for glutathione synthesis (32). This would ultimately result in an excessive release of Glu in the synaptic space (Fig. 1). Furthermore, a comparison of glutamate transport between normal and malignant astrocytes revealed a significant deficiency of sodium-dependent reuptake channels, namely excitatory amino acid transporters 1 and 2 (EAAT1 and EAAT2) (33,34). Moreover, research has indicated a complex mechanism for glutamate transport from glioma or metastatic tumor cells to neurons, utilizing structures similar to synapses found in a normally functioning brain (35) (Fig. 2). In another study on gliomas, glutamate was found to directly down-regulate GABA receptors on astrocytes, resulting in a loss of GABAergic inhibition (36).

3. The role of gene expression in BTRE

IDH1 mutation in low-grade gliomas and secondary glioblastomas. IDH, comprising 3 isoforms, IDH1, IDH2 and IDH3, plays a crucial role in the Krebs cycle, by facilitating the conversion of isocitrate to α-ketoglutarate (α-KG). In anaerobic conditions, lactate dehydrogenase A (LDHA) catalyzes the synthesis of L-lactate from pyruvate. LDHA levels are increased in most tumor types, and tumor cells utilize the enzyme to increase glycolysis and lactate production rates, even under optimal aerobic conditions. This phenomenon is known as the Warburg effect (37). Missense mutations in the IDH1 gene in gliomas results in the production of 2-hydroxyglutarate (2-HG) from α-KG (38). 2-HG is considered to facilitate seizures by enhancing mTOR activity for metabolic functions such as the production of LDHA (high levels of LDHA were observed in IDH1-mutated tissues treated with 2-HG) (39). The proposed mechanism is that 2-HG elevates levels of ribosomal protein S6, which plays a role in mTOR signaling (39). Other mechanisms by which 2-HG may induce epilepsy remain contentious. A study indicated that 2-HG, owing to its structural resemblance to glutamate, may imitate its function by binding to NMDARs, hence enhancing ion influx into neuronal cells and increasing seizure susceptibility (6). The role of 2-HG in epileptogenesis is further substantiated by a condition known as 2-hydroxyglutaric aciduria, characterized by elevated levels of 2-HG, with seizures that exacerbate as the disease progresses being one of the primary symptoms.

Tumor suppressor genes PTEN, TP53, NF1 and glioblastoma. The aggressive and anarchic growth pattern of glioblastomas (GBM) results in genetic mutations that can be detected even intratumorally (40). Tumor suppressor genes phosphatase and tensin homolog (PTEN), tumor protein p53 (TP53) and

