# Characteristics and Treatment of Seizures in Patients with High-Grade Glioma: A Review

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**KEYWORDS**

• Anaplastic astrocytoma • Epilepsy • High-grade glioma • Glioblastoma • Seizure

High-grade gliomas (HGGs), including anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM), are the most common primary tumors of the central nervous system.[1,2] Despite medical and surgical advances, the prognosis of patients with HGGs remains poor, with a median survival of approximately 22 months for AA and 12 months for GBM, even after surgery, irradiation, and chemotherapy.[2–4] Seizures are common in these patients, affecting between 25% and 60% of individuals with HGGs, and they are frequently the presenting symptom.[5–9] Tumor-related epilepsy affects patients' quality of life significantly, causes cognitive deterioration, and may result in significant morbidity.[5,10–13] However, the importance of seizure control in patients with HGG remains underappreciated because most neuro-oncologic studies and practices focus primarily on tumor progression and the overall survival. An understanding of the underlying risk factors and treatment options for seizures in patients with HGG is critical in their evaluation and treatment. This review briefly discusses the potential mechanistic underpinnings and predictors of seizures in HGGs, and focuses primarily on important therapeutic considerations.

## PREDICTORS, MECHANISMS, AND CHARACTERISTICS OF EPILEPSY IN PATIENTS WITH HGG

The predilection for seizures in patients with brain tumor has long been recognized, and was described by Hughlings Jackson in 1882.[14] Across various clinical series, 25% to 60% of individuals with HGGs experience seizures, suggesting that brains harboring these lesions possess a strong predisposition to epileptogenicity,[5,10–13] but seizures are not equally common among different types of gliomas. The highest rates of epilepsy are

This article has not been previously published in whole or in part or submitted elsewhere for review.
The authors have no conflicts of interest to disclose.

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Neurosurg Clin N Am 23 (2012) 227–235
doi:10.1016/j.nec.2012.01.009

observed in patients with low-grade gliomas (LGGs) (World Health Organization [WHO] grade I–II), whereas among patients with HGGs, seizures are more common in patients with AAs (WHO grade II) than in those with GBMs (WHO grade IV).[15–17] Smaller tumors and those growing less quickly are associated with higher rates of seizures than large tumors and rapidly growing lesions.[5–9,17,18] Although the reason for this trend is not known, proposed explanations include the predilection of HGG for white matter locations, the possibility that rapid growth might preclude the development of epileptogenesis, and the prospect that some patients with HGG do not survive long enough to develop epilepsy.[17–19]

HGGs located in superficial cortical areas are most likely to produce seizures,[17,20–23] as are tumors centered in the temporal or frontal lobes or the insula.[17,20,21,24–26] Lee and colleagues[17] analyzed tumor location in 124 glioma patients with seizures, and mapped aggregate tumor location using a summed-statistic image, as depicted in **Fig. 1**. These investigators also found that many HGGs causing seizures were located in the temporal lobe, followed by the frontal lobe. The inherent epileptogenicity of mesial temporal structures making seizures more likely in the temporal region is a possibility.[27,28] Furthermore, Spencer and colleagues[29,30] have suggested that "dual pathology," including any combination of foreign-tissue lesions, cortical dysgenesis, gliosis, or hippocampal sclerosis, further drives epileptogenesis in tumoral temporal lobe epilepsy. Some investigators have found

