Published in final edited form as:

Semin Radiat Oncol. 2015 July ; 25(3): 219–224. doi:10.1016/j.semradonc.2015.02.009.

Clinical Management of Seizures in Patients With Low-Grade Glioma

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Abstract

Seizures, transient disruptions of normal brain electrical activity, are common for patients with low-grade glioma (LGG) and significantly affect quality of life. Up to 75% of patients with a LGG will have seizures in the course of their disease (compared with 1%–2% of the general population). Depending on the type of abnormal electrical activity, the functional implications of seizure can impact any domain, including mental status, sensation or strength. In most cases, either the seizure or the medications used to treat the seizure may contribute to cognitive and psychosocial difficulties of various degrees of severity. Hence, effective management of seizures is a major priority for patients with LGG. Evidence-based guidelines suggest that levetiracetam is the best first-line agent for treatment of seizures in this population due to both its efficacy and tolerability. An important consideration in the field of neuro-oncology is that levetiracetam has very few drug interactions. Unfortunately, approximately one-third of patients with LGG have refractory epilepsy where additional agents such as valproic acid, or lacosamide, lamotrigine and nonpharmacologic therapies such as diet-based interventions, epilepsy surgery, and devices are considered.

Background

Seizures, transient disruptions of normal brain electrical activity affecting neurologic function, are the presenting sign of disease in 15%–50% of all gliomas and up to 83% of patients diagnosed with low-grade glioma (LGG).¹ In addition, across all patients with LGG, 60%–85% of people will have a seizure at some point in their disease course.^{2,3} Once a patient has a seizure, the recommendation is for lifelong antiepileptic drug (AED) therapy as the likelihood of having another seizure is high, particularly if there is evidence of tumor progression.² Fortunately, the modern era of AED has multiple good drug options for seizure management, and a proportion of patients have excellent seizure control with treatment of the tumor. Nevertheless, there is an important subset of patients that have seizures refractory to multiple agents and who require multidisciplinary care to optimize seizure control and minimize complications.

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The authors declare no conflicts of interest.

Seizure Terminology

Seizures are categorized as either generalized or focal.⁴ Generalized seizures are defined as epileptic events that involve networks across both sides of the brain. In adults, these seizures result in movements throughout the body (tonic, clonic, tonicclonic, or myoclonic) that are often accompanied by a change in consciousness. In children, generalized seizures may present without movements but with change in consciousness. These are called absence seizures. Such seizures are not common in adults, but in rare cases, adult patients may have subclinical status epilepticus, which is a seizure involving both hemispheres of the brain and affecting cognition but with limited motor manifestation.⁵ Generalized seizures are the most concerning seizure type as they are the most likely to result in injury or life-threatening complications. Fortunately, generalized seizures are quite rare in patients with LGG.

Focal seizures involve networks on only one side of the brain. The clinical manifestations of these events depend on what area of the brain they involve. Outside of the distinction between whether or not consciousness or awareness is affected, there is no classification for focal seizures (Table 1). Rather, they are described by their specific clinical manifestations such as focal motor seizure of the right upper extremity, sensory seizure involving the left face, or dyscognitive seizure. Focal seizures are generally “less severe” than generalized seizures as they tend to be brief and more limited in scope. However, focal seizures may also result in falls and injury similar to those noted in patients with generalized seizures. Moreover, focal seizures may become secondarily generalized.

Seizure Incidence in the Setting of LGG

All forms of LGG are associated with seizures, with some more prone to seizure activity than others. For example, oligodendroglial tumors are particularly notorious for seizure activity. This may be because oligodendrogliomas are more likely to involve the cortex, whereas most astrocytomas are situated in the white matter⁶ or it may be due to the biology of oligodendrogliomas. In general, epileptogenicity of the tumor is inversely correlated with its growth rate. For example, glioneuronal tumors, such as gangliogliomas and dysembryoplastic neuroepithelial tumors, which are profoundly slow growing, are associated with pharmacoresistant epilepsy in 90%–100% of patients.⁶ In a review of 711 patients with various forms of brain tumors, 62% of patients with “mixed glioma,” 53% of patients with oligodendroglioma, and 42% of patients with LGG had seizures compared with only 26% of patients with glioblastoma and 15% of patients with brain metastases.⁷ Similar data were presented in a review by DeAngelis et al, with 65%–95% of patients diagnosed with LGG presenting with seizure compared with 15%–25% of patients with glioblastoma presenting with seizure.⁸