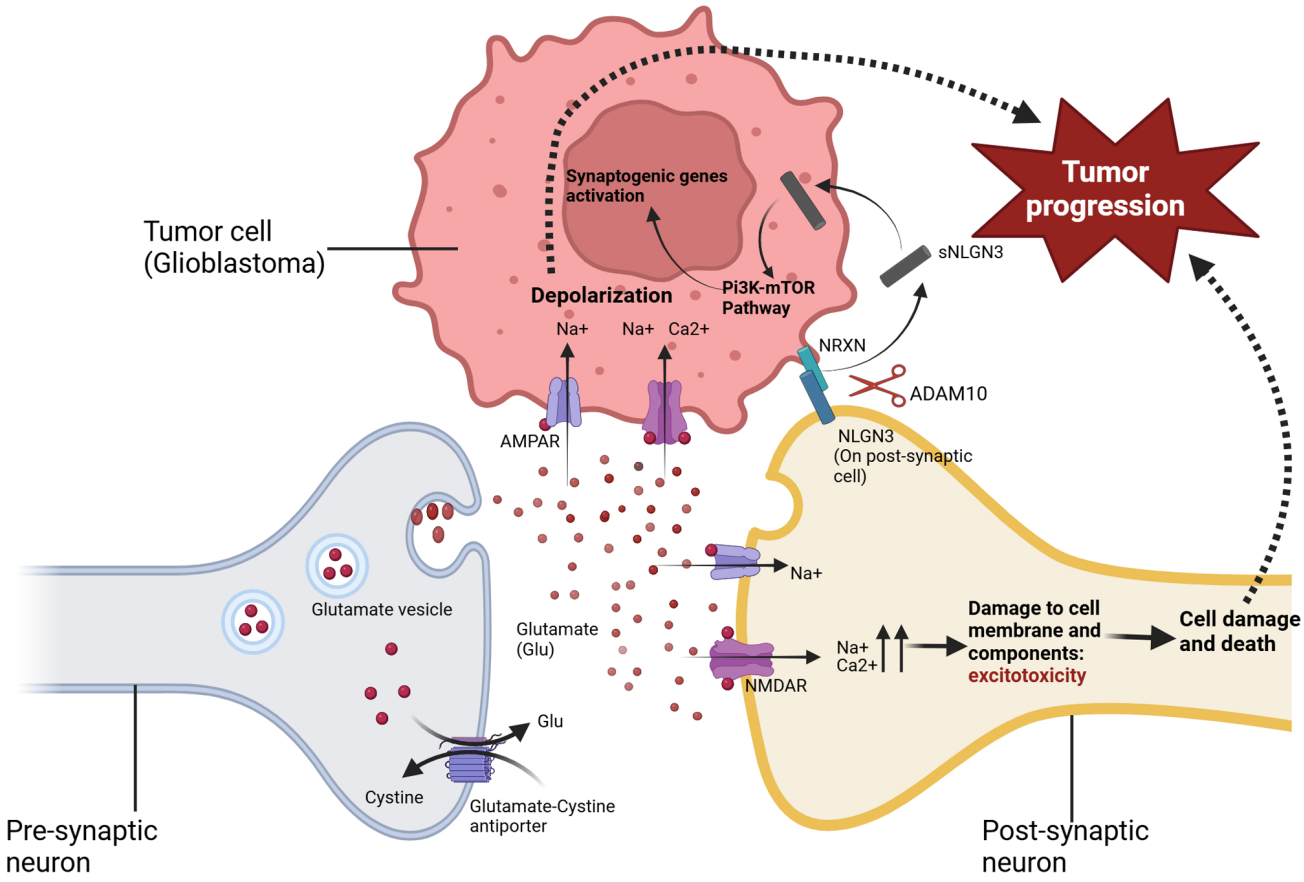

Figure 2. Illustration of a neuron to tumor synapse. Increased Glu release due to upregulation of AMPA and NMDA receptors by tumor cells leads to excitotoxicity and eventually neurons death, which are more likely to be replaced by tumor cells. At the same time, NLGN3, a protein involved in synapse formation, is cleaved from its NRXN counterpart and transformed into soluble NLGN3, which can then readily enter the tumor cell cytoplasm and activate the mTOR pathway. This results in overexpression of synaptogenic genes in the tumor cell nucleus, leading to even more tumor expansion. Finally, tumor cells can also express NMDA and AMPA receptors, and an influx of sodium and calcium ions can trigger a depolarization. All these events lead to tumor progression, as dying neurons are replaced by tumor cells, and the expression of genes involved with synapse formation leads to even more connections between tumor cells and normal neurons. Created with BioRender.com. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, NR2B subunit of N-methyl-D-aspartate; NLGN3, neuroligin 3; NRXN, neurexin.

Neurofibromin 1 (NF1) are affected by these mutations (41,42). It has been suggested that these changes promote tumorigenesis and subsequent tumor progression, while also contributing to epileptogenesis (43). In a healthy organism, PTEN downregulates the PI3K/AKT/mTOR pathway; however, in the context of GBM, a loss-of-function mutation in PTEN results in the disinhibition of this pathway, leading to excessive mTOR signaling (44). The role of PTEN in epileptogenesis was further suggested when scientists discovered that the targeted deletion of this gene generated seizures in animal models (45,46).

The NF1 gene, however, exerts a negative regulatory effect on the Ras (Ras/MAPK and Ras/PI3K) pathways, which are additional pathways involved in cell cycle activity. In GBM, a loss-of-function mutation in the NF1 gene results in the disinhibition of the Ras/MAPK pathway, which subsequently increases mTOR signaling (47). A study by Sabetghadam *et al* (48) showed that silencing of the NF1 gene in rats resulted in lowered seizure thresholds and increased severity.

TP53 (also known as P53) mutations in GBM are predominantly gain-of-function mutations, producing an altered P53 protein known as mut-P53. The latter stimulates the activation of receptor tyrosine kinases such as MNNG HOS transforming gene and EGFR (41), ultimately resulting in cell proliferation. The significance of P53 in epileptogenesis remains incompletely elucidated. Increased expression of P53 has been observed in rats and patients with TLE, particularly in the hippocampus (49,50). Engel *et al* (51) observed that following the triggering of epilepsy in experimental models, P53 levels increased significantly; this increase subsequently activates apoptotic and neuronal cell death processes, exacerbating imbalances and enhancing hyperexcitability. The study also demonstrated that the inhibition of P53 results in more severe seizures. This contrasts with the study by Burla *et al* (52) where P53 inhibition resulted in decreased seizures and inflammation. Nonetheless, inhibition of P53 has shown neuroprotective effects in a variety of conditions, including seizure-induced neuronal cell death (53,54). Further research is required to elucidate the role of P53 in epileptogenesis.

IGSF3 Gene mutation in glioma: The potassium hypothesis. Some studies showed that astrocytes are involved in potassium (K^+) buffering following synaptic depolarization, via inwardly rectifying K^+ channels (Kir 4.1) (55). Mutations or dysregulation of Kir 4.1 (also known as KCJN10) have been linked to seizures in various epileptic syndromes (56,57).

IGSF3 protein is a cell surface protein involved in cellular signaling and molecular binding among other functions. A recent study by Curry *et al* (58) found that mutations in IGSF3 (gain-of-function mutation) contributed to neuronal hyperexcitability. Following the binding of a mutated IGSF3 to Kir 4.1, there is inhibition of the latter's ability to buffer K+, resulting in synaptic remodeling and depolarization spreading (58). Previous studies linked extracellular K^+ concentration to ictogenesis (59). This represents a novel research direction on the mechanism of epileptogenesis in brain tumors, and further studies are encouraged to evaluate the IGFS3 gene as a potential therapeutic target in BTRE.

4. Risk factors for seizures in brain tumors

Preoperative risk factors for seizures in brain tumors include sex, tumor location and size, and the presence of peritumoral edema. Postoperative seizures are primarily associated with the extent of resection, the presence of preoperative seizures, and again, tumor size and location.

The occipital lobe exhibits the lowest propensity for epilepsy, whereas tumors located in the frontal and temporal lobes present the greatest seizure risk (60). Similarly, skull base tumors are less frequently associated with seizures compared with tumors located nearer to the cortex, such as convexity or parasagittal/parafalcine tumors.

Nonetheless, certain risk factors vary amongst different tumor types. IDH mutations in gliomas increase the incidence of seizures in younger patients, as low-grade gliomas (LGGs) are more prevalent in this demographic group. Regarding gliomas, a study revealed that high-grade gliomas associated with seizures were generally smaller, whereas low-grade gliomas were typically larger (61). This contrasts with meningiomas, where an increase in size correlates with a higher likelihood of seizures (62).

A significant component, other than location and size, associated with seizures in meningiomas is peritumoral edema. At a pathophysiological level, peritumoral edema is considered to contribute to a reduction in seizure threshold due to excess secretion of substances such as VEGF and glutamate (63). The male sex is linked to an increased risk of seizures in cases of meningiomas and brain metastasis (64,65). This is comprehensible, as the primary cancers that are most prone to spread to the brain are lung cancers and melanomas (66), and men are at an increased risk of developing lung cancers due to a greater prevalence of smoking and high-risk employment. The meningioma case is interesting as the tumor occurs more frequently in women than in men, with an approximate 3 to 1 ratio (1).

