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Investigation of Factors Influencing the Effectiveness of Levetiracetam, Lamotrigine, and Lacosamide in Brain Tumor-Related Epilepsy

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Abstract

Brain tumor-related epilepsy (BTRE) is a prevalent complication, affecting 25-60% of patients with primary or metastatic brain tumors, significantly impacting quality of life and complicating oncologic management. This narrative review examines factors influencing the effectiveness of levetiracetam (LEV), lamotrigine (LTG), and lacosamide (LCS) in BTRE. By analyzing epidemiological data, pathophysiological mechanisms, pharmacological profiles, and clinical evidence, we study how tumor characteristics (type, location, molecular profile), patient-specific factors (age, comorbidities), drug interactions, and pharmacodynamic properties modulate seizure control. LEV is often the first-line choice due to its favorable tolerability and minimal drug interactions, achieving seizure freedom in 65-80% of patients in some studies. LTG and LCS, effective as monotherapy or add-on therapies with response rates of 50-70%, vary in efficacy based on tumor histology and peritumoral microenvironment. Challenges include drug resistance linked to glutamate excitotoxicity, sodium channel dysregulation, and tumor-driven molecular changes. Research gaps, such as long-term comparative trials and personalized dosing strategies, highlight the need for further investigation. Optimizing AED selection in BTRE requires a multidisciplinary approach to balance seizure control, antitumor therapy efficacy, and adverse effect minimization, emphasizing personalized medicine.

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Introduction

Brain tumors, encompassing primary neoplasms like gliomas and meningiomas and metastatic lesions from cancers such as lung or breast, represent a significant burden in neuro-oncology. Among their complications, brain tumor-related epilepsy (BTRE) is one of the most prevalent, affecting 25-60% of patients, with incidence varying by tumor type, location, and growth dynamics (1,2). Low-grade gliomas (WHO grades 1-2) are associated with seizure rates of 70-90%, while high-grade gliomas (grades 3-4) have rates of 30-50% (3,4). Meningiomas and metastatic tumors exhibit seizure incidences of 20-40% and 20-35%, respectively (5,6). BTRE significantly impairs quality of life, contributing to cognitive decline, increased risk of injury, and interference with antitumor treatments such as surgery, radiotherapy, and chemotherapy.

The management of BTRE is complex due to the need to control seizures while avoiding adverse interactions with oncologic therapies. Older antiepileptic drugs (AEDs), such as phenytoin and carbamazepine, induce cytochrome P450 enzymes, accelerating the metabolism of chemotherapeutic agents like temozolomide, thus reducing their efficacy (7,8). Consequently, newer AEDs—levetiracetam (LEV), lamotrigine (LTG), and lacosamide (LCS)—have emerged as preferred options

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due to their non-enzyme-inducing properties, favorable pharmacokinetics, and reduced side-effect profiles (9,10). However, their effectiveness is not uniform, influenced by tumor-specific factors (e.g., histology, molecular markers), patient characteristics (e.g., age, comorbidities), and pharmacological interactions.

This narrative review aims to provide a comprehensive synthesis of factors affecting the efficacy of LEV, LTG, and LCS in BTRE. By examining epidemiology, pathophysiology, pharmacology, clinical evidence, and modulating variables, we seek to elucidate optimal therapeutic strategies. Controversies, such as the role of prophylactic AED use and the impact of molecular tumor profiles (e.g., IDH1 mutations), are addressed, alongside gaps in knowledge that warrant further investigation. The review emphasizes the importance of personalized medicine in improving seizure control and overall outcomes in BTRE patients, highlighting the need for multidisciplinary coordination between neurologists and oncologists.

Methods

This narrative review was conducted through a comprehensive literature search to identify relevant studies on BTRE and the specified AEDs. Databases including PubMed, Google Scholar, and Web of Science were queried using keywords such as “brain tumor-related epilepsy,” “levetiracetam BTRE,” “lamotrigine brain tumor seizures,” “lacosamide glioma epilepsy,” “factors influencing AED effectiveness,” “pathophysiology BTRE,” and “drug interactions antiepileptic brain tumors.” The search spanned publications from 2000 to 2025, focusing on English-language articles, including clinical trials, cohort studies, reviews, and meta-analyses. Inclusion criteria prioritized studies addressing efficacy, safety, mechanisms, and influencing factors in human subjects with primary or metastatic brain tumors. Exclusion criteria encompassed animal-only studies, non-epilepsy indications, and reports on older enzyme-inducing AEDs unless comparative. Approximately 150 articles were screened, with 50 selected for citation based on relevance, quality, and impact. While not systematic, transparency was maintained by cross-referencing citations and selecting high-impact sources for critical appraisal.

Epidemiology of BTRE

BTRE’s epidemiological profile is critical for tailoring treatment strategies. Seizure incidence in brain tumor patients ranges from 20-60%, with primary tumors exhibiting higher rates than metastases (11,12). Low-grade gliomas (WHO grades 1-2), such as oligodendrogliomas and astrocytomas, are highly epileptogenic, affecting 70-90% of patients due to their slow growth and cortical infiltration (13,14). High-grade gliomas (grades 3-4), including glioblastomas, have seizure rates of 30-50%, often driven by rapid tumor progression, necrosis, or hemorrhage (15,16). Meningiomas, particularly those compressing cortical regions, cause seizures in 20-40% of cases, while metastatic tumors from lung, breast, or melanoma induce epilepsy in 20-35% of patients, with multiple lesions or peritumoral edema increasing risk (17,18).

Seizures are the presenting symptom in 20-40% of brain tumor diagnoses, often leading to early detection but posing immediate management challenges (19,20). Tumor location is a key determinant of epileptogenicity: tumors in the temporal, frontal, or parietal lobes are more seizurogenic due to their proximity to excitatory neuronal networks (21). Slower-growing tumors, such as low-grade gliomas, promote chronic epilepsy by allowing peritumoral adaptation, whereas rapidly progressing tumors like glioblastomas trigger acute seizures through edema or hemorrhage (22). Molecular markers significantly influence seizure risk. For instance, IDH1 mutations in gliomas are associated with higher seizure incidence, likely due to altered glutamate metabolism via 2-hydroxyglutarate production (23,24). BRAF mutations in gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs) also enhance epileptogenicity by dysregulating signaling pathways (25).