Prophylaxis Against Seizures in Patients With LGG

Seizures can cause elevated intracranial pressure and result in falls, injuries, drowning, status epilepticus, or sudden unexpected death in epilepsy (SUDEP). Seizures can also negatively affect quality of life (QOL) through loss of driving privileges, social and work limitations, cognitive injury, and anxiety about any of the aforementioned issues. Although preventing seizures is a priority given the potential complications that they may cause,

current guidelines do not recommend prophylaxis for patients with glioma who have not had a seizure. Specifically, in patients with newly diagnosed brain tumors who have not had a clinical seizure, it is recommended to taper and discontinue AEDs postoperatively.⁹ This is based on data from a meta-analysis initially published in 2000 but reaffirmed in 2003 and 2008.^{10,11} The analysis reviewed 4 randomized clinical trials (level I evidence) and 8 cohort studies (level II evidence) comprising 1017 patients treated with AEDs including phenytoin, valproic acid, and phenobarbital. The results showed that across this group of patients there was no statistically significant difference between patients on AED prophylaxis and those not receiving prophylaxis in the odds ratio for seizure-free survival or seizure incidence. However, 42% of patients in the prophylaxis group had subtherapeutic drug levels, and 24% experienced side effects leading to change or discontinuation of AEDs. These 2 facts illustrate a major concern about these data: they were generated using only first-generation AEDs that have less favorable pharmacologic properties and tolerability profiles than the newer agents most commonly used today (Table 2). Moreover, historical AEDs predominantly comprise enzyme-inducing AEDs that can decrease the efficacy of dexamethasone and various chemotherapies owing to their effects on drug metabolism. Several relevant CYP3A4 substrates include cyclophosphamide, paclitaxel, docetaxel, etoposide, teniposide, tamoxifen, ifosfamide, doxorubicin, irinotecan as well as dexamethasone.

There are some advantages to the older AEDs. Agents such as phenytoin, valproic acid, and phenobarbital can be loaded very quickly when seizures need to be treated urgently, and there is a great deal of medical experience in managing these medications. Hence, there can be a short-term role for these medications in the management of seizures in patients with LGG. Again, it is worth noting that prior trial analyses did not consider the prophylactic efficacy of newer generation AEDs.

The guidelines for seizure management in the setting of gliomas are currently under review with groups such as the American Academy of Neurology. Based on the available data, prophylactic anticonvulsants are not recommended for patients with newly diagnosed brain tumors who have never had a seizure. Patients with LGG who have had a seizure should be treated with AEDs, and the recommendation is for the use of the modern agents such as levetiracetam, lacosamide, or lamotrigine, as these agents are well tolerated and have favorable pharmacologic profiles.

Treatment of Seizures in Patients With LGGs

The goal of seizure management in patients with LGG is complete control of seizures accomplished with a single agent that has tolerable side effects. Fortunately, this is quite often accomplished in patients with LGG. This success is owing to the fact that the AEDs available are generally quite effective and that the primary modalities used to address LGG (surgery and radiation therapy) can positively influence seizure control.

Specifically, if gross total resection (GTR) of the tumor can be accomplished, this dramatically improves seizure control. Englot et al¹² performed a systematic review of 773 patients across 20 published series and found that GTR of LGGs significantly improved

freedom from seizures compared with subtotal resection (odds ratio = 3.41, 95% CI: 2.36–4.93). Although GTR is unfortunately not always feasible, data suggest that the other modalities commonly used in the treatment of LGG also improve seizure control.

In the randomized controlled trial of the efficacy of early vs delayed radiotherapy (RT) for low-grade astrocytoma and oligodendrogliomas, 25% of the patients treated with RT vs 41% of the patients who did not get up-front RT reported seizures.¹³ A retrospective study showed that roughly 50% of patients with grade II or III gliomas had a reduction in seizure frequency 3 and 12 months after RT.¹⁴

Similarly, use of the alkylating agent temozolomide (TMZ, Temodar, Merck & Co, Kenilworth, NJ) may improve seizure control in patients with LGG. In a retrospective review of 104 patients with LGG with seizures who took TMZ as their initial tumor treatment, 44% of the patients had a 50% reduction in seizure frequency after 6 months of treatment. Interestingly, in this series and in the series by Ruda et al, improvement in seizure control was independent of magnetic resonance imaging findings.¹⁵ In another retrospective study, 69 patients with LGG and seizures were identified, with roughly half (39) treated with TMZ as their initial therapy and 30 observed without specific antitumor therapy. In the TMZ treatment group, 59% of patients had improved seizure control vs 13% in the control group, with 7 patients (18%) treated with TMZ having improvement independent of AED.¹⁶ Finally, in the phase II study of TMZ as a first-line therapy for patients with LGG, 54% of patients with seizures and LGG had improvement in seizure frequency, with 6 patients becoming seizure free.¹⁷

