

## Epilepsy in glioma patients: mechanisms, management, and impact of anticonvulsant therapy

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Seizures are a well-recognized symptom of primary brain tumors, and anticonvulsant use is common. This paper provides an overview of epilepsy and the use of anticonvulsants in glioma patients. Overall incidence and mechanisms of epileptogenesis are reviewed. Factors to consider with the use of antiepileptic drugs (AEDs) including incidence during the disease trajectory and prophylaxis along with considerations in the selection of anticonvulsant use (ie, potential side effects, drug interactions, adverse effects, and impact on survival) are also reviewed. Finally, areas for future research and exploring the pathophysiology and use of AEDs in this population are also discussed.

**Keywords:** anticonvulsant, epilepsy, glioma, seizure.

Seizures are a well-recognized symptom of primary brain tumors, and they can occur at any point along the illness trajectory. Seizures often herald the diagnosis or progression but can also occur in patients when there is no evidence of tumor growth. Although the underlying pathophysiology is not well understood, seizures may be provoked by a variety of factors including the impact of the tumor cells on peritumoral cortex, brain edema, increased intracranial pressure, metabolic derangements related to treatment, comorbid conditions, intercurrent illness, or medication.

The incidence of seizures is higher in patients with slow-growing tumors compared with more rapidly growing tumors. Low-grade glioma patients who present with seizures in the absence of neurologic deficits have favorable survival outcomes,<sup>1</sup> presumably because their tumors are slower growing and are more likely to have IDH1/2 mutations.<sup>2</sup> Overall, the incidence of seizures in patients with low-grade tumors is estimated to be between 70% and 90%. Seizures are more common in oligodendrogliomas than astrocytomas<sup>3</sup> and occur less frequently in older patients (aged  $\geq 50$ –60 y).<sup>4</sup> In patients with glioblastoma (GBM), the incidence has been reported to be between 30% and 62%, with two-thirds of seizures occurring at presentation and one third during the course of the disease;<sup>5–7</sup> however, a

recent report noted a higher incidence during the follow-up period (48%).<sup>4</sup> Seizures are most commonly associated with tumors of the frontal, temporal, and parietal lobes and are not typically observed with tumors of the deep structures, brainstem, or cerebellum.

Brain tumor-related seizures may be focal seizures with or without altered awareness, generalized tonic-clonic seizures, or focal seizures with secondary generalization. Focal seizures occur in nearly 40% of patients with GBM, with 40% of these patients then experiencing secondary generalized seizures.<sup>5</sup> Nearly a quarter of patients have both focal and generalized seizures, and status epilepticus has been reported in more than 10% of patients.<sup>5,8</sup> In a recent series, 76% of GBM patients were seizure-free before surgery as compared with 77%–92% after surgery. Seizure control seems to be directly proportional to the extent of resection.<sup>5,9</sup> In particular, gross total resection in patients with low-grade gliomas is associated with a higher rate of seizure control.<sup>10,11</sup>

Seizure recurrence or worsening seizure control may be associated with tumor progression following first-line treatment.<sup>8</sup> Interestingly, both radiation therapy and use of temozolomide are associated with reduction of seizure frequency,<sup>12</sup> especially in those with low-grade glioma.<sup>11,13</sup> Prolonged seizure control is

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associated with improved functional status, whereas drug-resistant epilepsy has a negative impact on quality of life and neurocognitive function.<sup>14</sup>

In this review, we discuss the mechanisms by which seizures occur in brain tumor patients. We then consider the use of antiepileptic drugs (AEDs) including drug selection, management, associated short- and long-term side effects, and impact on patient function and quality of life.

### Mechanism of Epileptogenesis

The mechanism of epileptogenesis in tumors is incompletely understood and is believed to be multifactorial. Seizures may occur in patients with tumors that are intra-axial/infiltrative or extra-axial/distortive.<sup>3</sup> Seizures arise electrographically from the peritumoral cortex in most patients with brain tumors due to induced changes in these regions,<sup>15,16</sup> rather than from the tumor proper, with the exception of glioneuronal tumors containing neuronal elements.<sup>17</sup>

The multiple mechanisms of epileptogenicity in brain tumors can be loosely classified as either being caused by direct effects of the tumor (tumorocentric) or due to changes in the extracellular milieu causing cortical hyperexcitability (epileptocentric).<sup>18,19</sup> The mechanisms of preoperative seizures likely differ from those of postoperative seizures. In the latter, surgical complications (particularly after awake surgery and rarely effects of chemoradiotherapy) are thought to contribute. Although mechanisms of preoperative seizures are likely to be more informative about the basis of tumor-associated epileptogenicity, postoperative seizures carry far greater clinical relevance.