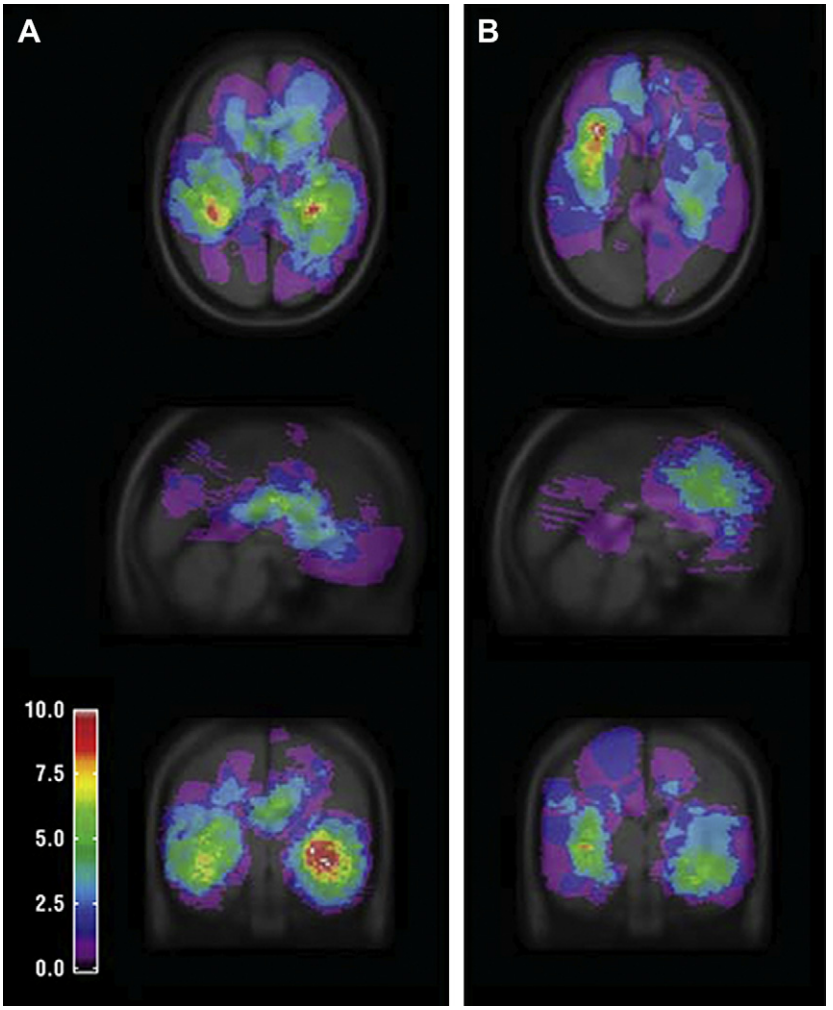


**Fig. 1.** Summed-statistic image showing the aggregate location of 124 tumors. At each voxel, the number of patients presenting with tumors is calculated. Maps are generated from the sum of the binary tumor masks for high-grade (*A*) and low-grade (*B*) gliomas. (*From* Lee JW, Wen PY, Hurwitz S, et al. Morphological characteristics of brain tumors causing seizures. Arch Neurol 2010;67:339; with permission.)

a lower likelihood of seizures in de novo GBMs than those having progressed from known LGGs,[8,18] and others have noted that seizures may sometimes precede radiographic evidence of malignant tumor transformation.[31] It is perhaps not surprising that epilepsy is more common in patients with multifocal disease than in those with a solitary tumor.[8]

Although the molecular pathophysiology of epileptogenicity in gliomas remains incompletely understood, several contributory mechanisms have been proposed. Peritumoral changes, such as hypoxia, neurotransmitter alterations, and blood-brain barrier disruption, have all been observed in parenchyma adjacent to brain tumors, and may contribute to epileptogenicity in patients with HGG.[32–36] Furthermore, although neurons are traditionally credited with seizure initiation, increasing evidence suggests that astrocytes also likely contribute to the induction and maturation of epileptogenesis.[37] Bordey and Sontheimer[38] observed that astrocytes from seizure foci in patients with temporal lobe epilepsy consistently express faster-activating sodium channels and diminished potassium buffering compared with normal cells. Downregulation of glutamine synthetase, an enzyme known to be deficient in sclerotic hippocampi of patients with temporal lobe epilepsy[39] and in brains of animal epilepsy models,[40] has also been observed in astrocytes of patients with HGG.[37] Thus, glutamate accumulation may represent another molecular contribution to seizure generation in patients with HGG. Although the process of epileptogenesis is known to occur over time, rapid ictogenesis may arise in the absence of epileptogenesis with acute pathophysiologic phenomena seen in gliomas, such as hemorrhage, edema, and electrolytic changes, thus causing early seizures in some patients.[18]

Seizure semiology with HGGs is variable, and may resemble seizure characteristics seen in defined anatomic epilepsy syndromes, but typically includes simple- and complex-partial seizures.[5,8] Secondary generalization is also not infrequent, and status epilepticus may occur.[5,8] Given the significant risk of epilepsy in these patients, seizures should be high on the differential diagnosis when a patient harboring a known HGG presents with altered mental status or novel sensorimotor symptoms.