AEDs for Patients With LGGs

There is limited level I data about the optimal AED for patients with LGG. According to a 2013 report from the International League Against Epilepsy (ILAE), there is level I evidence for levetiracetam, zonisamide, phenytoin, and carbamazepine as initial monotherapy for adults with partial-onset seizures.¹⁸ For patients with gliomas in particular, a prospective, randomized, nonblinded study of levetiracetam vs pregabalin showed that both agents were well tolerated and had excellent seizure control, with 76% of patients having seizure control in the levetiracetam group and 89% of patients having seizure control in the pregabalin group after 40 months of treatment.¹⁹ In a different prospective study, of the 15 patients who were followed for 12 months on levetiracetam (mean dosage 1991 mg/d), 14 of 15 patients were seizure free and 1 had 50% reduction of seizure frequency.²⁰ In another prospective study, 29 patients with gliomas and seizures were randomized to switch to levetiracetam from phenytoin within 24 hours of surgery or to continue phenytoin. At 6-month follow-up, 87% of the patients on levetiracetam and 75% of the patients on phenytoin were seizure free. Hence, both agents had excellent activity, but there were far more toxicities associated with phenytoin.²¹ Finally, 92% of patients with gliomas who completed the study period of 30 days achieved a >50% reduction in the number of seizures. In a retrospective review of 181 patients with glioblastoma and seizures treated with levetiracetam or valproic acid alone or together, there was similar efficacy with both levetiracetam (70% free from seizures) and valproic acid (77% free from seizures).²²

The available data indicate that the first-line agent for seizure management in patients with gliomas is levetiracetam. It is important to note that although the most reliable data in the setting of gliomas are for levetiracetam as a monotherapy, the Food and Drug Administration has approved levetiracetam as an adjunct agent. In addition, there are no specific data about optimal dosing of levetiracetam. The pharmacokinetics of levetiracetam is linear over the dose range of 500–5000 mg, with very little variability. The mean dose of levetiracetam used in the reported studies is roughly 1000 mg twice a day. This is in fact the most common dose used, but it is safe to escalate the dose to 1500 mg or 2000 mg twice a day. Levetiracetam is very safe with no risk of serious side effects, and only a 5%–10% risk of irritability or aggression. These side effects can be mediated in some cases with concurrent vitamin B6.

After levetiracetam, the next agents to consider are valproic acid, pregabalin, and lacosamide. Each of these agents has been tested specifically in patients with gliomas, and they have their relative strengths and limitations. For example, valproic acid has been associated with improved survival in some studies^{22,23}; however, it is associated with many toxicities (Table 2). Pregabalin has been shown to be as effective as levetiracetam in a series of studies of patients with gliomas^{19,24}; however, it is a controlled substance and is associated with several side effects including lethargy, dizziness, ataxia, and cognitive changes. Lacosamide, an agent that enhances the slow voltage-gated sodium channels, was approved as an adjunct therapy for partial complex seizures in 2009. It is overall well tolerated but at higher doses can be associated with behavior and cognitive changes. There is an ongoing randomized, double-blinded, placebo-controlled trial of lacosamide for seizure prophylaxis in patients with high-grade gliomas (NCT01432171).

Additional agents that are good options for patients with LGG are topiramate and lamotrigine. Topiramate has multiple mechanisms of action including affecting voltage-dependent sodium channels, gamma-aminobutyrate activity, and a subunit of the carbonic anhydrase enzyme. It is overall well tolerated and has activity against migraines and neuropathic pain in addition to antiepileptic activity. Lamotrigine is a phenyltriazine derivative used for both seizures and mood disorders. It has the advantage of being very well tolerated once full dose is achieved.

In summary, older AEDs such as phenytoin, phenobarbital, and carbamazepine are effective in short-term seizure control but have suboptimal pharmacologic properties and many adverse effects. Newer agents such as levetiracetam, lamotrigine, and lacosamide have fewer drug-drug interactions, better tolerability profiles, and are therefore preferred. There are data from a few, small prospective trials to support the use of levetiracetam as the first-line agent for management of seizures in patients with LGG.