Direct mass effects of the tumor alter the surrounding brain through edema,<sup>20</sup> vascular insufficiency,<sup>21</sup> and inflammation.<sup>22</sup> The peritumoral cortex in patients with seizures reveals changes in synaptic vesicles and glial gap junctions.<sup>3</sup> An increase in CX43 protein expression has been found in perilesional tissue of seizure associated with brain tumors, suggesting an increase in astrocytic gap junctions.<sup>23</sup> There is persistence of neurons in white matter, which is sometimes related to tumor pathology, that may predispose these patients to seizures.<sup>24</sup> Peritumoral pH is significantly elevated as compared with normal cortex. This is thought to increase the likelihood for seizures by multiple mechanisms including blocking inward K<sup>+</sup> currents,<sup>25</sup> inhibiting gamma-aminobutyric acid (GABA) conductance,<sup>26</sup> and removing inhibition on NMDA receptors.<sup>27</sup> Studies on the micro-organization of the peritumoral cortex have revealed loss of inhibitory synapses on pyramidal neurons.<sup>28</sup>

Changes in the extracellular milieu may cause cortical irritability, but this depends on the balance between excitatory and inhibitory factors, particularly neurotransmitters such as the chief inhibitory molecule, GABA. Alterations in GABA transmission are believed to contribute to the mechanism of various epilepsies. Measurements of GABA in cortical biopsies in humans have revealed mixed results, possibly because GABA levels are elevated due to the local ischemia associated with surgical resection.<sup>29</sup> In a microdialysis study of the extracellular space in gliomas, GABA and aspartate concentrations were found to be higher in tumors as compared with peritumoral or normal cortex in patients without epilepsy than in patients with epilepsy.<sup>30</sup>

Immunoreactivity studies revealed decreased glutamate decarboxylase activity of perilesional cortices. Either an increase or decrease in the immunoreactivity to GABA(A) alpha-1 subunit was observed in some patients.<sup>31</sup> Others have found more consistent decreases in GABAergic neurons in the peritumoral tissue identified as epileptogenic by electrocorticography as compared with normal tissue.<sup>32</sup> Autoradiographic studies of benzodiazepine receptors in astrocytomas have revealed an increased number of binding sites,<sup>33</sup> which may influence peritumoral GABA activity. Release of extracellular glutamate may downregulate neuronal and astrocytic GABA receptors.<sup>34,35</sup> Other studies have demonstrated that changes in chloride homeostasis in the peritumoral microenvironment may decrease GABAergic inhibition.<sup>36</sup>

Recent evidence has increasingly identified glutamate, the main excitatory neurotransmitter in the CNS, as a key driver for tumor-associated seizures.<sup>37</sup> Neurons release glutamate into the synaptic cleft, where it undergoes reuptake by glia and is converted into glutamine. This is transported to neighboring neurons, where it is reconverted into glutamate. Increased expression of several glutamate receptors was found in the reactive astrocytes of perilesional zones.<sup>38</sup> Although older microdialysis studies have found no relationship between high extracellular glutamate and seizure activity,<sup>30,39</sup> more recent studies have demonstrated increased concentrations of glutamate in both tumors and peritumoral glioma tissues in patients with tumor-associated seizures as compared with patients without tumor-associated seizures.<sup>40</sup>

The best-described role of glutamate in tumor-associated seizure involves the system  $x_c^-$ , an Na<sup>+</sup>-independent cysteine-glutamate transporter that is upregulated by oxidative stress in glioma cells.<sup>41</sup> In an animal model, this transporter causes marked increase in glutamate release from gliomas, resulting in neuronal hyperexcitability and electrographic seizures. In addition, glutamate levels are regulated by membrane glutamate transporter proteins, particularly by excitatory amino acid transporter (EAAT2) on astrocytes, which is the predominant mechanism by which glutamate is removed from the synaptic cleft.<sup>42</sup> Both an increase in system  $x_c^-$  expression and a decrease in EAAT2 expression have been demonstrated in human gliomas,<sup>40</sup> thus validating the animal models.

With advances in brain tumor genomics, there has been increasing interest in the role of genetics in tumor-associated seizures. Many changes in tumor-related gene and microRNA expression have been implicated in tumor-associated seizures.<sup>43-48</sup> Most of the putative genes are involved in cell cycling, cell proliferation, and abnormal membrane physiology. A definitive pathway linking gene expression changes and electrographic activity has not yet been found.

