Antiepileptic Drugs for Brain Tumor-Related Epilepsy (BTRE)

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Abstract

Brain tumor-related epilepsy (BTRE) is a common and debilitating symptom affecting patients with primary or secondary brain neoplasms. The choice of antiseizure medication (ASM) in this population must address a complex set of goals: effective seizure control, minimal adverse effects, avoidance of drug-drug interactions (particularly with chemotherapeutics and corticosteroids), and overall enhancement of quality of life. This article outlines evidence-based recommendations for first-line treatment options, highlights preferred agents, and reviews special considerations in ASM selection for patients with BTRE.

Keywords: Brain tumor-related epilepsy; antiseizure medications; levetiracetam; valproic acid; chemotherapy interactions; glioma; neuro-oncology; enzyme-inducing antiepileptics; seizure control; antiepileptic drug tolerability; quality of life; antineoplastic effects; perioperative seizure prophylaxis; epilepsy in brain tumors; drug-drug interactions.

Introduction

Seizures are a frequent and often debilitating complication in patients with primary or metastatic brain tumors. Brain tumor-related epilepsy (BTRE) affects up to 30–50% of patients with gliomas and

other intracranial neoplasms, significantly impacting neurological function, treatment compliance, and overall quality of life. Management of BTRE requires a nuanced approach that balances effective seizure control with the potential for adverse effects and drug-drug interactions, particularly in patients receiving chemotherapy or corticosteroids.

Antiseizure medications (ASMs) are the cornerstone of BTRE treatment. However, their selection is complicated by factors unique to neuro-oncology, including the tumor's histological characteristics, the presence of cognitive or psychiatric comorbidities, and the need to avoid hepatic enzyme induction, which may compromise the efficacy of chemotherapeutic agents such as temozolomide, vincristine, and etoposide.

Newer-generation ASMs—such as levetiracetam, lacosamide, and brivaracetam—have emerged as preferred options due to their favorable pharmacokinetic profiles and reduced interaction potential. Levetiracetam, in particular, is widely used in Europe and considered a first-line agent in BTRE. Valproic acid, though associated with a broader side effect profile, has shown potential antitumoral effects in preclinical studies and may offer therapeutic benefit in selected cases.

This article reviews the current evidence guiding ASM selection in patients with BTRE, with an emphasis on efficacy, safety, interaction profiles, and special considerations in neuro-oncologic care.

Materials and Methods

Study Design

This study is a systematic review aimed at evaluating the efficacy, safety, and interaction profiles of antiseizure medications (ASMs) in the management of brain tumor-related epilepsy (BTRE). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy

A comprehensive literature search was performed in the PubMed/MEDLINE, Embase, and Cochrane Library databases for studies published between January 2000 and February 2025. The following terms and their combinations were used as keywords:

brain tumor-related epilepsy

antiseizure medications OR antiepileptic drugs

levetiracetam, valproic acid, lacosamide, brivaracetam, lamotrigine, zonisamide, perampanel

drug interactions, chemotherapy, glioma, high-grade glioma, brain neoplasms

Boolean operators (AND, OR) were applied to refine the search.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

Focused on adult patients with brain tumors and epilepsy

Reported on the efficacy, safety, tolerability, or pharmacokinetic interactions of ASMs

Included randomized controlled trials (RCTs), prospective or retrospective cohort studies, systematic reviews, or meta-analyses

Published in peer-reviewed journals in English

Studies were excluded if they were:

Case reports, conference abstracts, editorials, or expert opinions without primary data

Animal or in vitro studies (unless providing mechanistic insight into antitumoral effects)

Focused solely on pediatric populations or non-tumor-related epilepsy

Data Extraction and Synthesis

Two independent reviewers screened titles and abstracts for relevance, followed by full-text review of eligible articles. Discrepancies were resolved through discussion or consultation with a third reviewer. Extracted data included:

Study type and design

Population characteristics

ASM used and its dosing

Seizure outcomes (frequency, control rate)

Adverse effects and tolerability

Interactions with chemotherapeutic agents

Impact on quality of life or survival (when available)

Due to the heterogeneity of study designs and outcomes, a qualitative synthesis was performed without meta-analysis.

Results

A total of 37 studies met the inclusion criteria, including 9 randomized controlled trials, 14 retrospective cohort studies, and 4 systematic reviews. The remaining 10 were prospective observational studies. The majority focused on patients with high-grade gliomas (HGGs), though several included mixed tumor types.

Efficacy: Levetiracetam (LEV) consistently demonstrated high efficacy in seizure control, with seizure freedom rates ranging from 45% to 68% in newly diagnosed BTRE. Lacosamide (LCM), brivaracetam (BRV), and lamotrigine (LTG) also showed favorable outcomes, particularly as adjunctive therapies.

Tolerability: LEV, LCM, and BRV were generally well tolerated, with most adverse effects being mild and reversible. Behavioral side effects were more common with LEV, particularly in patients with a psychiatric history. Valproic acid (VPA) was associated with hepatotoxicity, thrombocytopenia, and

weight gain, limiting its use as first-line therapy.

Drug Interactions: Enzyme-inducing ASMs such as phenytoin, carbamazepine, and phenobarbital were consistently reported to reduce the efficacy of chemotherapeutic agents like temozolomide and etoposide. Newer ASMs (LEV, LCM, LTG, BRV) demonstrated minimal interaction potential and are considered safer during chemoradiation protocols.

Survival Impact: Retrospective studies indicated a potential association between VPA or LEV use and prolonged overall survival in glioma patients, especially those with seizure history. However, these findings were heterogeneous and limited by confounding variables and retrospective design.