Brain metastasis exhibits a unique profile with specific risk factors exclusive to this category. Multiple metastasis heightens the risk of seizures in BM, as it increases the probability of a metastasis being located in a susceptible region. Studies have also shown that patients with melanoma or lung cancer as their primary tumor had an increased risk of developing seizures in case of brain invasion (67,68). In the case of melanomas, one rationale is that they are among the metastatic tumors most prone to induce intracranial hemorrhage and tumor bleeding, which is a risk factor for seizures in BM (68,69). Furthermore, a previous study by Urban *et al* (70) examined the impact of immune checkpoint inhibitors (ICIs) on epileptogenesis associated with brain metastasis. The study highlighted that new-onset status epilepticus occurred more frequently in patients receiving ICIs compared with those not undergoing this treatment (70), although it is important to note that the majority of patients in the ICIs group had melanoma as their primary malignancy, while lung cancer was the predominant pathology in the non-ICIs group. Additionally, a retrospective analysis of 348 patients with brain metastasis by Garcia *et al* (68) identified ICIs as a risk factor for late postoperative seizures. Overall, further research on this topic is necessary.

The extent of resection significantly influences the incidence of postoperative seizures across all tumor types. Complete resection diminishes the likelihood of postoperative seizure persistence. ASM prophylaxis has shown no impact on the risk of post-operative seizure, which may explain the rationale behind experts' recommendations against its usage in seizure-naïve patients. New-onset postoperative seizures are relatively rare and seem to be more closely associated with tumor grade, tumor recurrence/progression, and IDH1 mutation in glioma cases (71).

5. Seizures prognosis in brain tumors

It is estimated that 60-90% of patients with preoperative seizures due to brain tumors attain seizure freedom post-surgery, with glioneuronal tumors exhibiting the most favorable epilepsy prognosis, whereas seizures associated with glioblastomas tend to be more refractory and recurrent (4). Furthermore, seizures at the onset of disease serve as a favorable prognostic factor for long-term survival in brain tumors (72-74). Convexity tumors are more prone to be symptomatic in the early stages due to cortical irritation, facilitating earlier detection and intervention before progression to an advanced stage; total resection is also more attainable in these instances. Plus, IDH mutations are predominant in slow-growing, low-grade tumors, with a favorable prognosis compared with the more aggressive, high-grade ones. However, persistent seizures are a negative prognostic factor, as they are often indicative of tumor recurrence or progression (74).

De novo seizures are a relatively rare phenomenon after brain surgery, and research on this is notably limited. Danish researchers conducted a pivotal study revealing that the one-year incidence of *de novo* post-craniotomy epilepsy ranged from 3.8% in cases of congenital malformation to 27.6% in cases of cerebral abscess. The risk for intracranial tumors was 15.4%. This correlates with the 12.3% new seizure rate reported in the Englot *et al* (3) meta-analysis involving 4,709 meningioma patients in 2015. However, regarding the Danish study, the occurrence of *de novo* seizures varied among tumor types, and their incidence increased with time (75). Another study focused on meningiomas and *de novo* postoperative tonic-clonic seizures identified cerebral edema enlargement and hemorrhagic transformation of the edema as risk factors for the seizures (76). The role of surgery recurrence in postoperative *de novo* seizures remains contentious.

6. Current management of BTRE

Surgery and radio/chemotherapy. Surgery is a mainstay in the management of brain tumors and influences seizure freedom,

if seizures are part of the disease burden. Gross total resection has shown its efficacy in seizure control compared with partial resection in LGGs, meningiomas and BM (77,78). In GBM, the proliferative characteristics of the tumor may cause the diseased tissue to extend beyond the boundaries shown on a contrast-enhanced MRI. Thus, supra-total resection has shown greater efficacy in seizure control in GBM compared with gross total resection (79). In addition, a study about the relationship between the extent of resection and its impact on seizure freedom in temporal lobe LGGs and glioneuronal tumors revealed that gross total resection combined with hippocampectomy showed a higher seizure freedom rate compared with gross total resection alone (80), potentially suggesting a new strategy for managing BTRE in that specific region of the brain. Further studies are needed.

Over the years, numerous studies have proven the efficacy of radiotherapy on seizure control in LGGs (81-83), alongside chemotherapy with temozolomide (84,85). There appears to be less of a consensus for glioblastomas, with some studies suggesting radiotherapy is beneficial, while others reported an increase in seizures post-radiation (86). The systematic review by Wu *et al* (87) also identified seizures as a side effect of radiotherapy in higher-grade meningiomas (grades II and III), however with a low incidence. Acute seizures are a known risk associated with brain irradiation resulting from neuronal and vascular alterations that may ultimately lead to brain edema and can occur several months post-radiotherapy (88,89). The impact of radio/chemotherapy on seizure control in patients with brain tumors remains poorly researched, maybe accounting for the aforementioned contradictory findings. Further research is encouraged to evaluate the risk-benefit ratio of initiating radiotherapy in brain tumor patients with epilepsy.

Anti-seizure medications

Classification and indications. The use of ASMs in the context of BTRE poses a unique challenge. In addition to potential adverse side effects, the physician should also consider probable interactions with other anticancer therapies. The ideal medications should consequently be those that alleviate both of these difficulties. BTRE is categorized as focal seizures, with or without secondary generalization (4). Multiple professional organizations have advised against the administration of ASMs as a prophylactic treatment in seizure-naïve patients with brain lesions and have discredited the need to use ASMs for patients undergoing brain tumor surgery in the absence of seizures (90). However, it is not consistently implemented in practice (91,92).

The International League Against Epilepsy classification of some ASMs is as follows: Levetiracetam (LEV), Carbamazepine (CBZ), Phenytoin (PHT) and Zonisamide (ZSD) are classified as level A ASMs. At level B, Valproic Acid (VPA) is classified; at level C, Gabapentin (GBP), Lamotrigine (LMG), Oxcarbazepine (OXC), Phenobarbital (PHB), Topiramate (TOP) and Vigabatrin (VGB) are classified; and at level D, Clonazepam (CPM) and Primidone (PMD) (93). LEV has shown superior efficacy and fewer side effects compared with other ASMs for BTRE, establishing it as the preferable treatment for monotherapy, in addition to its being a class A anticonvulsant (94,95). Moreover, LEV has no pharmacological interactions with other drugs and has minimal enzymatic activity via cytochrome P450, making it suitable for poly-medicated patients (96). Some commonly used ASMs, their side effects, and their role in the management of BTRE are summarized in Table I; whereas the mechanism of action of the ASMs predominantly employed in BTRE instances is demonstrated in Fig. 3. Refractory seizures occur in ~15-40% of people with epilepsy due to brain tumors or other etiologies (97,98). In this case, an adjunctive ASM is typically implemented rather than altering the overall treatment regimen. Polytherapy combines drugs with different mechanisms of action to maximize the results. The combination of LEV and VPA has shown significant results in cases of drug-resistant seizures (99). It should be highlighted that ASM polytherapy should be avoided in patients with BTRE wherever possible. It can significantly impact the QoL of these patients. Some studies have in fact shown that patients on multiple ASMs exhibit a higher prevalence of psychiatric comorbidities and more frequently compared with those on monotherapy (100,101).