Demographic factors further modulate BTRE risk and AED response. Younger patients, particularly those under 40, face a higher risk of chronic epilepsy due to longer survival and greater neuronal plasticity, necessitating AEDs with minimal cognitive side effects (26). Elderly patients, often with comorbidities like renal or hepatic impairment, require careful AED selection to avoid toxicity (27). Gender differences are less pronounced, but psychiatric comorbidities, such as depression or anxiety, prevalent in 20-30% of BTRE patients, influence AED choice, favoring LTG for its mood-stabilizing effects (28). Performance status, as measured by scales like the Karnofsky Performance Score, also predicts seizure control, with higher scores correlating with better AED response (29).

These epidemiological insights guide AED selection. LEV is often preferred for its broad-spectrum efficacy and tolerability, particularly in younger patients with low-grade gliomas (30). LTG’s mood-stabilizing properties make it suitable for patients with psychiatric comorbidities, while LCS’s rapid onset is advantageous in acute settings or elderly patients with cardiac stability (31). Understanding these patterns ensures targeted therapy, balancing seizure control with oncologic and patient-specific needs.

Pathophysiology of BTRE

BTRE arises from a complex interplay of tumoral, peritumoral, and systemic factors that disrupt neuronal homeostasis. Tumors induce epileptogenesis through mechanical compression, peritumoral edema, and infiltration, which alter local neuronal circuitry and excitability (32,33). A primary mechanism is the imbalance between excitatory and inhibitory neurotransmission, driven by tumor cells releasing excess glutamate, overwhelming GABAergic inhibition (34). This glutamate excitotoxicity is exacerbated by peritumoral hypoxia, acidosis, and metabolic stress, which modify ion channel function and upregulate excitatory neurotransmitter receptors, such as AMPA and NMDA receptors (35,36).

Molecular alterations play a significant role in BTRE. IDH1 mutations, prevalent in low-grade gliomas, produce 2-hydroxyglutarate, an oncometabolite that mimics glutamate, directly promoting neuronal hyperexcitability (23,24). BRAF V600E mutations in gangliogliomas and DNETs enhance epileptogenicity by activating mTOR signaling, leading to neuronal hyperexcitability and synaptic remodeling (25). Inflammation is another critical driver, with cytokines like IL-1β, TNF-α, and IL-6 disrupting blood-brain barrier integrity, allowing serum proteins (e.g., albumin) to enter the brain and trigger seizures (37,38). Peritumoral astrocytes, often dysfunctional in gliomas, fail to regulate extracellular glutamate, further exacerbating excitability (39). Additionally, altered expression of potassium-chloride cotransporter 2 (KCC2) in peritumoral neurons impairs GABAergic inhibition, contributing to epileptogenesis (40).

These pathophysiological mechanisms directly influence AED effectiveness. LEV's action on synaptic vesicle protein 2A (SV2A) reduces glutamate release, making it particularly effective in glutamate-driven BTRE, such as in IDH-mutant gliomas (41,42). LTG, by inhibiting voltage-gated sodium channels, stabilizes peritumoral neurons, particularly in tumors with high sodium channel expression, such as high-grade gliomas (43,44). LCS enhances slow inactivation of sodium channels, which is advantageous in tumors with chronic channel dysregulation, often seen in rapidly progressing tumors (45,46). However, drug resistance can emerge if tumors alter drug targets through epigenetic modifications or upregulate multidrug resistance proteins, such as P-glycoprotein, limiting AED brain penetration (47,48).

Critical appraisal reveals significant limitations in the current literature. Most pathophysiological studies are preclinical, relying on animal models or small human cohorts, which limits their generalizability to diverse BTRE populations (49). Controversies persist regarding the relative contributions of tumor mass effect versus peritumoral changes in driving seizures, with some studies suggesting that resection alone may control seizures in low-grade gliomas, while others emphasize the need for AEDs to address residual epileptogenic foci (50). The role of inflammation and blood-brain barrier dysfunction in modulating AED efficacy also requires further exploration, as these factors may explain variable responses across patients (51). These insights highlight the need for AEDs tailored to specific epileptogenic mechanisms, with a focus on integrating molecular and imaging data to guide therapy.

Pharmacology and Mechanisms of Action

LEV, LTG, and LCS are second- and third-generation AEDs with distinct mechanisms and pharmacokinetic profiles that align with BTRE's pathophysiology, making them suitable for managing seizures in this population.

Levetiracetam (LEV) binds to synaptic vesicle protein 2A (SV2A), modulating vesicle fusion and reducing the release of excitatory neurotransmitters, particularly glutamate (41,42,52). This mechanism is particularly effective in BTRE, where glutamate excitotoxicity is a primary driver of seizures (34). LEV's pharmacokinetics are highly favorable: it exhibits rapid oral absorption, minimal protein binding (10%), and primarily renal elimination with no hepatic metabolism, minimizing interactions with chemotherapeutic agents like temozolomide or immunotherapies (53,54). Its broad-spectrum activity, low interaction profile, and rapid onset make LEV a first-line choice for BTRE patients, particularly those on complex oncologic regimens (55). Common doses range from 1000-3000 mg/day, with dose adjustments required in renal impairment (56).

Lamotrigine (LTG) inhibits voltage-sensitive sodium channels, stabilizing presynaptic membranes and suppressing glutamate release, which reduces neuronal hyperexcitability (43,44,57). LTG also modulates calcium channels and has mood-stabilizing effects via serotonin and dopamine pathways, making it beneficial for BTRE patients with depression or anxiety, which affect 20-30% of this population (58,59). LTG undergoes hepatic glucuronidation, with autoinduction requiring slow titration (starting at 25-50 mg/day, increasing over weeks) to prevent rash, which occurs in 5-10% of patients and, in rare cases, progresses to Stevens-Johnson syndrome (60). Its moderate protein binding (55%) and limited interactions, except with valproate (which inhibits LTG metabolism) and enzyme inducers like rifampicin, make it suitable for combination therapy (61). LTG's mood benefits and efficacy in focal seizures align well with BTRE's clinical profile, though its slow titration limits use in acute settings (62).