Recent data indicate that gliomas with IDH1/2 mutations are more likely than IDH1/2 wild-type tumors to cause seizures.<sup>49,50</sup> The exact mechanism of epileptogenicity of these tumors is uncertain. Interestingly, the level of glutamate is reduced in IDH-mutated tumors,<sup>50</sup> perhaps because of the impact of 2-hydroxyglutarate (2HG). Studies have shown that D-2HG binds to NMDA receptors and affects synaptic glutamate clearance.<sup>51,52</sup> It has been hypothesized that R-2HG may similarly activate NMDA receptors. A decrease in the function of alpha-ketoglutarate, a ketone with antiepileptic properties<sup>53</sup> that is competitively inhibited by 2HG,<sup>54</sup> may also contribute.

In addition, although IDH mutations have been associated with higher rates of preoperative seizures, there have been no differences from wild-type IDH in the rates of postoperative seizures,<sup>49</sup> thus emphasizing the concept that multiple mechanisms of tumor-associated seizures exist and that the process of epileptogenicity of preoperative seizures may be distinct from that of postoperative seizures.

While the structural and molecular impacts of brain tumors are important, the human epileptic phenomenon remains a network disease. Recently, analysis of signals from functional MRI, EEG, and magnetoencephalography have identified functional connectivity networks,<sup>55,56</sup> the disturbance of which may give rise to seizures.<sup>57-60</sup> These disturbances have been demonstrated in brain tumors,<sup>61,62</sup> and it has been hypothesized that these functional networks are directly affected by expression of proteins related to tumor-associated seizures.<sup>63</sup> In one study, preoperative seizures in brain tumors were linked to sub-optimal network topology.<sup>64</sup> In summary, the mechanisms of tumor-associated seizures are varied and reflect the genetic and pathologic heterogeneity of tumors. Elucidating the biochemical pathways and/or molecular alterations involved in the mechanisms of both epileptogenicity and tumor growth may lead to targeted therapies.<sup>65</sup>

### Mechanisms of Antiepileptic Drugs

The mechanism of action of antiepileptic drugs (AEDs) is also diverse, with many drugs acting on multiple targets and most being developed through empiric discovery. Matching a mechanism of action of a drug to a putative mechanism of tumor-associated seizures has been difficult and generally unsuccessful. Major known mechanisms of action and other properties of common AEDs are reviewed in Table 1.

### Use of Antiepileptic Drugs

When a brain tumor patient experiences clinically obvious seizures (an attack where there is no diagnostic doubt that it represents an epileptic seizure) from which they recover rapidly, EEG is not required to confirm the diagnosis or guide therapy. EEG may be useful for patients with nonconvulsive seizures, a prolonged period of altered mental status, or whenever there is clinical uncertainty about the diagnosis. Once the diagnosis of seizure is made, standard-of-care involves administration of an AED.<sup>66</sup> Patients with gliomas and other infiltrative lesions often require indefinite AED therapy. Though there is evidence that antineoplastic therapy in these cases may reduce seizure frequency,<sup>11,12,67,68</sup> seizure risk remains persistently elevated. This is in contrast to patients with meningiomas and other curable lesions, who frequently discontinue AEDs after surgery if the lesion has been completely resected and there is no injury to the underlying brain parenchyma.

In considering whether to start an AED in a brain tumor patient who is seizure-free, physicians must weigh potential benefits and harms. Benefits may include a reduced risk of first seizure or seizure recurrence, prevention of status epilepticus,<sup>69</sup> and improved quality-of-life.<sup>70</sup> Few high-quality studies have been reported to guide decision-making on the basis of these purported advantages. Potential harms are easier to quantify

and include treatment-related adverse effects, drug-drug interactions, and financial costs.

### Frequency of Postcraniotomy Seizures

Studies performed before the 1980s found a seizure risk of 15%–20% in brain tumor patients.<sup>71</sup> The risk was highest in the first month after biopsy or resection. More recent data suggest that seizure risk is variable and depends on tumor histology, location, extent of resection, and other factors.<sup>72</sup> Among 180 patients at one center who underwent resection of a convexity meningioma, 129 (72%) patients received AEDs, and 51 (28%) did not. There was only one seizure in the entire cohort (0.6%). In a cohort of 118 seizure-free GBM patients at one center who underwent a surgical procedure, approximately one-third went on to experience seizures regardless of the use of prophylactic AEDs.<sup>69</sup> Despite uncertainty about the actual seizure risk, prophylactic AED use is common among American neurosurgeons. In one survey, 70% reported routine AED use in patients undergoing glioma or metastasis resection.<sup>73</sup> Use of AEDs was also common in patients undergoing meningioma resection (54%). Only 21% of neurosurgeons reported AED use in patients having stereotactic biopsies. At another institution, more than 40% of patients having biopsies received perioperative AEDs.<sup>69</sup>