PRN exhibits a noteworthy profile regarding BTRE. In the United States, it is utilized in monotherapy against focal-onset seizures, with or without generalized tonic-clonic seizures. AMPA antagonism is a relatively novel concept in anti-epilepsy healthcare, with the first ASMs employing this mechanism emerging in the 2nd generation. The majority of ASMs available are ion channel blockers or GABA enhancers, and over time, there is a possibility for drug resistance to occur. Targeting NMDA receptors has so far produced limited outcomes, as they facilitate slow and long-lasting synaptic changes, which are essential for learning and memory processes. As a result, researchers have shifted their attention to AMPA receptor blockade. The most ubiquitous AMPA receptor antagonist, PRN, a 3rd generation ASM, holds significant potential. In clinical trials, it has shown minimal adverse reactions, with dizziness being the most common (123,124). Currently, the clinical dosage of PRN ranges from 2 to 12 mg daily, with an increased likelihood of adverse side effects at higher doses, while the improvements in efficacy do not appear to increase proportionally (124). Although PRN is utilized as monotherapy for epilepsy in a few countries, its efficacy in BTRE has predominantly been demonstrated when used as an adjunctive ASM. A recent study reported promising results when using PRN monotherapy in patients with brain tumors, although the sample size was limited (118). Future studies with larger cohorts are needed.

Drug on drug interactions. Enzyme-inducing ASMs (EIASMs) include PHT, PHB, CBZ, PMD, OXC and TOP. VPA functions as an enzyme inhibitor. EIASMs can shorten the bioavailability of other ASMs in polytherapy; however, this is often not challenging, as the additional drug compensates for the diminished efficacy of the others. Yet still, physicians should bear these interactions in mind when implementing anti-seizure polytherapy, particularly with ASMs such as LMG that pose further challenges in clinical use.

The most sensible area for meticulous monitoring of these interactions is chemotherapy. A systematic review by Bénit and Vecht (125) estimated that EIASMs could increase the clearance of chemotherapeutic agents by 2 to 3-fold the normal rate. Glucocorticoids are also a mainstay in the

Table I. Anti-epileptic drugs and their characteristics.

ASMs	Generation	Mechanism of action	Commonly reported adverse side effects	Serious adverse side effects	Additional notes	(Ref.) showing its efficacy in BTRE monotherapy
Levetiracetam	2nd	Binds to synaptic protein SVA2	Anxiety, fatigue, mood disorders, depression	Suicide ideation (extremely rare)	Vit B6 shows efficacy in countering the psychiatric side effects (102)	(94,95)
Valproic acid	1st	Na+ and Ca^{2+} channels blocking; GABA enhancement	Weight gain, hair loss, hyperammonemia, transaminitis, tremor, rash, fatigue	Thrombocytopenia, hepatotoxicity, SJS	Risk of hepatotoxicity and thrombocytopenia increased with chemotherapy agents (103,104); enzymatic induction	(105)
Lacosamide	3rd	Na^+ Channel blocking	Drowsiness, headache, dizziness, fatigue	PR prolongation, ataxia, SJS, rash, syncope	Contraindicated in patient with 2nd or 3rd degree heart block (106)	(107,108)
Lamotrigine	2nd	Na^+ channel blocking	Cardiac conduction abnormalities	Bronchospasm, SJS, rash, angioedema, CNS depression blood dyscrasias	One of the most common drugs to cause SJS	Not reported, Add-on therapy only (109)
Topiramate	2nd	-AMPA antagonism -Na^+ channel blocking -GABA enhancement	Dizziness, fatigue, anorexia, irritability, confusion, metabolic acidosis, weight loss	Acute angle closure glaucoma, nephro-lithiasis, SJS, rash	Potential agent for the treatment of obesity (110)	(111)
Zonisamide	2nd	Na+ and Ca^{2+} channels blockade	Somnolence, weight loss, rash, renal calculi, dizziness, fatigue	Nephrolithiasis, SJS, rash, glaucoma	Avoid in patients with sulfa allergies	No studies, add-on only (112)
Phenytoin	1st	Na^+ channel blocking	Transaminitis, rash, gingival hyperplasia, nausea, GI tract irritation, hirsutism	SJS, rash, DRESS syndrome, hepato-toxicity,	ASM most associated with skin-related adverse reactions (113,114); teratogenic, responsible for a condition called Fetal Hydantoin Syndrome	Not reported
Carbamazepine	1st	Na^+ channel blocking	dizziness, ataxia, slurred speech, vertigo, leuko-penia, agranulocytosis, skin rash	Aplastic anemia, hepatotoxicity, hyponatremia, SJS, rash, DRESS syndrome	Long-term use (>10 years) may lead to decreased bone density; enzymatic inducer; may cause bone marrow suppression	Not reported

Table I. Continued.