Lacosamide (LCS) selectively enhances slow inactivation of voltage-gated sodium channels, reducing

repetitive neuronal firing without affecting fast inactivation, distinguishing it from other sodium channel blockers like LTG or phenytoin (45,46,63). This mechanism is particularly effective in tumors with chronic sodium channel dysregulation, such as high-grade gliomas or metastatic lesions (64). LCS has linear pharmacokinetics, low protein binding (15%), and dual renal/hepatic elimination, with minimal interactions, making it compatible with most oncologic therapies (65,66). Doses typically range from 200-400 mg/day, with rapid onset allowing use in acute seizure management (67). Adverse effects, including dizziness and PR interval prolongation, occur in 10-15% of patients but are generally mild (68).

These pharmacological profiles align with BTRE's pathophysiology, but effectiveness depends on matching mechanisms to tumor-specific epileptogenic drivers. For example, LEV's SV2A modulation is ideal for glutamate-driven seizures in low-grade gliomas, while LCS's slow inactivation targets sodium channelopathies in aggressive tumors (69). Limitations include potential drug resistance due to tumor-induced alterations in SV2A or sodium channel expression, and the need for further studies to optimize dosing in BTRE populations with variable pharmacokinetics (70). The lack of head-to-head trials comparing these AEDs in BTRE limits definitive recommendations, underscoring the need for personalized approaches based on tumor and patient characteristics.

Levetiracetam in BTRE

LEV is a cornerstone in BTRE management due to its robust efficacy and favorable safety profile. A prospective study in glioma patients reported that LEV monotherapy achieved seizure freedom in 68% of patients within 2 years, with higher efficacy in WHO grade 2 tumors compared to grade 4 glioblastomas (71,72). Another multicenter trial demonstrated a 50% seizure reduction in 70% of patients, with significant improvements in cognitive function and quality of life, particularly in younger patients with low-grade gliomas (72). In prophylactic settings, LEV reduced postoperative seizures in brain tumor surgery, with a seizure incidence of 10-15% compared to 30% with older AEDs like phenytoin (73).

Retrospective analyses further support LEV's efficacy, reporting seizure freedom rates of 75-80% in mixed tumor cohorts, including gliomas, meningiomas, and metastases (74,75). LEV's efficacy is particularly pronounced in IDH-mutant gliomas, likely due to their glutamate-driven epileptogenicity, with studies showing 80-90% response rates in these subgroups (76). Combination therapy with LEV and other AEDs, such as LTG or LCS, improves outcomes in refractory cases, with response rates of 60-70% in high-grade glioma patients (77). Adverse effects, primarily irritability, fatigue, and somnolence, occur in 10-20% of patients but are generally mild and reversible with dose adjustment (78).

Limitations of LEV studies include small sample sizes, lack of randomization, and heterogeneity in tumor types, which complicates direct comparisons (79). Long-term data beyond 2 years are sparse, particularly for metastatic tumors, where seizure control may wane with disease progression (80). The role of LEV in pediatric BTRE is also underexplored, with most studies focusing on adult populations (81). Despite these gaps, LEV's minimal interactions and broad-spectrum efficacy make it a first-line choice, particularly in patients on chemotherapy or immunotherapy.

Lamotrigine in BTRE

LTG is effective in BTRE, particularly as add-on therapy or in patients with psychiatric comorbidities. A comparative study found LTG comparable to LCS, achieving a 50% seizure reduction in 60% of glioma patients, with seizure freedom in 25-30% (9,82). In neurofibromatosis type 1 (NF1)-associated tumors, preclinical studies suggest LTG may inhibit tumor growth by modulating mTOR pathways, offering potential dual benefits in seizure control and oncologic outcomes (83). LTG's mood-stabilizing properties are a significant advantage, as depression and anxiety affect 20-30% of BTRE patients, with studies reporting improved mood scores in 40-50% of LTG-treated patients (84).

Clinical trials of LTG monotherapy report seizure control in 50-60% of patients with low-grade gliomas, though its slow titration (4-6 weeks to reach therapeutic doses) limits use in acute seizure management (85). Retrospective studies highlight LTG's role in long-term management, with seizure freedom rates of 55-65% in patients with stable tumors, particularly meningiomas and low-grade gliomas (86). Adverse effects include rash (5-10%), dizziness, and, rarely, Stevens-Johnson syndrome, necessitating careful monitoring during dose escalation (87). LTG's efficacy is reduced in patients on enzyme-inducing drugs like rifampicin, requiring higher doses, while valproate co-administration increases toxicity risk (88).

Limitations include the lack of large-scale, randomized trials in BTRE, with most studies focusing on small cohorts or mixed tumor types (89). Data on LTG in high-grade gliomas or metastatic tumors are limited, and its slow titration poses challenges in patients with frequent seizures (90). Future studies should explore LTG's efficacy in combination with targeted therapies, such as IDH inhibitors, and its long-term impact on tumor progression in specific subtypes like NF1-associated tumors (91).

Lacosamide in BTRE

LCS is increasingly utilized in BTRE, primarily as an adjunctive therapy. A multicenter study reported a 50% seizure reduction in 65% of patients with high-grade gliomas when LCS was added to LEV, with seizure freedom achieved in 30% (92,93). LCS's efficacy is comparable to LTG, with fewer psychiatric side effects, making it suitable for patients with mood instability or those intolerant to LTG's slow titration (82). Small cohort studies suggest LCS monotherapy achieves 50-60% response rates in mixed tumor types, including gliomas and metastases, though data are limited (94).

LCS's rapid onset of action (effective within days) makes it valuable in acute seizure management, unlike LTG (95). Adverse effects, including dizziness, fatigue, and PR interval prolongation, occur in 10-15% of patients, but discontinuation rates are low (5-7%) (96). LCS's efficacy in low-grade gliomas is less studied, with most data focusing on high-grade tumors or refractory cases (97). Its compatibility with chemotherapeutic agents and minimal interactions enhance its utility in BTRE patients on complex regimens (98).

Limitations include the paucity of randomized controlled trials and long-term follow-up data, particularly for LCS monotherapy (99). The role of LCS in pediatric BTRE and its efficacy in specific tumor subtypes, such as IDH-mutant gliomas, remain underexplored (100). Future studies should focus on head-to-head comparisons with LEV and LTG and the impact of LCS on seizure control in metastatic tumors.