### Prophylaxis

The evidence base supporting prophylactic perioperative AED use in this population is limited. A 1983 clinical trial randomly assigned 281 patients undergoing supratentorial craniotomy to phenytoin or placebo.<sup>74</sup> The most common indications for surgery included head injury (57%), aneurysm (20%), intra-axial tumor (16%), and meningioma (7%). No statistical significance in rates of seizures was observed between patients in the phenytoin group (6%) versus the placebo group (9%). When the data were stratified by time after surgery, the difference was found to be significant in the 7–72 day subgroup, indicating a reduction in seizures from postoperative day 7 to day 72 with the use of phenytoin compared with placebo. Although this study included a relatively small number of brain tumor patients and achieved significance only upon unplanned, post hoc subgroup analysis, it is often cited as the rationale for continued use of prophylactic AED use in this setting.

In the face of uncertainty about the value of prophylactic AED use for brain tumor patients in the perioperative period, a number of additional controlled clinical trials were conducted.<sup>71,75,76</sup> None of these found significant differences in seizure rates between the AED group and the placebo or no-treatment group. In 1996, a meta-analysis assessed 839 patients undergoing supratentorial craniotomy between 1980 and 1995 and found no statistically significant benefit.<sup>77</sup> Only 3 controlled studies were of adequate quality for inclusion. A subsequent meta-analysis published in 2011 looked at 19 studies with nearly 700 patients undergoing meningioma resection and also found no benefit.<sup>78</sup> The risk of early postoperative seizures was ~1.5% and of late seizure ~9%, regardless of AED use. Most recently, a Cochrane group meta-analysis evaluated 1398 patients undergoing craniotomy for a variety of nontraumatic indications. There was little evidence to support a benefit

**Table 1.** Properties of commonly used antiepileptic drugs in brain tumor-related seizures

Name	Mechanism of Action	Metabolism/Biotransformation	Half Life/Titration Rate	Peak Plasma Concentration ( $T_{max}$ )
Carbamazepine 2 times/day p.o.	Sodium channel blocker	Hepatic (CYP450 3A4, UGT2B7).	16–24 hours Slow titration	12 hours (2 hours liquid)
Phenobarbital Once daily p.o./i.v.	Enhances GABA(A) receptor	Hepatic (hydroxylation and glucuronidation)	53–118 hours	8–12 hours
Phenytoin Once daily p.o./i.v.	Sodium channel blocker	Hepatic (>95%): CYP2C9>CYP2C19 Titration - rapid	Average 22 hours (6 hours at low conc./ 60 hours at high conc) Fast titration	>2–4 hours after oral dose [30 minutes with IM injection]
Levetiracetam 2 times/day p.o./i.v.; once daily extended release available	Synaptic Vesicle Protein 2A (SV2A) inhibition	Unknown/Little metabolism. - 24% of dose enzymatic hydrolysis. Estimated 95% renal clearance.	6–8 hours Fast titration	1.3 hours
Lamotrigine 2 times/day p.o.; once daily extended release available	Sodium channel modulator	40% excreted by the kidneys. Hepatic - UDP -glucuronyl transferases UGT1A4 co-enzyme. By inhibiting this enzyme, valproic acid causes slower metabolism of lamotrigine	14–103 hours (mean 33 hours) Very slow titration	2–3 hours (delayed slightly by food)
Valproate 2 times/day p.o./i.v.	Enhanced GABA tone	Hepatic: mitochondrial beta-oxidation/ CYP450/glucuronidation UGT1A4 inhibitor	8–20 hours Fast titration	~2 hours
Topiramate 2 times/day p.o.; extended release available	Multiple Na <sup>+</sup> channel blockade, enhanced GABA, AMPA inhibition)	Mixed metabolism ~20% metabolized (50% if taking concomitant inducers) Hydroxylation, hydrolysis and glucuronidation	21 hours Slow titration	2–3 hours
Lacosamide 2 times/day p.o./i.v.	Sodium channel blocker	In vitro: CYP2C9, CYP2C19, CYP3A4 Mixed metabolism	13 hours Slow titration	0.5–4 hours
Gabapentin 3 times/day p.o.	Calcium channel modulator	Renal	Slow titration	3–3.5 hours (affected by food)
Pregabalin 2 times/day / 3 times/day p.o.	Calcium channel modulator	Renal	Slow titration	1–1.5 hours (affected by food)
Perampanel Once daily	AMPA receptor antagonist	CTP3A4; cytochrome P450 inducer at very high concentrations	105 hours Slow titration	0.5–2.5 hours

Abbreviation: conc, concentration.

or lack of benefit.<sup>79</sup> A recent retrospective study assessed 202 patients undergoing supratentorial craniotomy for brain tumors (43% metastases, 50% gliomas).<sup>80</sup> Of these, 134 patients (66%) received prophylactic AEDs. The overall postoperative seizure rate was 23%. There was no significant difference in the proportion of patients who experienced seizures or in the time to seizure depending on prophylactic AED use. In a recent clinical trial, 123 patients with metastases and gliomas undergoing supratentorial craniotomy were randomly assigned to phenytoin prophylaxis or observation. The trial was stopped prematurely because of slow accrual. Although power was

much lower than anticipated, there was no significant difference in seizure risk between groups (18% in the observation group, 24% in the phenytoin group).