Intractable Seizures

Unfortunately, one-third of patients with brain tumor–related seizures have pharmacoresistance to medical management.^{22,25} These patients are at risk for the most severe complications of epilepsy. In these instances, the first recommendation is to add additional agents. In general, it is optimal to choose agents that have complementary

mechanisms of action such as levetiracetam and valproic acid or lacosamide. Generally, addition of a second agent improves seizure control in only 13% of patients, and addition of a third agent helps an additional 4% of patients.²⁶ This has not been expressly investigated in patients with glioma but does suggest that for the patients with LGG with ongoing seizures despite appropriate AEDs, additional measures should be considered.

Epilepsy surgery can be effective if the source of the seizure can be identified via long-term electroencephalography. Although there are no specific data about the efficacy of epilepsy surgery for patients with LGG, for the right set of circumstances, this is a strategy that can be very effective. Another possible approach is vagus nerve stimulation with an implantable device. In 1 retrospective study, 50% (8/16) patients had improvement in seizure frequency. The improvement in seizure frequency was directly related to tumor behavior, with seizure control in those patients who had stable tumors.²⁷ Finally, diet-based therapies such as the ketogenic diet or the modified Atkins diet are increasingly being followed by patients with gliomas.^{28,29} These diets have been shown to be effective for intractable seizures owing to other causes, and there is new evidence to suggest that they may have antitumor activity.^{28,30} Additional data are required to have a better understanding about the efficacy of dietary modification for seizure control in patients with glioma.

Effect of Seizures on QOL and Cognition

LGG complicated by seizures has a deleterious effect on patients' function and QOL. It can be difficult to assign the cause of various side effects to the seizures, vs the seizure medications, the tumor, or the tumor treatments. For example, up to 90% of patients with LGG experience long-term cognitive abnormalities.³¹ These may be due to the tumor or the late effects of the surgery, RT, chemotherapy, or anti-epileptic medications. Given that seizures are so common in patients with LGG and that they commonly cause multiple morbidities, it is reasonable to presume that seizure frequency directly contributes to neurologic health and health-related QOL (HRQOL). For example, in 156 patients with LGG, higher seizure frequency was associated with reduced cognitive function in all domains as well as lower HRQOL.³² In addition to affecting cognitive function and HRQOL, seizures can affect functional activities of daily living. Specifically, once a person has a seizure, all states require that it be reported to the appropriate motor vehicles office (in 6 states, this is done by the medical team, but in 44 states, patients self-report). The longest state-required interval from seizure to restoration of driving privileges in the United States is 18 months. However, most states restrict driving for 3–6 months.

Conclusions

Seizures are common and often the presenting symptom of patients with newly diagnosed LGG. Fortunately, for most, these events can be readily controlled with a single-agent AED. The modern AEDs have better therapeutic profiles and improved tolerability compared with historical agents. This is critical, as patients with gliomas who have had a seizure often require lifelong therapy, and the historical agents were associated with significant neurologic dysfunction. Importantly, surgery, radiation, and chemotherapy treatments directed at the tumor often improve seizure control. Despite this and the excellent activity of

AEDs, nearly a third of patients with LGG have intractable epilepsy. These patients require multidisciplinary management of their seizures to reduce side effects of multiple therapies and improve seizure control.

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Table 1

Seizure Classification

Seizure types	Generalized seizure (Tonicclonic, absence, myoclonic, or atonic)	Focal seizure with impairment of consciousness (previously complex partial seizure)	Focal seizure without impairment of consciousness (previously simple partial seizure)
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Table 2