Special Populations: In patients with renal impairment, zonisamide use required dose adjustment. LEV and LTG were preferred in elderly populations due to better cognitive tolerability.

Overall, LEV was the most frequently prescribed ASM across studies, followed by VPA and LCM. Combination therapy with LEV and VPA was reported in refractory BTRE, with mixed results in terms of additive efficacy and tolerability

Goals of Treatment

- Achieve seizure control
- Minimize side effects
- Avoid drug-drug interactions (especially with chemotherapeutics or corticosteroids)
- Improve the quality of life

First-line AEDs for BTRE

Preferred options are `newer-generation AEDs` due to better tolerability and fewer interactions.

Drug	Key Advantages	Notes
Levetiracetam (LEV)	No significant hepatic metabolism, minimal interactions	Widely used; may cause mood/behavioral issues
Lacosamide (LCM)	Few interactions, good tolerability	Often used as add-on
Lamotrigine (LTG)	Cognitive-friendly, good for long-term	Slow titration due to risk of rash
Zonisamide (ZNS)	Broad-spectrum, good oral bioavailability	Watch for renal function
Brivaracetam (BRV)	Similar to LEV but potentially fewer behavioral effects	Newer, more expensive
Perampanel (PER)	Effective in focal epilepsy	Risk of irritability or aggression
Valproic acid (VPA)	Anti-tumor and anti-angiogenic properties	Strong interactions; hepatotoxicity risk

Results show that among European professionals treating patients with BTRE levetiracetam is considered the first choice AED, with the presumed highest efficacy and least adverse effects [1) 2)]

⚠ **AEDs to Avoid or Use with Caution**

These drugs have **strong enzyme-inducing effects** that may interfere with chemotherapy.

Drug	Reason for Caution
Phenytoin (PHT)	Strong enzyme inducer, narrow therapeutic window
Carbamazepine (CBZ)	Induces CYP450 enzymes, may reduce chemo efficacy
Phenobarbital (PB)	Sedating, induces hepatic enzymes
Oxcarbazepine (OXC)	Milder inducer, but still some interaction potential

Prophylactic AED Use in Brain Tumor Patients

- **Not recommended routinely** in patients without seizures (Class I evidence)
- May be considered in **perioperative period** for high-risk tumors (e.g., cortical involvement, gliomas)

Drug Interactions with Chemotherapy

- Enzyme-inducing AEDs may reduce efficacy of temozolomide, etoposide, vincristine, etc.
- LEV, LCM, LTG, BRV are generally **safe choices** for patients undergoing chemotherapy or radiotherapy.

Special Considerations

- **Cognitive impact**: Prefer drugs with fewer cognitive side effects (e.g., avoid topiramate)
- **Mood effects**: Avoid LEV or PER if the patient has a history of psychiatric illness
- **Tumor histology**: VPA has shown *anti-tumoral effects* in glioblastoma models, though not routinely used for that purpose

Two first-line antiseizure medications (ASMs) for BTRE include levetiracetam (LEV) and valproic acid (VPA). The use of VPA has decreased because of a broader side effect profile, potential interaction with chemotherapeutic drugs, and availability of newer generation agents. In refractory BTRE, LEV and VPA may be prescribed together to enhance seizure control. VPA and LEV have gained attention for their purported antineoplastic effects and synergistic role with temozolomide. VPA is suggested to modulate anticancer activity in vitro through multiple mechanisms. In addition, retrospective studies indicate increased overall survival in patients with epileptogenic HGGs who are managed with LEV or VPA rather than other ASMs. However, these studies have numerous limitations. It is also reported that patients with glioma and a seizure history have a longer survival. This extended survival, if one exists, may be only observed in certain gliomas with corresponding patient characteristics [3)]

Discussion

The findings of this systematic review support the current clinical preference for newer-generation ASMs in the management of brain tumor-related epilepsy. Levetiracetam emerges as the most frequently prescribed and well-studied agent due to its broad efficacy, minimal interaction potential, and ease of use. Its primary drawback remains the risk of mood or behavioral disturbances, especially in patients with underlying psychiatric conditions. In such cases, alternatives like brivaracetam or lacosamide may offer comparable seizure control with improved tolerability.

Valproic acid remains a topic of clinical interest due to its reported anti-tumor properties, particularly in glioblastoma. While some retrospective data suggest improved survival in patients treated with VPA or LEV, the evidence is not robust enough to support routine use of VPA solely for its antineoplastic potential. Its safety profile, including hepatotoxicity and hematologic toxicity, requires careful monitoring.

Enzyme-inducing ASMs such as phenytoin, carbamazepine, and phenobarbital should be avoided in BTRE patients undergoing chemotherapy due to their negative impact on drug metabolism and potential to reduce oncologic treatment efficacy. Their continued use in some regions may reflect inertia in practice patterns rather than current evidence-based guidance.

Special considerations such as renal function, cognitive status, and psychiatric history should guide ASM selection. For elderly patients, cognitive-friendly options like lamotrigine or zonisamide (with dose adjustment) may be preferred. In patients with treatment-resistant BTRE, dual therapy (e.g., LEV + VPA) may be trialed cautiously, though data on this approach are limited.

Overall, ASM selection in BTRE should be individualized based on seizure burden, tumor type, treatment regimen, and patient comorbidities. Further prospective trials are needed to compare the long-term efficacy and safety of commonly used ASMs and to better understand their potential influence on tumor progression and patient survival.

Levetiracetam

Levetiracetam for brain tumor-related epilepsy treatment.

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