A number of studies have also been conducted to evaluate prophylactic AED use in brain tumor patients without seizures after the perioperative period.<sup>81,82</sup> Similar to the perioperative studies, these studies suffer from heterogeneity in terms of types of tumors included, AED(s) employed, and outcome measures, making it difficult to draw persuasive conclusions. No published studies have adequately assessed seizure prophylaxis in patients deemed at higher risk for seizures such as those

with cortical, temporal lobe, or hemorrhagic lesions. Another potentially important limitation of these studies (and nearly all published studies relating to seizure prevention in the brain tumor population) is the apparent absence of a statistical plan with power analysis to determine sample size. Statistical power to detect a benefit of prophylactic AED use may have been low, particularly since seizures are relatively uncommon events and the study populations are often heterogeneous. Those caveats aside, the evidence does not support prophylactic AED use in the postoperative setting either. A randomized study in 1996 compared 74 newly diagnosed brain tumor patients treated with valproic acid to placebo.<sup>82</sup> The overall seizure rate in this cohort, which consisted primarily of patients with brain metastases, was 30%, with no evidence for significant benefit of valproic acid. A 2003 study randomly assigned 100 patients with newly diagnosed brain tumors to an AED or placebo.<sup>81</sup> The overall seizure rate was 26%, with no significant impact of AED use. Three meta-analyses have also been published, none of which reported a benefit with respect to seizure prevention.<sup>83–85</sup> A Cochrane group meta-analysis found an increased rate of adverse events in patients who received prophylactic phenytoin, phenobarbital, or valproic acid.<sup>85</sup> A randomized, double-blind, placebo-controlled trial is currently accruing patients to address persistent questions about the value of prophylactic AED use in newly diagnosed glioblastoma patients (NCT01432171). After tumor resection, study participants who had not experienced seizures were randomly assigned to levetiracetam or placebo and observed for up to one year, with the primary endpoint being time to first seizure. Electrographic predictors of seizure in this population are also being collected and analyzed. Results are expected to be available in 2017.

### Considerations in Selecting Antiepileptic Drugs

There is no simple algorithm that can be employed when choosing an AED for a brain tumor patient with seizures. The published literature currently lacks high-quality comparative effectiveness data. Although some older AEDs have been compared head to head,<sup>74–76,86,87</sup> methodological problems limit the value of the results. In the past, phenytoin represented the AED of choice because of its ready availability, ease of administration (oral or parenteral), efficacy, and low cost. Recent decades have seen an explosion in the number of alternative AEDs, few of which have been rigorously studied in the brain tumor population. Today, older cytochrome P450 (CYP450) enzyme-inducing AEDs such as phenytoin, carbamazepine, and phenobarbital have been largely replaced by newer AEDs with fewer side effects and drug interactions. These and other considerations such as convenience, availability, and cost should be factored in when physicians select AEDs for brain tumor patients. There are no principal differences for AED selection between adult patients with focal epilepsy or those with tumor-related epilepsy, with the choice being based on evaluation of perceived risk versus benefit for the individual patient.<sup>88</sup> Decisive factors of selection among approved AEDs are individual factors such as age, weight, associated drug use, or presence of other morbidities.<sup>89</sup>

Among brain tumor patients in the United States today, levetiracetam may be the most commonly prescribed AED. Levetiracetam has a number of advantages including a lack of

drug-drug interactions and excellent tolerability. The drug is also affordable because of its recently acquired generic drug status. It has a rapid onset of action, does not require blood-level monitoring, is effective in treating both focal and generalized seizures, and is available in an extended release oral and dose equivalent intravenous formulation. Additionally, it has possible antiemetic properties<sup>90</sup> and was recently shown to inhibit O-6 methylguanine-DNA methyltransferase (MGMT) and potentially increase survival.<sup>91,92</sup> An increasing number of physicians who treat brain tumor patients recommend levetiracetam as the first-line AED in this population.<sup>9</sup>

