Medical and neurologic management of brain tumor patients

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Purpose of review
This article discusses commonly encountered medical and neurological complications in patients with brain tumors and highlights recommendations for their management based on updated evidence.

Recent findings
Use of dexamethasone is correlated with worse prognosis in patients with glioblastoma, and in brain metastases, high doses may lead to increased side effects without additional clinical benefit. There are multiple antiseizure medications (ASM) to choose from and possible interactions and toxicity must be considered when choosing an agent. Additionally, there is growing interest in the use of AMPA receptor blockers as ASM in patients with brain tumors. Nonpharmacological strategies for the management of fatigue remain paramount. Cognitive decline is common after whole brain radiation (WBRT) and hippocampal-sparing WBRT results in superior cognitive outcomes. Venous thromboembolism is a common complication and there is growing evidence on the use of direct oral anticoagulants (DOACs) in this population.

Summary
There is evolving evidence on the management of medical and neurological complications in patients with brain tumors. These complications, require early identification and multidisciplinary collaboration and expertise.

Keywords
brain tumor, cognitive decline, seizure, vasogenic edema, venous thromboembolism

INTRODUCTION

Primary malignant brain tumors occur in 7.02 per 100 000 people and carry a high morbidity and mortality [1]. Brain metastases are far more common and occur in 10–40% of patients with cancer and with improving systemic therapies, their number is expected to grow [2]. Regardless of their primary etiology, patients with brain tumors are at a high risk of medical and neurological complications including progressive symptoms from vasogenic edema, seizures, fatigue, mood disorders, cognitive decline, and venous thromboembolism (VTE). This review discusses these complications and highlights updated evidence and recommendations for their evaluation and management.

MANAGEMENT OF VASOGENIC EDEMA

Peritumoral edema occurs in brain tumors because of disruption of blood–brain barrier permeability and can lead to focal neurological symptoms and elevation in intracranial pressure. The management of peritumoral edema has relied on the use of steroids since the 1950s; and dexamethasone has long been the agent of choice due its excellent oral bioavailability and lack of mineralocorticoid effect (which minimizes electrolyte disturbances) [3,4].

However, the effectiveness of steroids in improving symptoms must be weighed against their deleterious effects. Their use can result in Cushing's syndrome, weight gain, hyperglycemia, diabetes, proximal myopathy, osteoporosis, gastritis, arterial hypertension, and psychiatric side effects including insomnia, irritability, and depression [5]. Moreover, dexamethasone use was associated with worse

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KEY POINTS

- Prophylactic antiseizure medications are not recommended in brain tumor patients who have not experienced seizures.
- We recommend dosing dexamethasone daily or twice daily and limiting its use to those patients who have symptoms attributable to vasogenic edema.
- We recommend nonpharmacological strategies for the management of fatigue in all patients with brain tumors.
- Hippocampal-sparing WBRT results in improved cognitive outcomes, and we recommend the use of memantine in patients receiving WBRT.
- Either DOACS or LMWH can be considered for the management of VTE in this population

overall survival (OS) and progression-free survival (PFS) in patients with glioblastoma in two meta-analyses; and in brain metastases, higher doses may result in increased side effects without an increased clinical benefit [6–8].

Typical dexamethasone doses used range from 4 to 16 mg/day. However, dosing frequency is based on little evidence and remains varied across specialties and institutions. In 1961, Galicich *et al.* [9] reported clinical improvement in 13 out of 14 patients treated with an initial bolus of 10–40 mg of dexamethasone followed by 4 mg every 6 h. Since then, dosing dexamethasone every 6 h became standard practice among most institutions. In 1991, Weissman *et al.* [10] reported on administration of dexamethasone twice daily in patients with brain metastases undergoing radiation with good effectiveness. However, dosing every 6 h remains standard practice in many institutions. Due to the long half-life of the drug, there is little rationale for dosing every 6 h and sustained benefit has been shown in glioma animal models with twice daily dosing [11]. Moreover, dosing every 6 h requires disturbing sleep for medication administration, which is especially important given the high prevalence of fatigue among patients with brain tumors. For patients with brain metastases, a joint American Society of Clinical Oncology (ASCO)/Society for Neuro-Oncology (SNO) expert panel recommended an initial dose of dexamethasone 4–8 mg/daily for patients with mild symptoms and up to 16 mg/daily for severe symptoms [12].