## SURGICAL AND ADJUVANT TREATMENT OF HGGS ASSOCIATED WITH EPILEPSY

Although several groups have studied seizure outcomes in the surgical treatment of LGGs,[15,22,41] only one study to the authors' knowledge has specifically examined predictors of seizure freedom in the surgical resection of HGGs.[5] Chaichana and colleagues[5] retrospectively analyzed 648 patients with surgically resected HGG, of whom 24% presented with seizures. Preoperative seizures were observed to be more common in younger patients, as well as with AA (compared with GBM), and with cortically based and temporal lobe lesions. Twelve months after surgical resection (gross total in 33%), 77% of patients with preoperative seizures were seizure free (Engel class I),[33] whereas only 5% experienced no improvement in seizures (Engel class IV). Seizure freedom was somewhat less common in patients who suffered from uncontrolled epilepsy before surgery, although 56% of these individuals also achieved seizure freedom postoperatively. The investigators also noted that individuals with parietal lobe lesions were least likely to achieve seizure freedom postoperatively. Seizure recurrence in patients initially seizure-free after surgery was independently associated with tumor recurrence. These results suggest that seizure freedom can be achieved in the resection of HGGs, even in some patients with medically refractory epilepsy, and thus should represent an important goal in the surgical treatment of these patients. Nevertheless, given the limitations of retrospective study design and the lack of confirmatory investigations, further studies in this area are important.

In patients with LGG, various investigators have reported that gross-total resection predicts a higher likelihood of postoperative seizure freedom.[15,22,41] Chaichana and colleagues[5] did not observe a similar relationship between resection extent and seizure outcome in HGGs, and, to the author's knowledge no other studies have investigated this question in HGGs. Similarly, although the use of intraoperative electrocorticography in LGG resection has been advocated to delineate epileptic cortex surrounding the tumor,[41,42] this has not been studied in HGGs. Thus, although there is mounting evidence suggesting that extent of resection may influence patient survival in HGGs,[43,44] it is unknown whether this factor also affects seizure outcome.

There is some evidence that chemotherapy or radiotherapy may also positively affect the seizure burden in patients with brain tumors. In a small case series, Chalifoux and Elisevich[45] describe a significant seizure reduction in unresected patients with HGG after ionizing radiation treatment, with benefit extending beyond the early postradiation period.[45] Similar positive effects on seizure frequency have been described in patients with LGG after radiotherapy[46] or chemotherapy with temozolomide.[47] Antitumor therapy by surgery,

cranial radiation, or chemotherapy may all contribute to reduced seizure burden in patients with glioma.[48] Although more prospective data are important in evaluating the possible effects of chemotherapy and radiotherapy on seizure profiles, adjuvant antineoplastic therapy should not be considered antiepileptic treatment.

## ANTIEPILEPTIC MEDICATIONS IN PATIENTS WITH HGG

Although surgery and adjuvant antitumor therapies improve the overall and progression-free survival in patients with HGG, they very rarely result in a cure. Antiepileptic drugs (AEDs) are therefore the mainstay of seizure treatment in these patients, and understanding the approach, efficacy, and serious side effects of AED treatment is critically important in reducing patient morbidity and improving patients' quality of life. Some investigators have reported that although seizures are less common in patients with HGGs than in those with LGGs, they may be more difficult to control in patients with malignant lesions.[18]

The general approach to AED treatment in patients with glioma, as in all patients with epilepsy, is to first use a single AED at the lowest dose that effectively controls seizures, followed by additional trials of serial monotherapy versus polytherapy as necessary.[48–50] Common first-line agents used in glioma-related epilepsy include valproic acid and phenytoin,[49–51] and more recently levetiracetam has been proposed as monotherapy for tumoral epilepsy.[48,49,52,53] Topiramate and lamotrigine are also sometimes used as initial first-line monotherapy.[48] Van Breemen and colleagues[50] advocate for valproic acid as an efficacious first-line AED in patients with glioma who also have epilepsy, reporting a 79% responder rate and seizure freedom in 52% of patients with monotherapy. Valproic acid is also the most commonly used agent in children with focal epilepsy,[54] and a recent phase I study suggests that it is well tolerated in pediatric patients with brain tumor, with phase II results pending.[51] Phenytoin is also frequently used as initial monotherapy, and in one study it was associated with 730 (median) seizure-free days in patients with glioma suffering from at least 1 seizure.[49] More recently, monotherapy with the newer agent levetiracetam has been reported to be efficacious in this population, with benefits over valproic acid and phenytoin, including the ability to forgo the monitoring of serum level, a lower incidence of toxicity, and the lack of significant drug interactions.[48,49,52,53] However, none of these studies were performed with the rigor required for inclusion in a Cochrane review on the topic.[55] The only study meeting the Cochrane meta-analysis criteria was an unblinded, randomized trial of phenytoin continuation versus change to levetiracetam at the time of surgery.[56] This study showed similar efficacy and side effects for both arms with a suggestion of more balance problems in the phenytoin arm. As a possible confounder, more patients dropped out of the levetiracetam arm and were not included in the analysis.[56]