Lacosamide is a newer agent with similar properties that is being prescribed with increasing frequency. Recent reports indicate it may be an effective add-on therapy, with 66% of patients reporting a reduction in seizures, 30% reporting stable seizures, and the majority not reporting any side effects.<sup>93</sup> Dizziness is the main, most common dose-limiting adverse event. Other commonly used AEDs include valproic acid and lamotrigine. Valproic acid is an older agent that may theoretically increase chemotherapy toxicity by virtue of its CYP450 inhibitory properties. When compared with the newer nonenzyme-inducing AEDs, valproic acid has a significantly narrower therapeutic index. Lamotrigine would likely be used more frequently if not for the requirement to slowly titrate the dose to minimize risk of Stevens-Johnson syndrome, particularly in the setting of combination therapy with valproic acid. Table 1 summarizes the key features of AEDs that may be used in brain tumor patients.

### Drug Interactions

Many AEDs have drug-drug interactions that are clinically relevant in the brain tumor population. The older enzyme-inducing AEDs are well known to accelerate the metabolism of dexamethasone.<sup>94,95</sup> Other weak enzyme inducers include topiramate, oxcarbazepine, and rufinamide. A number of chemotherapy agents that are metabolized by the CYP450 system have reduced serum levels in patients taking enzyme-inducing AEDs. Because valproic acid is a CYP450 inhibitor, it has the potential to increase the toxicity of selected chemotherapy drugs. Perampnel, at clinically relevant doses, does not induce or inhibit CYP, although it is a weak inducer at supratherapeutic doses.<sup>96</sup> Common examples of chemotherapy agents that are metabolized through the CYP450 pathway include irinotecan, erlotinib, imatinib, and procarbazine in addition to nitrosoureas. The CYP450 isozymes that are most often implicated in AED-chemotherapy interactions include CYP3A4, CYP2C9, and CYP2C19.<sup>97</sup> The most important clinical implication is that patients who must receive AEDs and concurrent chemotherapy, particularly with agents metabolized through these pathways, should be monitored closely for toxicity and seizures. In addition, this may increase clearance of the chemotherapy with the potential impact on efficacy. When appropriate, serum AED levels should be monitored serially as well.

### Duration of Antiepileptic Drug Therapy

In light of evidence that phenytoin reduces seizure risk in the first week after traumatic brain injury,<sup>98</sup> an American Academy of Neurology practice parameter recommends tapering

anticonvulsants after the first postoperative week.<sup>83</sup> In practice, particularly for patients who are tolerating AED therapy well, many physicians continue AEDs indefinitely. There are very limited published data concerning predictors of seizure recurrence upon AED withdrawal in the brain tumor population. In one retrospective observational study of 169 patients with low-grade gliomas and meningiomas, the strongest independent predictor of postoperative seizure was in fact continuation (rather than discontinuation) of AEDs.<sup>99</sup> This paradoxical observation likely reflects the physicians' suspicion of high seizure risk rather than any unintended effect of AED therapy. Among the 111 patients whose AEDs were withdrawn or who never started on AEDs, 11 experienced seizures (10%). No significant predictors of seizure recurrence were identified in the relatively small cohort.

EEGs appear to be of little value for evaluating risk of recurrence. One study evaluated 62 seizure-free epilepsy patients who had AEDs withdrawn. Forty-one had recurrent seizures, but EEGs prior to cessation showed more sharp waves in those less likely to relapse, with a trend towards more spike-wave complexes in the relapse group.<sup>100</sup> In the general epilepsy population, another study enrolled patients who were seizure-free for a minimum of 2 years on AEDs.<sup>101</sup> The risk of seizure relapse in patients who tapered off of AEDs was 15% versus 7% for those remaining on treatment (relative risk difference: 2.5). However, there was an improvement of neurocognitive function from 11% to 28% with cessation of seizure medication. Additionally, prolonged use of anticonvulsants, particularly first generation agents (eg, phenytoin, phenobarbital) can cause cognitive dysfunction. This risk must be balanced with the prognosis of the underlying tumor and the complications from seizure recurrence. Ultimately, the evidence base to guide AED discontinuation does not provide clear direction. Physicians should rely on established principles from the general epilepsy population to make individualized determinations about AED withdrawal. Factors for consideration in these decisions include the tumor type, size, and location of any residual tumor, expected tumor growth, seizure type and history, AED-related side effects, and patient preference. Careful evaluation of the brain imaging is recommended to insure that there is no evidence of tumor progression before considering cessation of anticonvulsant medications. Conversely, a recurrence of epilepsy after prolonged control warrants an evaluation for possible tumor recurrence.