ASMs	Generation	Mechanism of action	Commonly reported adverse side effects	Serious adverse side effects	Additional notes	(Ref.) showing its efficacy in BTRE monotherapy
Oxcarbazepine	2nd	Na+ channel blocking	Fatigue, lightheadedness, weight gain, alopecia	Hyponatremia, SJS, rash	Cytochrome enzyme interactions	(115,116)
Eslicarbazepine	3rd	Na+ channel blocking	Hyponatremia, somnolence, nausea, fatigue, rash	SJS, rash, hepatotoxicity, hyponatremia, blood dyscrasias		None, Add-on only (117)
Perampanel	3rd	AMPA antagonism	Dizziness, vertigo, fatigue, aggressiveness, agitation, irritability, anxiety, nausea	Suicidal ideation	Quickly emerging as a first-line monotherapy alternative for BTRE, more studies needed	(118)
Gabapentin	2nd	A2δ Ca channel subunit inhibition	Dizziness, fatigue, peripheral edema, weight.			Not reported, add-on only (119)
Cenobamate	3rd	GABA enhancement, Na+ channel blocking	Hyperkalemia, fatigue, dizziness,	QT shortening, DRESS	Cytochrome enzymes interaction	Not reported
Clobazam	1st	GABA-A-receptor agonism	Fatigue, dizziness, nausea, dry mouth	Somnolence, sedation		Not reported, add-on only (120)
Tiagabine	2nd	GABA enhancement	GI track upset (diarrhea), fatigue, dizziness, anxiety, tremor, depression	CNS depression, rash	Side effects commonly reported	Not reported, add-on only (121)
Brivaracetam	3rd	SVA2 binding	Fatigue, dizziness, anxiety, depression, irritability	Hypersensitivity reactions		Not reported; Add-on only (122)

DRESS, Drug reaction with eosinophilia and systemic symptoms (severe adverse drug reaction with extensive skin rash, visceral organ failure, lymphadenopathy, eosinophilia and atypical lymphocytosis); SJS, Steven-Johnson Syndrome; CNS, central nervous system; ASM, anti-seizure medication; GABA, gamma-aminobutyric acid; GI, gastrointestinal; BTRE, brain tumor-related epilepsy; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid.

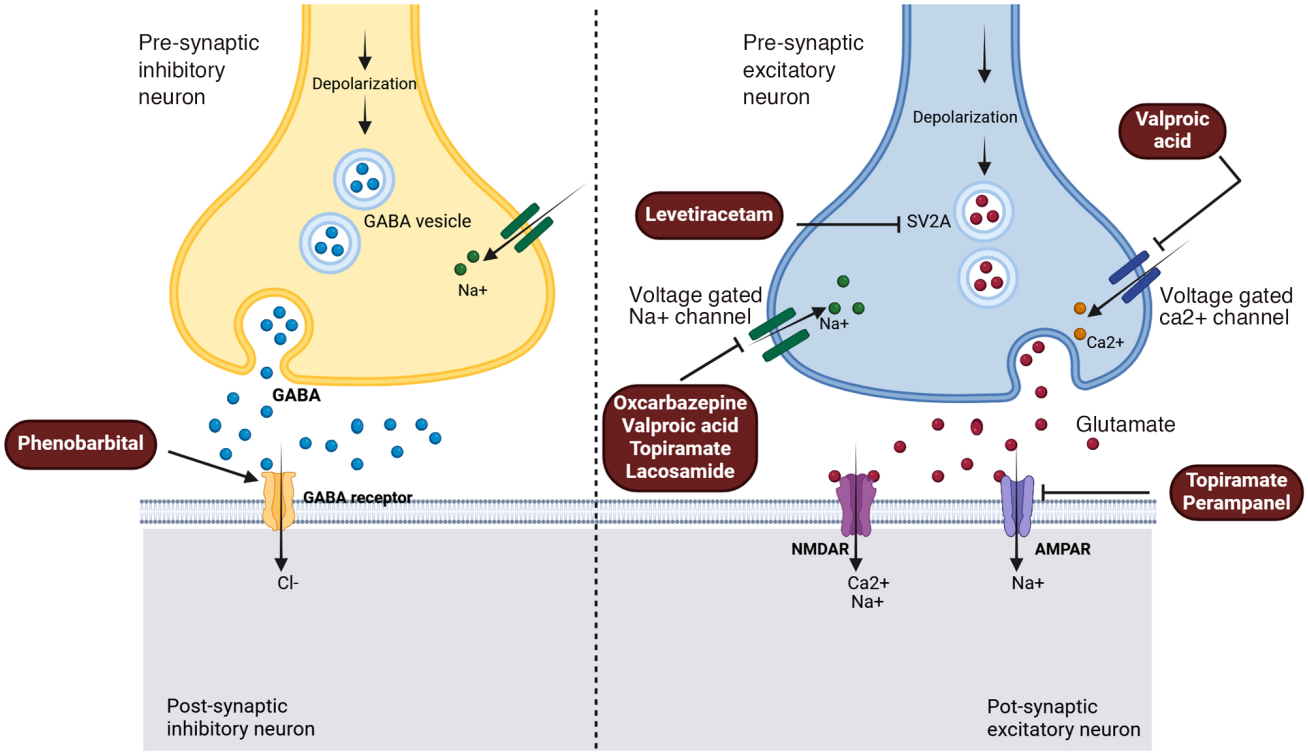

Figure 3. Mechanisms of action of select ASMs. Levetiracetam inhibits the SV2A, a transmembrane protein regulating the role of calcium in inducing neurotransmitter vesicle fusion with the cell membrane. Valproic acid inhibits voltage-gated calcium and sodium channels on presynaptic neuron. Topiramate and Perampanel exert their influence through AMPA receptors antagonism on post-synaptic neurons. Oxcarbazepine, Lacosamide and Topiramate can also act by blocking sodium channels on pre-synaptic neurons. An old ASM, phenobarbital, enhances the activity of GABA receptors on post-synaptic neurons to potentiate inhibitory signal transmission. Created with BioRender. ASMs, anti-seizure medications; SV2A, synaptic vesicle protein 2A; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; GABA, gamma-aminobutyric acid; NMDA, NR2B subunit of N-methyl-D-aspartate.

treatment plan for patients with brain tumor. A study showed that dexamethasone (DXM) bioavailability was only 33% in neurosurgical patients on phenytoin, whereas it was 84% in those not receiving any ASMs (126). The inverse effect also occurs; DXM as an enzyme inducer can reduce PHT levels while also increasing it through a protein-binding mechanism (88). VPA is still routinely used in BTRE monotherapy and exhibits notable drug interactions, such as increasing the toxicity of nitrosoureas, cisplatin and etoposide (103). Inversely, cisplatin reduces the bioavailability of VPA, possibly affecting seizure control (127). All these challenges have resulted in the emergence of new classes of ASMs with minimal enzymatic activity, encouraging physicians to choose these over older generations. The chemotherapeutic drug temozolomide also presents an effective profile in glioma treatment due to its dearth of pharmacologic interactions with ASMs, as it is not metabolized by hepatic enzymes.