When AED monotherapy fails to adequately control seizures in patients with glioma, there is disagreement over whether to trial a second agent as monotherapy or to add an adjunct medication, provided the absence of significant side effects with the initial AED. Although a common approach is to attempt 1 or 2 serial monotherapy trials as necessary, reserving polytherapy for refractory cases,[49] other practitioners have advocated add-on therapy immediately after initial drug failure. Van Breemen and colleagues[50] report encouraging results with the addition of levetiracetam to valproic acid, and Newton and colleagues[57] observed a 90% rate of benefit and 59% rate of seizure freedom when adding levetiracetam to a patient's existing regimen. Based on these varied approaches to patients who fail initial monotherapy, a randomized, controlled trial of serial monotherapy versus polytherapy comparing various agents in tumoral epilepsy is certainly warranted.

Side effects and toxicity of AED are critical considerations in patients with HGG, particularly given the importance of quality of life in this almost universally terminal illness. AEDs are associated with significant adverse effects,[58–60] including cognitive deficits,[61–63] and first-generation medications may result in a higher incidence of side effects in patients with glioma than in other epileptics.[6,49,64] In a large European survey of patients with epilepsy, Baker and colleagues[65] found that 31% of individuals changed their AED at least once in the past year because of side effects, and 44% were worried about possible side effects related to AEDs. Other researchers have shown that adverse AED effects have the single greatest influence on quality of life in patients with controlled seizures,[66] and that patients would prefer to pay more for medications with improved side-effect profiles.[67]

Although phenytoin is commonly used, given the favorable efficacy it is associated with a significant number of drug interactions, and its common dose–related side effects (disequilibrium and drowsiness) are often poorly tolerated by patients with brain tumors. Additional side effects include rash, drowsiness, dizziness, and hirsutism, with Stevens-Johnson syndrome being the most feared adverse event.[49] Moreover, monitoring of serum

level is necessary, and toxic levels frequently occur in the therapeutic dose range because of zero-order kinetics.[49] Along with carbamazepine and oxcarbazepine, phenytoin may cause leukopenia, necessitating the monitoring of blood count during initial treatment.[68,69] Valproic acid has a lower incidence of adverse effects, but can result in thrombocytopenia, and the monitoring of serum level can be challenging because of the variable pharmacokinetics.[68,69] The second-generation AEDs, although not necessarily associated with greater efficacy than first-generation medications, may in some circumstances possess improved tolerability.[49] Monitoring of levels is not necessary with these newer agents, as many are not metabolized by the hepatic P450 system, and significant drug interactions are rare.[49] Levetiracetam is renally excreted and typically well tolerated, with infrequent side effects including somnolence, nausea/vomiting, headache, and insomnia.[53] Two recent studies of levetiracetam in patients with glioma cited little or no medication discontinuation secondary to adverse effects.[52,53]

Another important consideration of AED treatment in patients with HGG is the potential for interaction with chemotherapy. CYP3A4 enzyme-inducing AEDs, such as phenytoin, carbamazepine, and oxcarbazepine, may increase the clearance of drugs metabolized by the P450 system, including numerous chemotherapeutic agents (including thiotepa, taxanes, irinotecan, imatinib, gefitinib, temsirolimus, erlotinib, tipifarnib, and vorinostat), as well as corticosteroids such as dexamethasone, which are frequently prescribed to reduce peritumoral edema.[49,70–75] This may be less of a concern with valproic acid, a weak CYP3A4 inducer, and noninducing agents such as levetiracetam and lamotrigine, and potential chemotherapeutic interactions with topiramate require further study.[75] Not all AED interactions with chemotherapeutic agents are deleterious. Bobustuc and colleagues[76] recently observed that levetiracetam may inhibit the expression of the DNA-repair enzyme $O^6$-methylguanine-DNA methyltransferase in vitro, and therefore sensitize glioma cells to the alkylating agent temozolomide. Furthermore, Jaeckle and colleagues[77] reviewed data from patients with HGG treated with enzyme-inducing anticonvulsants (used largely for prophylaxis), finding paradoxically that patients treated with these drugs survived longer than those who did not undergo treatment, this increase in survival being independent of seizure activity. It is not clear whether this observation was due to an effect on chemotherapy, an effect on the tumor directly, or a confounding variable not accounted for in their detailed multivariate analysis. In general, epilepsy providers must be aware of these potential drug interactions between AEDs and chemotherapy, to ensure optimal coordination of antiepileptic and neuro-oncologic treatment in patients with HGG.