### Impact on Survival

Because valproic acid functions as a histone deacetylase inhibitor, it may have synergistic antiglioma activity with radiation therapy.<sup>102</sup> Retrospective observational and clinical trial data suggested that adding valproic acid to standard temozolomide and radiation therapy in newly diagnosed glioblastoma patients may prolong survival at the expense of increased thrombocytopenia and leukopenia.<sup>6,103</sup> A recent meta-analysis confirmed the purported survival benefit.<sup>104</sup> However, some conflicting evidence has been published,<sup>105</sup> and a definitive randomized trial is needed to settle the question.

### Adverse Effects

Side effects of AEDs can be generally classified as clinically overt or subtle. The subtle adverse effects often persist and are frequently misattributed to the underlying condition,

radiation or chemotherapy, or a psychological reaction to the illness. The overt side effects include rash, allergy, neutropenia, thrombocytopenia, and electrolyte or liver function disturbance. The subtle side effects include mood or behavioral problems, fatigue, and neurocognitive dysfunction.

The frequency of overt AED side effects is, in practice, likely similar to the general epilepsy population with perhaps the exception of rash. In general, rash occurs in 4%–6% of patients on phenytoin, carbamazepine, or lamotrigine compared with <1% on levetiracetam, valproate, gabapentin, topiramate, or vigabatrin.<sup>106</sup> Mild drug rashes are more common in patients with brain tumors on AEDs. This has been hypothesized to relate to radiation therapy,<sup>107,108</sup> but the relationship has not been established.<sup>109</sup> Radiation causes sensitization of the skin, and any drug rash is typically more confluent in radiated areas. An increased rate of introduction (loading) and high AED drug levels increases the likelihood of rash.<sup>110</sup> Brain tumor patients frequently receive other drugs that may cause severe rash including nonsteroidal anti-inflammatory drugs, corticosteroids, and antibiotics. Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS, TEN) are among the severe cutaneous drug reactions reported in the literature that can be initiated by different classes of AEDs. A recent recommendation has been to use HLA B\*15:02 and HLA-A\*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions (SJS/TEN) prior to starting carbamazepine, although the positive predictive value is low.<sup>111</sup>

Alterations in laboratory studies may also be associated with AED therapy. Hyponatremia occurs most commonly with carbamazepine and oxcarbamazine but can be caused by other agents such as proton pump inhibitors.<sup>112</sup> Blood dyscrasias are rare but can occur with any AED. The risk is greater in patients aged 60 years and older (4/100 000) than in younger patients (2/100 000).<sup>113</sup> Leukopenia is more commonly associated with carbamazepine.<sup>114</sup> Drug-induced thrombocytopenia is most commonly associated with valproate and is strongly correlated with elevated trough values.<sup>115</sup> In patients receiving chemotherapy (procarbazine, lomustine, and vincristine (PCV) or temozolomide) and valproate, there is an increased frequency of grade 3 or 4 hematological toxicity.<sup>103,116</sup> Liver-enzyme abnormalities are seen more commonly with valproate, carbamazepine, phenytoin, and phenobarbital as compared with the newer AEDs.

Weight gain may be an issue with valproate, gabapentin, and pregabalin, while weight loss is more common with topiramate and zonisamide. Topiramate can cause angle-closure glaucoma and renal stones in addition to higher than expected incidence of psychiatric adverse events including psychosis (4%) and aggressive behavior (6%).<sup>117</sup> Vigabatrin is rarely used now because of irreversible visual field defects and the requirement for frequent visual field assessment. Lacosamide may cause cardiac conduction defects; therefore electrocardiograms are recommended before increasing the dosage in patients with a history of cardiac disease.

Although the newer AEDs have fewer overt side effects than the older agents and fewer drug-drug interactions, some of the newer AEDs are associated with side effects of mood disturbance, behavioral changes, fatigue, and disabling cognitive complications, which may be difficult to attribute to the AEDs because of other associated risk factors. However, these are

common symptoms in the brain tumor patient population, as evidenced by a recent survey of brain tumor patients where fatigue was a concern in 64%, memory in 58%, concentration in 57%, mood in 47%, sleep in 40%, and anger and irritability in 38% of patients.<sup>118</sup> Trying to disentangle the effect of AEDs from other tumor and treatment-related comorbidities requires focused history-taking. It is imperative to establish the timing of symptom onset in relation to the introduction of an AED or a change in AED dose.