Comorbidities. Patients with brain tumors often present additional health complications that require extra precautions while using ASMs. Furthermore, the management of comorbidities may occasionally benefit from certain anti-seizure medications. Patients with brain tumors who also experience migraine headaches may benefit from VPA, ZSD and TOP (128,129). In the mentally disabled, ASM monotherapy should be prioritized whenever feasible due to the higher susceptibility of this population to the adverse effects of ASMs (130). Patients with behavioral issues should avoid LEV, Brivaracetam, PRN and TOP. VPA appears to be well tolerated in patients with psychiatric problems such as anxiety, depression, or psychosis, but LEV should be avoided in this group (130).

Concerning infectious comorbidities, anti-tuberculosis drugs Isoniazid and Rifampicin exert opposing effects on the metabolism of VPA (131). Numerous studies present conflicting results on the impact of VPA on viral load in patients with HIV (132-134). Further studies with larger cohorts are needed to evaluate potential interactions between VPA and antiretroviral drugs. In patients with HIV, LEV should be prioritized, with TOP as a second line option (130).

Seizures resulting from brain tumors during pregnancy are thankfully a rare phenomenon. PHT is a highly teratogenic ASM, responsible for the Fetal Hydantoin Syndrome; it should be considered a last-line option of treatment during pregnancy. Studies suggest that VPA is also responsible for numerous birth defects. In a large French cohort study by Blotiere *et al* (135), they investigated the risk of developing 23 distinct malformations due to prenatal exposure to 10 different ASMs; VPA emerged as the most teratogenic, with TOP also identified as a significant risk factor. ASMs suitable for BTRE monotherapy, such as LEV, OXC and the adjunct ASM LMG, were the least likely to cause birth defects (135). These results corroborated the findings of a previous study on the same topic (136). Furthermore, VPA would also be responsible for developmental and cognitive impairments in children born to mothers who received this ASM during pregnancy (137,138).

Antitumor effect of ASMs. Some of the mechanisms underlying epileptogenesis are also involved in tumor growth and progression. Tumor-to-neuron synapses act bidirectionally; the tumor increases neuronal excitability by upregulating AMPA receptor activity and glutamate release, while neurons release a mitogen known as neuroligin-3, which stimulates tumor growth through the activation of the PI3K-mTOR pathway (35,139,140). Further evidence of this mechanism was shown when AMPA receptor antagonist Perampanel (PRN) successfully slowed down tumor growth (140). Another growth mechanism is considered to involve NMDA receptors, as blockade of these receptors was successful in mitigating tumor growth in another study (141). This then presupposes that tumor treatment should influence epileptic activity, and vice-versa. Over the years, studies have emerged about the potential role of ASMs in improving survivability in brain tumor patients, to varying degrees of results. The majority of the studies have focused on LEV and VPA, due to their greater potential.

LEV has been shown to inhibit O6-Methylguanine-DNA Methyltransferase (MGMT), a DNA repair enzyme involved in the proliferation of cancer cells (142). A few retrospective studies concluded that LEV improved survival in patients undergoing chemotherapy with temozolomide for glioblastoma (143,144). However, a meta-analysis and a prospective randomized control trial, both featuring larger sample sizes and more curated statistical methodologies, found no evidence supporting the efficacy of LEV as an antineoplastic agent in patients with GBM (145,146). The differences in outcome across these studies suggest the potential influence of additional factors, such as the molecular profile of the GBM (MGMT methylated vs non-methylated; IDH-mutant vs. IDH-wild type). This presents a promising avenue for future research.

The role of VPA as an antineoplastic agent is less controversial than that of LEV, and it is the most extensively researched in this context, possibly due to the initial identification of potential beneficial effects of ASMs on survival in brain tumors involving this drug (147). Survival rate is increased when combining VPA with temozolomide for glioblastoma management (85,148,149). VPA can act as a histone deacetylase inhibitor (HDACI), particularly at high doses (150,151). HDACIs are a new group of anticancer agents that induce cell cycle arrest and eventually apoptosis in cancer cells. Another hypothesis is that VPA, through its enzyme inhibitory activity, increases the bioavailability of temozolomide, hence augmenting its chemotherapeutic efficacy (149).

Other ASMs have displayed antitumor effects, mostly in a preclinical setting. Salmaggi *et al* (152) and Lange *et al* (153) investigated the influence of PRN on tumor growth *in vitro*. Both studies concluded that PRN limits tumor growth by promoting cell apoptosis (152,153). Interestingly, Lange *et al* (154) discovered no advantage in survival improvement regarding the role of PRN on tumor progression *in vivo* (154). Brivaracetam and Lacosamide (LCM) have also demonstrated antineoplastic properties in *in vitro* experiments (155). Additionally, studies indicated that LCM and CBZ exhibit HDAC inhibition activity (156,157), suggesting a similar mechanism to VPA in inhibiting tumor growth; this requires further exploration. Other studies have shown the antiproliferative effects of LMG and PHT on breast cancers (158,159). Future studies could help determine if these two ASMs should be prioritized for seizures resulting from BM related to a breast tumor.

Withdrawal of ASMs. There is no consensus on the timing of discontinuation of ASMs in patients with BTRE, necessitating cooperation between the patient and their physician. Factors influencing ASM withdrawal include patient preference, cognitive or significant side effects, polypharmacy, and sedation or fatigue. Notable risk factors for postoperative seizures include a history of preoperative seizures, tumor progression, incomplete surgical resection and tumor location, particularly in the temporal, insular and frontal lobes.