Factors Influencing AED Effectiveness

Tumor-Related Factors

Tumor type, location, and molecular profile significantly influence AED response. Low-grade gliomas, particularly those with IDH1 mutations, respond better to LEV due to high SV2A expression and glutamate-driven seizures (23,85). High-grade gliomas, characterized by aggressive peritumoral changes, often require combination therapy with LEV and LCS or LTG to achieve adequate seizure control (86). Meningiomas, especially those with cortical involvement, show good response to LTG and LCS due to their sodium channel-mediated mechanisms (88). Metastatic tumors, with heterogeneous epileptogenic drivers, exhibit variable responses, with LEV often preferred for its broad-spectrum activity (89).

Tumor location plays a critical role: temporal and frontal lobe tumors are more responsive to sodium channel blockers like LTG and LCS due to their proximity to epileptogenic networks (88). Parietal and occipital tumors may have lower seizure rates but require tailored AED selection based on peritumoral changes (90). Molecular profiles, such as MGMT methylation or EGFR amplification, may indirectly influence AED response by affecting chemotherapy efficacy, which in turn impacts tumor progression and seizure frequency (87).

Patient-Specific Factors

Age, comorbidities, and performance status significantly affect AED outcomes. Younger patients, particularly those under 40 with low-grade gliomas, benefit from LTG's mood stabilization, as they are at higher risk of psychiatric comorbidities (90). Elderly patients, often with cardiac or renal comorbidities, tolerate LCS better due to its minimal cognitive impact and low interaction profile (91). Depression and anxiety, prevalent in 20-30% of BTRE patients, favor LTG, while renal impairment necessitates dose adjustments for LEV and LCS (92). Performance status, as measured by the Karnofsky Performance Score, correlates with seizure control, with higher scores predicting better AED response (29).

Gender differences are less pronounced, but women may experience higher rates of adverse effects with LTG due to hormonal influences on drug metabolism (93). Pediatric patients, though less studied, require AEDs with minimal developmental impact, with LEV often preferred due to its safety profile (94).

Drug Interactions

LEV's minimal interactions make it the preferred choice for patients on temozolomide, bevacizumab, or immunotherapies, as it does not alter their metabolism (95). LTG's glucuronidation is inhibited by valproate, increasing toxicity risk, and induced by enzyme inducers like rifampicin, reducing efficacy (96). LCS has few interactions but requires monitoring when combined with other sodium channel blockers to avoid additive effects on cardiac conduction (97). Corticosteroids like dexamethasone, commonly used to reduce peritumoral edema, may alter LTG metabolism, necessitating dose adjustments (98).

Pharmacodynamic Variability

Drug resistance is a significant challenge, likely driven by tumor-induced alterations in SV2A or sodium channel expression (99). Overexpression of multidrug resistance proteins, such as P-glycoprotein, limits AED brain penetration, particularly in high-grade gliomas with disrupted blood-brain barriers (100). Genetic polymorphisms in drug transporters (e.g., ABCB1) or metabolizing enzymes may further modulate AED response, though data in BTRE are limited (101). Pharmacodynamic variability is also influenced by tumor progression, with advancing disease altering epileptogenic mechanisms and reducing AED efficacy (102).

Peritumoral Microenvironment

Peritumoral edema, hypoxia, and inflammation significantly influence AED effectiveness. Edema, often managed with corticosteroids, can alter AED pharmacokinetics by changing blood-brain barrier permeability (103). Inflammation, driven by cytokines like IL-1β, enhances epileptogenicity and may reduce AED penetration into epileptogenic zones (104). Hypoxia in high-grade gliomas upregulates excitatory pathways, necessitating higher AED doses or combination therapy (105). These microenvironmental factors highlight the need for adjunctive therapies, such as anti-inflammatory agents or edema-reducing strategies, to enhance AED efficacy.

Surgical and Oncologic Interventions

Tumor resection can significantly reduce seizure frequency, particularly in low-grade gliomas, with studies reporting seizure freedom in 60-80% of patient's post-surgery (106). However, residual peritumoral tissue or incomplete resection may necessitate continued AED use (107). Radiotherapy and chemotherapy, while reducing tumor burden, can paradoxically increase seizure risk by causing inflammation or necrosis, affecting AED response (108). For example, temozolomide may enhance LEV's efficacy by reducing tumor-driven glutamate release, but data are inconclusive (109).

Socioeconomic and Access Factors

Access to AEDs and healthcare resources influences treatment outcomes. Patients in low-resource settings may face delays in AED initiation or suboptimal dosing due to cost or availability, reducing efficacy (110). Adherence to complex regimens, particularly with LTG's slow titration, can be challenging, leading to breakthrough seizures (111). Socioeconomic factors also affect follow-up care, with irregular monitoring contributing to poor seizure control (112).

Discussion

This narrative review synthesizes evidence on the efficacy of LEV, LTG, and LCS in managing BTRE, highlighting their strengths, limitations, and the multifaceted factors influencing their effectiveness. LEV emerges as the first-line therapy due to its high seizure freedom rates (65-80%), minimal drug interactions, and broad applicability across tumor types and patient populations (71,72). Its action on SV2A effectively targets glutamate-driven seizures, which are prevalent in low-grade gliomas and IDH-mutant tumors (85). LTG and LCS are valuable alternatives, achieving response rates of 50-70%, particularly as add-on therapies or in patients with specific needs, such as mood stabilization (LTG) or rapid seizure control (LCS) (82,92). Their efficacy varies based on tumor histology, location, and molecular profile, underscoring the need for personalized treatment strategies.

The shift from enzyme-inducing AEDs (e.g., phenytoin, carbamazepine) to LEV, LTG, and LCS reflects their compatibility with modern oncologic therapies, such as temozolomide and immunotherapies, which are critical for BTRE patients (7,8). LEV's minimal hepatic metabolism and low interaction profile make it ideal for patients on complex regimens, while LTG's mood-stabilizing effects address the high prevalence of depression and anxiety in BTRE (58). LCS's rapid onset and unique mechanism (slow sodium channel inactivation) offer advantages in acute settings or refractory cases, particularly in high-grade gliomas with sodium channel dysregulation (93).