### *Mood and Behavior in Brain Tumor-related Epilepsy*

The prevalence of major depressive disorder (MDD) in the general population is between 2% and 5%.<sup>119,120</sup> A meta-analysis involving 43 892 people from 199 randomized controlled trials of 11 AEDs demonstrated a nearly 2-fold increase in suicidal behavior or thoughts in those taking an AED.<sup>121</sup> Within the first 8 months following glioma diagnosis, 20% of patients became clinically depressed.<sup>122</sup> Clinicians can screen for depression in high-functioning glioma patients using the Hospital Anxiety and Depression Scale (HAD-D at a threshold of 8+), or the Patient Health Questionnaire-9 (PHQ-9 at a threshold of 10+). Patients scoring above these thresholds need clinical assessment to diagnose or exclude depression.<sup>123</sup> Depression is most frequently associated with starting phenobarbital, vigabatrin, levetiracetam, felbamate, or topiramate. Depression can also be associated with stopping AEDs such as carbamazepine, oxcarbazepine, valproic acid, and lamotrigine. Therefore, obtaining a detailed history of AED use can be informative.

Although there are no randomized controlled trials of antidepressant treatment in glioma,<sup>124</sup> treatment of MDD should include psychotherapy and antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), which are equally effective.<sup>122</sup> The side-effect profile probably favors SSRIs.<sup>125</sup> Common antidepressants will not worsen epilepsy; however, bupropion, clomipramine, and amoxapine can be associated with lowered seizure threshold. Fluoxetine elevates phenytoin levels.

### *Behavior*

Behavioral changes are common in glioma. Symptoms of anger, loss of emotional control, indifference, and change in behavior are commonly reported.<sup>126</sup> These changes can in part be explained by grief or an adjustment disorder. Although rare, some brain tumors present with neurobehavioral or psychiatric symptoms only.<sup>127</sup> Hallucinations and psychosis have been reported in brain tumor patients. Behavioral side effects of drugs such as steroids and AEDs occur in up to 10% of patients started on AEDs.<sup>128,129</sup> Some of the newer AEDs, particularly levetiracetam and perampanel, have been associated with aggressive behavior and anger. An AAN/CNS practice guideline recommends, “Behavioral and cognitive side effects need to be better evaluated, especially for new AED[s], and individual risks as well as group differences assessed on tests of cognition”.<sup>130</sup> Psychiatric side effects seem to be particularly uncommon with lamotrigine, gabapentin, oxcarbazepine, and vigabatrin.

### *Fatigue*

Fatigue is defined as abnormal tiredness that may vary in severity and pattern, does not improve with sleep, and

negatively interferes with daily functioning. Fatigue is very commonly associated with AEDs.<sup>131</sup> Non-AED contributors to fatigue likely include the tumor itself as well as surgery, radiotherapy, and chemotherapy. Drugs acting on the GABAergic system (such as phenobarbital and benzodiazepines) often cause fatigue, whereas drugs that work by other mechanisms are less common culprits.<sup>131</sup>

In a prospective single-center study of patients attending a neuro-oncology clinic, patients were classified as experiencing low or high levels of fatigue. High levels of fatigue were associated with the use of nonenzyme-inducing AEDs (15/17; 88%) compared with enzyme-inducing AEDs (2/17; 12%) ( $P = .016$ ).<sup>132</sup>

### *Cognition*

Cognitive problems are common in patients with a suspected brain tumor at the time of diagnosis. In a study of neurosurgical patients with suspected brain tumor, 25% did not have the capacity to provide informed consent;<sup>133</sup> however, AED-related cognitive adverse effects are well recognized. The most common AED-related cognitive effects include psychomotor slowing, reduced vigilance, and memory impairment.<sup>134</sup> Sedating AEDs such as phenobarbital and benzodiazepines are common culprits, but every AED has been implicated. In a study of nearly 1200 patients with focal seizures, “intolerable” cognitive side effects (as reported by patients) occurred with topiramate (21.5%), carbamazepine (9.9%), oxcarbazepine (11.6%), levetiracetam (10.4%), valproate (8.3%), lamotrigine (8.9%), and gabapentin (7.3%).<sup>135</sup> Quality-of-life studies in more than 5000 patients with epilepsy demonstrated that reducing side effects and achieving better control of seizures are keys to improving the quality of life for people with epilepsy.<sup>136</sup>

### *Conclusions*

Management of seizures is complex—even more so in patients with brain tumors. The overall incidence of seizures varies, based on the type and grade of tumors, and therapeutic approach. Although the mechanism underlying the occurrence of seizures is poorly understood, there is increasing evidence for the role of glutamate and genomic alterations, which result in its dysregulation, although a direct link between these changes and electrical activity has not yet been elucidated. Levetiracetam is the most commonly prescribed AED for use in patients with brain tumors in the United States. The use of AED prophylaxis remains controversial, as does the duration of AED use. A variety of clinically overt and more subtle adverse effects may occur in AED-treated patients. Much of what we know about the use of AEDs is based on experience with the general epilepsy population. Future studies exploring the pathophysiology of seizures in brain tumor patients as well as use of AEDs in this population warrant further focused evaluation.

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