A final question is whether to initiate prophylactic AED therapy in the patient with HGG who has not had a seizure. Various investigators have advocated for prophylaxis in patients with brain tumors, citing efficacy in preventing seizures, despite the risk of adverse effects of medication.[78–80] In 1996, a randomized controlled trial of valproic acid prophylaxis in adults with brain tumors showed that patients receiving the prophylactic AED actually had a nonsignificantly higher rate of seizures compared with those taking placebo.[81] Subsequently, the American Academy of Neurology recommended against long-term prophylactic AEDs in patients who are newly diagnosed with brain tumor,[6] and a meta-analysis of the relevant literature provided further evidence that AEDs should not be used prophylactically.[82] One exception is that AED prophylaxis may be considered for 1 week following surgical resection, given the higher incidence of postoperative seizures during this time,[6,83–87] although even the evidence supporting this practice remains inconclusive.[88] Thus, while prophylactic AEDs remain commonly prescribed in patients with HGGs and other tumors,[18,89–91] the preponderance of evidence and clinical guidelines recommend strongly against this practice, and the use of perioperative AEDs will require further scrutiny.

## SUMMARY AND RECOMMENDATIONS

HGGs are the most common primary brain tumor and are often associated with seizures, particularly with lesions involving the temporal or frontal neocortex. Seizure control is a critical but often underappreciated goal in the treatment of patients harboring these malignant lesions. Although surgical resection of HGGs may reduce the seizure burden in these individuals, insufficient evidence exists regarding the surgical factors that contribute to seizure freedom. The authors' recommendation based on the recognized impact of seizures on the quality of life in patients with HGG is that patients with medically intractable seizures be considered for a palliative resection guided by electrocorticography and functional mapping. Many patients treated at their center have benefited from this approach. Similarly, although other antitumoral treatments such as chemotherapy and irradiation may improve a patient's seizure profile, these adjunctive treatments should not be considered as antiepileptic

**Table 1**
**Factors affecting anticonvulsant choice in patients with HGG**

| | |
|---|---|
| Avoid or adjust dose with chemotherapy | DPH, CBZ, VPA, OXC |
| Avoid with bone marrow suppression | DPH, CBZ, VPA |
| Avoid with mood or thought disorder | LEV, TPM, ZON |
| Avoid with SIADH | OXC, CBZ |
| Avoid if immediate effect required | LMT, TPM |
| Avoid if cost is an issue (no generics) | PGB, LAC |

*Abbreviations:* CBZ, carbamazepine; DPH, phenytoin; LAC, lacosamide; LEV, levetiracetam; LMT, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; SIADH, syndrome of inappropriate antidiuretic hormone; TPM, topiramate; VPA, sodium valproate; ZON, zonisamide.

therapy. AEDs remain the mainstay of seizure treatment in patients with HGG, and antiepileptic medication should be started after a tumor-related seizure, but should not be used prophylactically in the absence of seizure activity. Although Class I evidence is not available to guide the management of AED in patients who present with seizures, the authors offer the following practical suggestions: (1) because many patients undergo chemotherapy, it is preferable to choose a medicine that does not affect chemotherapy levels or exacerbate chemotherapy-induced bone marrow suppression (**Table 1**); (2) because patients presenting anew are not otherwise protected from seizures, medications with a slow titration are usually not acceptable (see **Table 1**); and (3) newer medications without generic equivalents or obvious advantages over other medications should not be first-line choices (see **Table 1**). Based on these criteria, levetiracetam and zonisamide seem to be ideal medications for initiating treatment. Both can be started at a dose known to be effective (for levetiracetam, 500 mg twice daily, and zonisamide, 100 mg/d). Failure to respond sufficiently to initial treatment warrants referral for subspecialty seizure care. Although HGG remains almost universally a terminal illness, seizure control is a critical goal in the treatment of these patients, given the deleterious effects of epilepsy on patients' quality of life.

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