In a prospective observational study, Koekkoek *et al* (160) proposed that the cessation of ASM medication should be evaluated based on tumor progression risk. The study revealed that 26% of patients who discontinued ASMs experienced recurrent seizures, with 58% of these individuals exhibiting tumor progression. In another study by Das *et al* (161), the effects of ASM discontinuation were examined in patients who underwent surgery for LGGs and meningiomas. Among the 111 patients who either had their medications withdrawn or never initiated anti-seizure therapy, only 9.9% experienced seizures. Notably, postoperative seizures occurred in 28% of patients who maintained uninterrupted ASMs treatment (161). This highlights the clinician's decision to continue ASMs in patients with risk factors for postoperative seizures.

The timing of withdrawal is also important. For non-tumor-related epilepsy, epileptologists suggest it is safe to discontinue ASMs after 1 year of seizure freedom; nevertheless, this choice varies significantly across clinicians (162,163). Research on tumor-associated epilepsy is limited. In a study by Jiang *et al* (164) on seizure relapse in glioma patients, 28 patients experienced relapse, with 20 of them (71.4%) relapsing within 6 months following the withdrawal of ASMs. All patients included in the study were on anti-seizure medication for at least 2 years postoperatively prior to withdrawal (164). In summary, withdrawal remains a contentious topic with no consensus; it is hoped that future studies could help guide practitioners in decision-making about discontinuation of ASMs.

7. New avenues for the management of BTRE

There is ongoing research focused on new targets for the development of ASMs. While the majority of this research is centered on primary epilepsy, certain mechanisms described in the physiopathology section of the present review are relevant to epilepsy due to causes other than brain tumors. This suggests that prospective new molecules resulting from these studies may still be beneficial to patients suffering from BTRE. Some new molecules, under investigation, and targeting mechanisms outlined in the pathophysiology section of this review are discussed below. Ongoing initiatives are being made to cure epilepsy by directly targeting epileptogenesis to alter the disease process or develop preventive measures.

Targeting new pathways

Targeting isocitrate dehydrogenase and glycolysis. Generally, tumor cells utilize more energy than normal for their metabolism compared with normal cells. With IDH mutation, glioma

cells mostly utilize glycolysis for ATP production, rather than the Krebs cycle (Warburg effect), and they upregulate GLUT1 and GLUT3 transporters expression to further augment energy production (165). 2-deoxy-D-glucose (2DG), a glycolysis inhibitor, is currently the focus of several preclinical trials for the treatment of various cancers, including GBM (166). PET imaging studies with radiolabeled 2DG have shown increased glucose utilization in epileptic brain regions during the ictal phase of seizures, correlating with increased neuronal activity (167). This suggests a possible anti-seizure effect of 2DG. Both the acute and chronic anti-seizure effects of 2DG were evidenced in a study by. Stafstrom *et al* (168), whilst another study found that long-term administration of the drug was pro-convulsant (169). A proposed rationale for these contradictory results was that 2DG, by blocking glucose entry into cells, could lead to seizures, as hypoglycemia-induced seizures are a well-documented phenomenon (169). Additionally, some cardiac side effects have been reported in preclinical trials involving 2DG (170), further undermining its safety profile for clinical application.

Ivosidenib is an IDH1 inhibitor approved for treating acute myeloid leukemia. Its efficacy as an ASM is currently confined to a limited number of case reports, with seizure control being a secondary objective in one instance (171,172). It is anticipated that these reports will stimulate further interest in the function of this molecule as an anti-seizure agent and result in more comprehensive and definitive research.

Targeting the agents of neuroinflammation. HMGB1 overexpression during neuroinflammation leads to downstream activation of PICs such as TLR4, and other factors such as receptor for RAGE and NF-κB. It is then stipulated that the HMGB1/TLR4/RAGE/NF-κB signaling pathway is responsible for the overexpression of P-glycoprotein (P-gp), a transporter protein associated with drug-resistant epilepsy (DRE) (173,174). This has led to various studies on HMGB1 blockage for the treatment of DRE, including the development of the monoclonal antibody anti-HMGB1 mAb, which has proved its anti-seizure potential in animal models (175-177). Anti-HMGB1 mAb has also shown its efficacy in a variety of CNS diseases, some of which may entail seizures (178).

BBB breakdown secondary to neuroinflammation positions astrocytes as well as PICs as potential new targets for the development of new ASMs. VX-765 (Belnacasan), an inhibitor of interleukin converting enzyme/caspase-1, which subsequently inhibits IL-1β and HMGB1 downstream, has shown anti-seizure efficacy (179), and possesses a favorable clinical profile (180). In other studies, the antagonism of TLR4 and IL-1R1 with Anakinra, a second-line drug used in the treatment of rheumatoid arthritis, diminished seizure activity in animal models (27,181,182), presumably via decreased expression of NMDA glutamate receptors. Anakinra has mostly been utilized in the care of febrile infection-related epilepsy syndrome in humans, yielding positive results (183-185). Most of the evidence derives from case reports; hence, studies with larger cohorts may be warranted. Elsewhere, research has shown that the activation of the ALK5/TGF-β signaling pathway in astrocytes, facilitated by albumin following BBB breakdown, promotes seizures via excitatory synaptogenesis (186). The mechanism involves the overactivity of this pathway, which inhibits K^+ buffering by decreasing Kir 4.1 channel function and glutamate reuptake abilities of astrocytes (187). The ALK5/TGF-β pathway then constitutes another target for the development of novel anti-seizure medications.

Another prospect for inhibition in the fight against seizures and epilepsy is the complement receptor C5ar1. Complement activation is a critical occurrence in inflammation, and the study by Benson *et al* (188) found that pro-inflammatory receptor C5ar1 was upregulated in rats following induced status epilepticus. Utilizing the C5ar1 inhibitor PMX35, they effectively diminished both the frequency and severity of acute and chronic seizures (188). The proposed mechanism posits that the inhibition of C5ar1 results in a decreased release of PICs, including TNF-α and IL-1β.