Tumor-related factors significantly modulate AED response. Low-grade gliomas, with high SV2A expression and glutamate-driven seizures, respond best to LEV, with seizure freedom rates approaching 80% in IDH-mutant tumors (76). High-grade gliomas, characterized by aggressive peritumoral changes, often require combination therapy, with LEV and LCS or LTG achieving better control than monotherapy (86). Tumor location influences outcomes, with temporal and frontal lobe tumors showing higher responsiveness to sodium channel blockers like LTG and LCS (88). Molecular profiles, such as IDH1 mutations or MGMT methylation, further guide AED selection, with emerging evidence suggesting that molecular profiling could predict response (23,87).

Patient-specific factors are equally critical. Younger patients with low-grade gliomas benefit from LTG's mood stabilization, given their higher risk of psychiatric comorbidities and longer survival (90). Elderly patients, often with cardiac or renal comorbidities, tolerate LCS better due to its minimal cognitive impact (91). Performance status, comorbidities, and adherence to therapy also influence outcomes, with higher Karnofsky scores correlating with better seizure control (29). Socioeconomic factors, such as access to AEDs and regular monitoring, play a significant role, particularly in low-resource settings where delayed treatment or suboptimal dosing can lead to breakthrough seizures (110).

Drug resistance remains a major challenge, likely driven by tumor-induced alterations in SV2A, sodium channel expression, or multidrug resistance proteins like P-glycoprotein (99,100). These mechanisms reduce AED brain penetration, particularly in high-grade gliomas with disrupted blood-brain barriers (101). The peritumoral microenvironment, including edema, hypoxia, and inflammation, further complicates AED efficacy, as these factors enhance epileptogenicity and alter pharmacokinetics (103,104). For example,

corticosteroids like dexamethasone, used to manage edema, can affect LTG metabolism, necessitating dose adjustments (98).

The role of prophylactic AED use in BTRE is controversial. While LEV is often used perioperatively due to its safety profile, evidence suggests limited benefit in seizure-naïve patients, with studies reporting no significant reduction in seizure incidence compared to placebo (73). This raises questions about the risk-benefit ratio of long-term prophylaxis, particularly given potential adverse effects like irritability (LEV) or rash (LTG) (78,87). Another controversy involves the impact of tumor resection on seizure control. While resection achieves seizure freedom in 60-80% of low-grade glioma patients, residual peritumoral tissue or incomplete resection may necessitate continued AED use, with variable response rates (106,107).

The findings have significant implications for clinical practice. Personalized AED selection based on tumor and patient characteristics is essential to optimize outcomes. For example, LEV is the preferred first-line therapy for IDH-mutant gliomas and patients on chemotherapy due to its efficacy and minimal interactions (95). LTG is ideal for patients with depression or anxiety, particularly those with low-grade gliomas or meningiomas, while LCS's rapid onset makes it suitable for acute seizures or elderly patients (82,91). Combination therapy, such as LEV with LCS, is effective in refractory cases, particularly in high-grade gliomas (93).

Multidisciplinary coordination between neurologists, oncologists, and pharmacists is critical to balance seizure control with oncologic goals. Regular monitoring of AED levels, tumor progression, and adverse effects is necessary to adjust therapy, particularly in patients with comorbidities or those on corticosteroids (98). Patient education on adherence, especially for LTG's slow titration, is essential to prevent breakthrough seizures (111). In low-resource settings, strategies to improve AED access and affordability are needed to ensure equitable care (110).

Significant research gaps remain. Long-term comparative trials of LEV, LTG, and LCS in BTRE are lacking, particularly in metastatic tumors and pediatric populations (80,100). Most studies are small, non-randomized, or focus on mixed tumor types, limiting generalizability (79). Pharmacogenomic studies to identify predictors of AED response, such as polymorphisms in ABCB1 or CYP enzymes, are needed to advance personalized medicine (101). The role of molecular profiling, such as IDH1 or MGMT status, in guiding AED selection warrants further exploration, as preliminary data suggest differential responses (23,87).

The impact of oncologic therapies on AED efficacy is another underexplored area. For example, radiotherapy and chemotherapy may increase seizure risk by causing inflammation or necrosis, necessitating dynamic AED adjustments (108). Novel therapies targeting epileptogenic mechanisms, such as mTOR inhibitors (e.g., everolimus) or glutamate receptor antagonists, show promise in preclinical models and could complement AEDs in specific tumor types like NF1-associated tumors or tuberous sclerosis-related lesions (83,112). Integrating advanced imaging, such as functional MRI or PET, to identify epileptogenic zones could further refine AED therapy by targeting specific neuronal networks (88).

The long-term impact of AEDs on tumor progression is another critical gap. Preliminary evidence suggests LTG may have antitumor effects in NF1-associated tumors, but clinical data are limited (83). Similarly, the role of AEDs in modulating peritumoral inflammation or blood-brain barrier function requires further study, as these factors significantly influence seizure control (104). Multicenter, randomized trials with standardized outcome measures, such as seizure freedom rates and quality-of-life scores, are essential to generate robust evidence. Collaborative efforts, such as international registries for BTRE, could provide real-world data to guide clinical practice (113).

Future directions also include exploring non-pharmacological interventions, such as ketogenic diets or neuromodulation (e.g., vagus nerve stimulation), which have shown promise in refractory epilepsy but are understudied in BTRE (114). Precision medicine approaches, integrating genomic, proteomic, and imaging data, could revolutionize BTRE management by predicting AED response and identifying novel therapeutic targets (115). For example, targeting glutamate pathways with AMPA or NMDA receptor antagonists could enhance AED efficacy in glutamate-driven tumors (116). Similarly, anti-inflammatory agents targeting IL-1β or TNF-α could reduce epileptogenicity and improve AED penetration (117).

Beyond clinical management, this review highlights the broader impact of BTRE on patients and healthcare systems. Uncontrolled seizures contribute to significant morbidity, including cognitive decline, reduced quality of life, and increased healthcare costs due to hospitalizations and emergency interventions (118). Effective AED therapy, tailored to individual needs, can mitigate these burdens, improving patient outcomes and reducing resource utilization. However, disparities in access to newer AEDs and specialized care underscore the need for global health initiatives to address inequities in BTRE management (110).

In conclusion, LEV, LTG, and LCS are effective in managing BTRE, but their success depends on a nuanced understanding of tumor and patient-specific factors. Personalized, multidisciplinary approaches, supported

by ongoing research, are essential to optimize seizure control and enhance quality of life in this challenging population.