Antiepileptic Agents

Drug	Form	Advantages	Disadvantages	Mechanism of Action	Oral Dose Range
Phenytoin (Dilantin, Pfizer Inc New York, NY; Phenytek, Mylan Pharmaceuticals, Canonsburg, PA)	Intravenously/orally	Target therapeutic range, widely available laboratory assays, generic available, and can be rapidly loaded.	General neurologic side effects [*] , nausea, vomiting, headache, hirsutism, gingival hyperplasia, coarse facies, lymphadenopathy, osteomalacia, and toxic epidermal necrolysis. Multiple drug interactions (P450 and protein binding).	Modulates neuronal voltage-dependent sodium and calcium channels	300–400 mg/d, divided bid-tid
Phenobarbital (generic only)	Intravenously/orally	Target therapeutic range, widely available laboratory assays, long half-life, generic available, and can be rapidly loaded.	General neurologic side effects [*] , mood and personality changes, lethargy, nausea, vomiting, rash, and porphyria exacerbation. Multiple drug interactions.	Depresses the central nervous system, and produces anesthesia and sedation	50–100 mg bid-tid
Valproic acid (Depakene, AbbVie Inc, Chicago, IL)	Intravenously/orally	Target therapeutic range, widely available laboratory assays, possible antitumor effect, and can be rapidly loaded.	General neurologic side effects [*] , weight gain, nausea, vomiting, headache, hair loss, <i>hepatic toxicity</i> , and <i>hyperammonemia</i>	Increases GABA effects and may inhibit glutamate/NMDA receptor-mediated neuronal excitation	30–60 mg/kg/d, divided bid-tid
Carbamazepine (Carbatrol, Shire Pharmaceuticals, Dublin, Ireland; Tegretol, Novartis Pharmaceuticals Corp, Basel, Switzerland)	Orally	Target therapeutic range and widely available laboratory assays	General neurologic side effects [*] , rash, nausea, vomiting, and <i>hyponatremia</i> . Multiple drug interactions.	Reduces polysynaptic response, and blocks posttetanic potentiation	800–1200 mg/d, divided bid-qid
Levetiracetam (Keppra, UCB Pharma Inc, Brussels, Belgium)	Intravenously/orally	Wide therapeutic range, well tolerated, available in generic formulation, <10% protein binding, non-P450 metabolism, and can be rapidly loaded.	Laboratory assay is not readily available, and rare side effect is irritability or behavior change, which can be addressed with B6 supplementation.	Unknown, selectively prevents hypersynchronization of epileptiform burst firing	500–1500 mg bid
Lamotrigine (Lamictal, GlaxoSmithKline, Middlesex, United Kingdom)	Orally	Laboratory level readily available and target therapeutic range.	Rash including Stevens Johnson and toxic (more common in children and when given with valproic acid), hypersensitivity reactions. Can exacerbate tics in children and contribute to insomnia. Requires titration.	Inhibits voltage-dependent sodium channels, decreases presynaptic glutamate and aspartate release	200 mg bid
Topiramate (Topamax, Janssen Pharmaceuticals Inc, Titusville, NJ)	Orally	Has activity against migraine and neuropathic pain and is well tolerated	Nephrolithiasis, open-angle glaucoma, hypohidrosis, behavior or cognitive change, weight loss, metabolic acidosis, and paresthesias. Requires titration.	Affects voltage-dependent sodium channels, gamma-aminobutyrate activity, and a subunit of the carbonic anhydrase enzyme.	100–200 mg bid
Zonisamide (Zonegran, Eisai Inc, Tokyo, Japan)	Orally	Well tolerated	Rash, kidney stones, hypohidrosis, irritability, weight loss, and photosensitivity. Requires titration.	Blocks voltage-dependent sodium and calcium channels and inhibits carbonic anhydrase	100–600 mg/d, divided qd-bid

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Drug	Form	Advantages	Disadvantages	Mechanism of Action	Oral Dose Range
Lacosamide (Vimpat, UCB Pharma Inc, Brussels, Belgium)	Intravenously/orally	Well tolerated and has minimal interaction with other drugs	Dizziness at high doses	Enhances slow inactivation of voltage-gated sodium channels	100–200 mg bid
Gabapentin (Gralise, Depomed Inc, Newark, CA; Neurontin, Pfizer Inc, New York, NY)	Orally	Can be loaded and non-P450 metabolism	Weight gain, peripheral edema, and behavioral changes. Requires titration to doses effective for seizure control (>1200 mg/d).	Blocks voltage-dependent calcium channels	300–1200 mg tid
Oxcarbazepine (Trileptal, Novartis Pharmaceuticals Corp, Basel, Switzerland)	Orally	Laboratory level readily available and target therapeutic range, non-P450 metabolism	Requires titration. Hyponatremia and rash	Blocks voltage-sensitive sodium channels	600–1200 mg bid
Clobazam (Onfi, Lundbeck, Valby, Denmark)	Orally	Long acting and rapid seizure control	Can cause withdrawal symptoms if suddenly stopped	Binds to benzodiazepine receptors and enhances GABA effects	10–20 mg bid

Abbreviations: GABA, γ -aminobutyric acid; NMDA, N-methyl-D-aspartate.

* General neurologic side effects include fatigue, decreased concentration, impaired memory, dizziness, imbalance, ataxia, blurred vision, nystagmus, tremor, and sensory changes.