The mTOR pathway inhibitors. The mammalian target of rapamycin (mTOR) plays a crucial role in several phases of the cell cycle and is primarily composed of two subunit complexes: mTORC1 and mTORC2. The complex mTORC1 facilitates the overexpression of AMPA receptors *in vitro* (189). mTOR inhibitors, such as rapamycin, have shown antiepileptic properties in animal models across multiple studies (190,191). Nonetheless, other studies have indicated that rapamycin exhibits inconsistency in its efficacy against seizures (192,193). The extensive range of mTOR signaling targets in the brain may explain the inconsistent findings among these studies. Everolimus, a rapamycin derivative, utilized in the treatment of some cancers, has shown efficacy in refractory seizures (194,195), and is currently used for the management of seizures in patients with tuberous sclerosis complex (196). Other mTOR inhibitors currently studied for their anti-seizure effects include the immunosuppressant mycophenolate, novel drugs PQR620 and PQR530, as well as natural compounds curcumin and resveratrol (197-201). PQR620 and PQR530 showed enhanced efficacy compared with rapamycin and everolimus for the management of seizures due to their expedited penetration of brain tissues (199).

Improving experimental models and approach to development of new ASMs. Researchers mostly rely on animal models to elucidate the pathogenesis of epilepsy and develop new drugs. Given that BTRE seizures are classified as focal with secondary generalization, the animal model most suitable for research is the kindling epilepsy model (202). However, the predominant models for ASM screenings are the pentylenetetrazol and maximum electroshock models (acute models). Experiments with these two models were unable to demonstrate the antiepileptic characteristics of LEV, characteristics that were ultimately identified using the kindling model (202). Due to financial constraints, the kindling model is not widely utilized; yet, to develop new therapeutic agents targeted specifically at BTRE, it is imperative to devise new, more economical models that function similarly to the kindling model.

All ASMs attain their objective by diminishing neuronal excitability in the brain, and given that this activity is crucial for normal cerebral functions, most ASMs are associated with a plethora of adverse side effects. Side effects may result in non-compliance with treatment, incurring significant costs and serving as a primary factor for breakthrough of seizures (203,204). The prolonged administration of these drugs necessitates careful consideration of adverse effects. For development of new ASMs, the efficacy is consequently at risk of being jeopardized by safety concerns. The development of

agents that specifically target cell populations or circuits may enhance efficacy and improve tolerance (205). A previous study concentrated on this strategy, yielding promising results (206). Furthermore, researchers have long endeavored to develop therapies that target epileptogenesis, which, in the context of BTRE, could facilitate the establishment of preventive care and/or disease-modifying therapies (DMTs). The objective is to integrate different drugs with different mechanisms of action (some may not necessarily be ASMs), to simultaneously target multiple pathways involved in epileptogenesis, and to delineate pertinent circuits (207). The Search Tool for Interacting Chemicals is an extensive database that encompasses known and predicted interactions between chemical molecules and proteins across numerous species (208), and is utilized to determine optimal pairings. Studies using this methodology yielded combinations demonstrating promising outcomes, including LEV/TOP, LEV/TOP/GBP and LEV/Atorvastatin/Ceftriaxone (209,210). Notably, none of these combos succeeded in retaining the neuroprotective effect associated with the individual administration of some of the drugs (209,210). Nevertheless, further research would significantly aid in identifying new combinations.

8. Discussion and conclusion

BTRE remains a crucial public health concern, with its pathophysiological mechanisms not yet fully elucidated. Neuroinflammation significantly contributes, as do genetic mutations. Mechanical compression of tumors can induce stress that results in the release of PICs from glial cells. These PICs not only alter the electrical activity of the brain through changes in ion channel traffic and receptor expression modulation, but they can also trigger the BBB's rupture to amplify inflammation. The risk of seizure development varies with the type of brain tumor, with prevalent risk factors encompassing tumor location, size, histopathology and level of resection.

Currently, no cure for epilepsy exists, and available treatments are solely symptomatic, aimed at alleviating seizures. LEV, a modulator of neurotransmitter release through synaptic vesicle 2A binding, is currently the recommended drug for BTRE. Other agents are rapidly emerging as monotherapy alternatives, with PRN receiving special attention. The minimal drug-drug interactions, selectivity for AMPARs, and antitumor properties represent an appealing profile. Numerous anti-seizure drugs are presently undergoing various stages of development, some with new mechanisms of action and others aimed at restructuring already existing ASMs (204).

In recent years, research aimed at discovering a cure for epilepsy has achieved minimal yet significant progress. Anti-epileptogenesis has recently been a focal center of discussions on epilepsy therapy. Focused on prevention and disease modification, the achievement of anti-epileptogenesis by drug combinations would signal a significant scientific breakthrough. Especially for BTRE, the prospects are intriguing: Preventive ASM therapy in a meningioma patient with large peritumoral edema, a patient with IDH1 mutated glioma, or a melanoma patient with multiple brain metastasis. However, research on preventive anti-seizure therapy is impeded by prolonged experiment durations due to the necessity of monitoring the onset of epilepsy (or its absence, indicating successful prevention), which may last for numerous years (207,211). Consequently, most endeavors in this research area are directed towards disease modification, with the aspiration of finding a cure. DMT may also mitigate the adverse side effects associated with ASMs, whose risk escalates with prolonged usage.

New therapies require evaluation, necessitating the use of animal models. Efforts have been made to create new models, and the pursuit of developing more cost-effective and efficient alternatives aimed at BTRE may be vital for this patient population. Organizations such as the Epilepsy Therapy Screening Program (ETSP), a division of the National Institute of Neurological Disorders and Stroke in the USA, have played a significant role in this field. The ETSP allows researchers globally to evaluate new compounds through its diverse array of animal models tailored for various circumstances (212,213). Animal models developed for epilepsy prevention and disease modification research have recently been incorporated into the ETSP catalog (204).

Finally, epileptogenesis and tumorigenesis are closely interconnected processes, wherein seizures induce neuronal cell death via excitotoxicity, subsequently leading to the replacement of dead neurons with tumor cells for tumor proliferation. It is hoped that future studies will facilitate the development of a new therapeutic approach that simultaneously slows down tumor progression and prevents seizures.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 82270825).

Availability of data and materials

Not applicable.

Authors' contributions

CDD chose the research subject, researched the literature for relevant articles and wrote the drafts. DOF performed language and grammar editing. CT and XL revised the manuscript drafts and restructured the content, and provided access to tools used to generate the figures in the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, Quillbot artificial intelligence tool was used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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