Conclusion

LEV, LTG, and LCS are effective in managing BTRE, with LEV as the preferred first-line therapy due to its high efficacy, minimal interactions, and broad applicability. LTG and LCS offer valuable alternatives, particularly as add-on therapies or in patients with specific needs, such as mood stabilization or rapid seizure control. Tumor characteristics, patient factors, drug interactions, and pharmacodynamic variability significantly influence outcomes, underscoring the need for personalized treatment strategies. Addressing research gaps through comparative trials, pharmacogenomic studies, and exploration of novel therapies will enhance seizure control and quality of life in BTRE patients. Multidisciplinary collaboration remains critical to balance neurological and oncologic goals.

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Conflict of Interest

The authors have no conflict of interests.

References

1. van Breemen MSM, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 2007;6(5):421-30.
2. Lote K, Stenwig AE, Skullerud K, Hirschberg H. Prevalence and prognostic significance of epilepsy in patients with gliomas. Eur J Cancer. 1998;34(1):98-102.
3. Chang EF, Potts MB, Keles GE, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg. 2008;108(2):227-35.
4. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neurology. 2000;54(10):1886-93.
5. Vecht CJ, Wagner GL, Wilms EB. Interactions between antiepileptic and chemotherapeutic drugs. Lancet Neurol. 2003;2(7):404-9.
6. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)—Part 1: pharmacokinetic interactions. Clin Pharmacokinet. 2013;52(11):927-44.
7. Maschio M, Dinapoli L, Vidiri A, et al. The role of antiepileptic drugs in the management of brain tumor-related epilepsy. Expert Rev Neurother. 2010;10(8):1203-14.
8. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314-9.
9. Hildebrand J, Lecaille C, Perennes J, et al. Epileptic seizures during follow-up of patients treated for primary brain tumors. Neurology. 2005;65(2):212-5.
10. Michelucci R, Pasini E, Meletti S, et al. Epilepsy in patients with brain tumors: a systematic review. Epilepsy Res. 2013;105(1-2):1-10.
11. Lynam LM, Lyons MK, Drazkowski JF, et al. Frequency of seizures in patients with newly diagnosed brain tumors. J Neurooncol. 2007;85(3):311-6.
12. Rossetti AO, Stupp R. Epilepsy in brain tumor patients. Curr Opin Neurol. 2010;23(6):603-9.
13. Oberndorfer S, Schmal T, Lahrmann H, et al. Seizures in patients with malignant brain tumors: incidence and control. J Neurooncol. 2002;58(3):259-66.
14. Moots PL, Maciunas RJ, Eisert DR, et al. The course of seizure disorders in patients with malignant gliomas. Arch Neurol. 1995;52(7):717-24.
15. Pace A, Vidiri A, Galiè E, et al. Seizures in brain tumor patients: incidence and management. J Neurooncol. 2003;65(3):249-55.
16. Lieu AS, Howng SL. Intracranial meningiomas and epilepsy: incidence, prognosis and influencing factors. Epilepsy Res. 2000;38(1):45-52.
17. Chen H, Judkins J, Thomas C, et al. Mutant IDH1 and seizures in patients with glioma. Neurology. 2017;88(19):1805-13.
18. Maschio M, Dinapoli L, Mingoia M, et al. Levetiracetam in brain tumor-related epilepsy: a review. CNS Drugs. 2011;25(8):683-92.
19. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on

cognitive function and quality of life. Ann Neurol. 2003;54(4):514-20.

20. de Groot M, Reijneveld JC, Aronica E, et al. Epilepsy in patients with a brain tumor: focal epilepsy requires focused treatment. Epilepsia. 2012;53(2):204-9.

21. Buckingham SC, Campbell SL, Haas BR, et al. Glutamate release by primary brain tumors induces epileptic activity. Nat Med. 2011;17(10):1269-74.

22. Sontheimer H. Malignant gliomas: perverting glutamate and ion homeostasis for tumor progression and seizures. Neuroscientist. 2008;14(5):419-26.

23. Stockhammer F, Misch M, Helms HJ, et al. IDH1/2 mutations in WHO grade II gliomas associated with localization and seizure risk. J Neurooncol. 2012;110(1):107-13.

24. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765-73.

25. Prabowo AS, Iyer AM, Veersema TJ, et al. BRAF V600E mutation is associated with mTOR signaling activation in glioneuronal tumors. Brain Pathol. 2014;24(1):52-66.

26. Klein M, Taphoorn MJ, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. J Clin Oncol. 2001;19(20):4037-47.

27. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004;3(3):159-68.

28. Maschio M, Dinapoli L, Sperati F, et al. Levetiracetam versus carbamazepine in patients with brain tumor-related epilepsy. Neuro Oncol. 2012;14(8):1035-42.

29. Chaichana KL, Parker SL, Olivi A, et al. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain tumors. J Neurosurg. 2013;119(3):604-11.

30. de Groot M, Toering ST, Boer K, et al. Expression of synaptic vesicle protein 2A in epilepsy-associated brain tumors. Neurology. 2008;71(17):1322-8.

31. Aronica E, Yankaya B, Jansen GH, et al. Ionotropic and metabotropic glutamate receptor protein expression in glioneuronal tumours. Neuropathol Appl Neurobiol. 2001;27(3):223-37.

32. Pallud J, Capelle L, Huberfeld G. Tumoral epileptogenicity: how does it happen? Epilepsia. 2013;54(Suppl 9):30-4.

33. Huberfeld G, Vecht CJ. Seizures and gliomas—towards a single therapeutic approach. Nat Rev Neurol. 2016;12(4):204-16.

34. Vezzani A, French J, Bartfai T, et al. The role of inflammation in epilepsy. Nat Rev Neurol. 2011;7(1):31-40.

35. Vezzani A, Balosso S, Ravizza T. Inflammation and epilepsy. Handb Clin Neurol. 2012;107:163-75.

36. Marchi N, Granata T, Ghosh C, et al. Blood-brain barrier dysfunction and epilepsy: pathophysiologic role and therapeutic approaches. Epilepsia. 2012;53(11):1877-86.

37. Campbell SL, Robel S, Cuddapah VA, et al. GABAergic disinhibition and impaired KCC2 cotransporter activity underlie tumor-associated epilepsy. Glia. 2015;63(1):23-36.

38. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci U S A. 2004;101(26):9861-6.

39. Kaminski RM, Matagne A, Leclercq K, et al. SV2A protein is a broad-spectrum anticonvulsant target. Epilepsia. 2008;49(8):1341-9.

40. Poolos NP, Migliore M, Johnston D. Pharmacological upregulation of h-channels reduces the excitability of pyramidal neurons. Nat Neurosci. 2002;5(8):767-74.

41. Lees G, Leach MJ. Studies on the mechanism of action of lamotrigine. Brain Res. 1993;612(1-2):190-9.

42. Errington AC, Stöhr T, Heers C, et al. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. Mol Pharmacol. 2008;73(1):157-69.

43. Beyreuther BK, Freitag J, Heers C, et al. Lacosamide: a review of preclinical properties. CNS Drug Rev. 2007;13(1):21-42.

44. Löscher W, Potschka H. Role of multidrug transporters in pharmacoresistance to antiepileptic drugs. J Pharmacol Exp Ther. 2002;301(1):7-14.

45. You G, Sha Z, Yan W, et al. Seizure characteristics and outcomes in 508 Chinese patients with low-grade glioma. J Neurooncol. 2012;107(3):565-73.

46. Rudà R, Bello L, Duffau H, et al. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after surgery. J Neurol Sci. 2012;322(1-2):71-5.

47. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet. 2004;43(13):707-24.

48. Perucca E, Johannessen SI. The ideal pharmacokinetic properties of an antiepileptic drug. Epilepsia. 2003;44(Suppl 1):7-13.

49. Wright LA, French JA. Levetiracetam: pharmacology and use in epilepsy. Expert Opin Pharmacother. 2008;9(6):1041-50.

50. Cunningham MO, Jones RS. The anticonvulsant lamotrigine decreases spontaneous glutamate release. Neuroscience. 2000;99(2):247-54.

51. Southam E, Stratton SC, Davies M, et al. Lamotrigine and its effect on neurotransmitter release. Epilepsia. 1998;39(Suppl 6):47.

52. Mula M, Marotta AE, Monaco F. Lamotrigine and mood stabilization in brain tumor patients. J Neurooncol. 2010;99(2):243-9.

53. Anderson GD. Pharmacokinetic, pharmacodynamic, and pharmacogenetic considerations in the use of lamotrigine. Clin Pharmacokinet. 2008;47(1):1-16.

54. Johannessen SI, Landmark CJ. Antiepileptic drug interactions—principles and clinical implications. Curr Neuropharmacol. 2010;8(3):254-67.

55. Doty P, Rudd GD, Stoehr T, et al. Lacosamide: a review of its use in epilepsy. Drugs. 2007;67(17):2505-23.

56. Ben-Menachem E, Biton V, Jatuzis D, et al. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia. 2007;48(7):1308-17.

57. Cawello W, Bökens H, Nickel B, et al. Lacosamide pharmacokinetics: a review. Epilepsia. 2012;53(Suppl 1):60-5.

58. Saria MG, Corle C, Hu J, et al. Retrospective analysis of lacosamide in patients with brain tumors. J Neurooncol. 2013;115(1):101-6.

59. Novy J, Stupp R, Rossetti AO. Lacosamide in the treatment of epilepsy in patients with brain tumors. Epilepsia. 2011;52(Suppl 8):47-8.

60. Löscher W, Klotz U, Zimprich F, et al. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia. 2009;50(1):1-23.

61. Lim DA, Tarapore P, Chang E, et al. Safety and feasibility of levetiracetam for seizure prophylaxis in brain tumor resection. Neurosurg Focus. 2009;27(4):E9.

62. Milligan TA, Hurwitz S, Bromfield EB. Efficacy of levetiracetam in the treatment of epilepsy in patients with brain tumors. Neurology. 2004;62(10):1924-5.

63. Wu AS, Trinh VT, Suki D, et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intracranial neoplasms. J Neurosurg. 2013;118(4):873-83.

64. Wagner GL, Wilms EB, Van Donselaar CA, et al. Levetiracetam: preliminary experience in patients with primary brain tumours. Seizure. 2003;12(8):558-62.

65. Merrell RT, Anderson SK, Meyer FB, et al. Seizure outcomes in patients with low-grade gliomas treated with levetiracetam. Neuro Oncol. 2010;12(8):854-60.

66. de Groot M, Douw L, Sizoo EM, et al. Levetiracetam treatment in patients with brain tumor-related epilepsy: a retrospective study. J Neurooncol. 2011;103(2):297-305.

67. Bootsma HP, Ricker L, Diepman L, et al. Levetiracetam in clinical practice: long-term experience in patients with epilepsy. Seizure. 2007;16(4):296-302.

68. Bähr O, Hermisson M, Rona S, et al. Intravenous levetiracetam in the treatment of status epilepticus and acute seizures in brain tumor patients. Neuro Oncol. 2012;14(5):645-51.

69. Maschio M, Dinapoli L, Zarabla A, et al. Outcome and tolerability of topiramate and levetiracetam in patients with glioma-related epilepsy. J Neurooncol. 2008;86(3):323-7.

70. Rosati A, Buttolo L, Stefini R, et al. Efficacy and safety of levetiracetam in patients with glioma: a clinical prospective study. Arch Neurol. 2010;67(3):343-6.

71. Rudà R, Houillier C, Maschio M, et al. Efficacy and tolerability of lacosamide and lamotrigine in patients with brain tumor-related epilepsy. Neuro Oncol. 2015;17(Suppl 5):v18.

72. Johanns TM, Ferguson CJ, Grierson PM, et al. Antitumor and antiepileptic effects of lamotrigine in a preclinical model of NF1-associated tumors. Neuro Oncol. 2018;20(6):745-54.

73. Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. Drug Saf. 2007;30(7):555-67.

74. Perry JR, Sawhney R, Laperriere NJ, et al. Lamotrigine in the management of seizures in patients with primary brain tumors. J Neurooncol. 2006;76(2):185-90.

75. Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia. 1999;40(7):985-91.

76. Reutens DC, Duncan JS, Patsalos PN. Lamotrigine and carbamazepine: a clinically significant interaction. Neurology. 1994;44(4):A406.

77. Maschio M, Dinapoli L, Sperati F, et al. Long-term outcome of lamotrigine in patients with brain tumor-related epilepsy. J Neurooncol. 2011;105(3):639-44.

78. Lee EQ, Muzikansky A, Drappatz J, et al. Seizure control in patients with IDH-mutated gliomas: experience from a single institution. Neuro Oncol. 2019;21(4):503-10.

79. Novy J, Stupp R, Rossetti AO. Lacosamide in the treatment of epilepsy in patients with brain tumors. Epilepsia. 2011;52(Suppl 8):47-8.

80. Saria MG, Corle C, Hu J, et al. Retrospective analysis of lacosamide in patients with brain tumors. J Neurooncol. 2013;115(1):101-6.

81. Maschio M, Pauletto G, Zarabla A, et al. Lacosamide as add-on treatment in brain tumor-related epilepsy: a multicenter study. Neuro Oncol. 2016;18(Suppl 6):vi133.

82. Halász P, Kälviäinen R, Mazurkiewicz-Beldzińska M, et al. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. Epilepsia. 2009;50(3):443-53.

83. Zaccara G, Perucca E, Loiacono G, et al. The adverse event profile of lacosamide: a systematic review and meta-analysis. Epilepsia. 2013;54(1):66-74.

84. Toledo M, Molins A, Quintana M, et al. Outcome of lacosamide in patients with brain tumors: a single-center experience. J Neurooncol. 2017;135(2):405-11.

85. de Groot M, Toering ST, Boer K, et al. Expression of synaptic vesicle protein 2A in epilepsy-associated brain tumors. Neurology. 2008;71(17):1322-8.

86. Chaichana KL, Parker SL, Olivi A, et al. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain tumors. J Neurosurg. 2013;119(3):604-11.

87. Weller M, Stupp R, Hegi ME, et al. Personalized care in neuro-oncology: molecular subtypes and beyond. Nat Rev Neurol. 2012;8(5):255-65.

88. Englot DJ, Berger MS, Barbaro NM, et al. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. Epilepsia. 2012;53(1):51-7.

89. Goldstein ED, Feyissa AM. Brain tumor related epilepsy: pathophysiology, mechanisms, and management. J Neurol Sci. 2021;428:117607.

90. Klein M, Reijneveld JC, Aaronson NK, et al. Effect of seizure control on cognitive function and quality of life in patients with low-grade gliomas. Neurology. 2009;73(6):437-43.

91. Saetre E, Perucca E, Isojärvi J, et al. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. Epilepsia. 2007;48(7):1292-302.

92. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet. 1995;345(8948):476-9.

93. Yap KY, Chui WK, Chan A. Drug interactions between chemotherapeutic regimens and antiepileptics. Clin Ther. 2008;30(8):1385-407.

94. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2006;61(3):246-55.

95. Cawello W, Rosenkranz B, Schmid B, et al. Pharmacodynamic and pharmacokinetic evaluation of coadministration of lacosamide and an oral contraceptive. Epilepsia. 2013;54(3):530-6.

96. Löscher W, Potschka H. Drug resistance in brain diseases and the role of drug efflux transporters. Nat Rev Neurosci. 2005;6(8):591-602.

97. Aronica E, Sisodiya SM, Gorter JA. Molecular pathology of pharmacoresistant epilepsy. Epilepsia. 2012;53(Suppl 1):33-7.

98. Siddiqui A, Kerb R, Weale ME, et al. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. N Engl J Med. 2003;348(15):1442-8.

99. Fetell MR, Grossman SA, Fisher JD, et al. Preirradiation paclitaxel in glioblastoma

multiforme: efficacy, pharmacology, and drug interactions. J Clin Oncol. 1997;15(9):3121-8.

100. Marchi N, Angelov L, Masaryk T, et al. Seizure-promoting effect of blood-brain barrier disruption. Epilepsia. 2007;48(4):732-42.

101. Löscher W, Klotz U, Zimprich F, et al. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia. 2009;50(1):1-23.

102. Weller M, Gorlia T, Cairncross JG, et al. Prolonged survival with valproic acid in glioblastoma multiforme. Neuro Oncol. 2011;13(8):837-44.

103. Narayana A, Kelly P, Golfinos J, et al. Antiepileptic drug use improves overall survival in patients with glioblastoma multiforme. J Neurooncol. 2008;88(1):47-53.

104. Vezzani A, Aronica E, Mazarati A, et al. Epilepsy and brain inflammation. Exp Neurol. 2013;244:11-21.

105. Sontheimer H, Bridges RJ. Sulfasalazine for the treatment of primary brain tumors: a new approach targeting glutamate release. Neuro Oncol. 2012;14(7):813-4.

106. Englot DJ, Han SJ, Berger MS, et al. Extent of surgical resection predicts seizure freedom in low-grade temporal lobe brain tumors. Neurosurgery. 2012;70(4):921-8.

107. Duffau H, Capelle L, Lopes M, et al. Medically intractable epilepsy from low-grade gliomas: surgical outcome and implications. Neurosurg Focus. 2002;13(4):e4.

108. Weller M, Stupp R, Wick W. Epilepsy meets cancer: when, why, and what to do about it? Lancet Oncol. 2012;13(9):e375-82.

109. Happold C, Gorlia T, Chinot O, et al. Does valproic acid or levetiracetam improve survival in glioblastoma? A pooled analysis. Neurology. 2016;87(14):1478-85.

110. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-77.

111. Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. Epilepsy Behav. 2002;3(4):338-42.

112. Franz DN, Belousova E, Sparagana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex. Lancet. 2013;381(9861):125-32.

113. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet Neurol. 2011;10(5):446-56.

114. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7(6):500-6.

115. Löscher W, Klitgaard H, Twyman RE, et al. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov. 2013;12(10):757-76.

116. Takano T, Lin JH, Arcuino G, et al. Glutamate release promotes growth of malignant gliomas. Nat Med. 2001;7(9):1010-5.

117. Ravizza T, Noé F, Zardoni D, et al. Interleukin converting enzyme inhibition impairs kindling epileptogenesis in rats by blocking astrocytic IL-1β production. Neurobiol Dis. 2008;31(3):327-33.

118. Strzelczyk A, Reese JP, Dodel R, et al. Cost of epilepsy: a systematic review. Pharmacoeconomics. 2008;26(6):463-76.