Thus, we advocate for limiting the use of steroids in patients with brain tumors to those who are symptomatic and where we attempt to identify the smallest beneficial dose and use it for the shortest amount of time possible. Moreover, our recommendation is to consolidate dexamethasone doses to once or twice daily, rather than every 6 h as we consider it to be noninferior and to promote sleep [13].

Patients who require steroids for a prolonged time or at high doses are especially susceptible to side effects and require special consideration. There is an increased risk of *Pneumocystis jirovecii* pneumonia and prophylaxis with either trimethoprim sulfamethoxazole, atovaquone, dapsone, or pentamidine should be considered in patients who may require steroids for more than 4 weeks [4,14]. Additionally, steroids lead to an increased risk of osteoporosis, which is also increased by some antiseizure medications (Table 1) [15,16▪]. Thus, in patients who require dexamethasone doses larger than 0.5 mg/day for more than 3 months, calcium and vitamin D supplementation should be started, and fracture risk assessment with dual-energy x-ray absorptiometry (DXA) or spinal x-ray is recommended [17]. Moreover, in those who require high doses of steroids, use of an H2 inhibitor or proton pump inhibitor is encouraged for prevention of gastritis, gastrointestinal hemorrhage, and peptic ulcers [4]. In patients with high steroid requirements, bevacizumab (which targets vascular endothelial growth factor) can be considered as a steroid-sparing agent. Importantly, it does not impact OS and may limit clinical trial eligibility, however, results in symptomatic improvement [18–20]. Although this must be weighed against its risks, which include hypertension, hemorrhage, gastrointestinal (GI) perforation, VTE, and ischemic stroke [21,22]. Additionally, bevacizumab has been studied for the management of radiation necrosis with multiple trials reporting a benefit [23–26].

SEIZURES

The prevalence of seizures in patients with brain tumors varies depending on histology and tumor location and ranges from 20 to 94% [27]. Importantly, seizures are more common in isocitrate dehydrogenase (IDH)-mutant gliomas than in glioblastoma or brain metastases, and there is an inverse correlation between the tumor growth rate and seizure frequency [28]. Moreover, 2-hydroxyglutarate, which is produced by the IDH mutation has been shown to increase neuronal activity and epileptogenesis and this effect can be reversed with the use of IDH inhibitors in preclinical models [29].

In 2000, the American Academy of Neurology assessed the role of prophylaxis with antiseizure medications (ASM) in patients with brain tumors and concluded that, outside of the perioperative period, there was no role for seizure prophylaxis in patients who do not have a history of seizures

Table 1. Antiseizure medication formulations, mechanisms of action with additional considerations and reported TRE seizure response rates

Antiseizure medication	Formulation/approved for children	Primary mechanism of action	Most commonly reported side effects	Serious side effects	Reported efficacy for use as monotherapy in TRE	Additional considerations
Brivaracetam	Tablet, liquid, i.v./yes	Binds to SV2A (a synaptic vesicle glycoprotein)	Fatigue, dizziness, anxiety, agitation, depression	Hypersensitivity reactions	Not reported	–
Carbamazepine	Tablet, liquid/yes	Na^+ channel blocking	Transaminitis, hyponatremia, blood dyscrasias, rash/SJS, nausea, vomiting	Aplastic anemia, hepatotoxicity, hyponatremia, rash/TEN/SJS, hypersensitivity reactions, decreased bone density (use >10 years)	6 mo seizure freedom: 28% [30] 12 mo seizure freedom: 30–55% [30]	CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP1A2, UGT1A4 inducer May cause bone marrow suppression
Cenobamate	Tablet/no	Na+ channel blocking Enhancing GABA	Fatigue, dizziness, hyperkalemia	QT shortening, drug reaction with eosinophilia	Not reported	CYP2C19 inhibitor, CYP3A4/5, CYP2B6 inducer
Clobazam	Tablet, liquid/yes	$GABA_A$-receptor agonist	Fatigue, dizziness, dry mouth, nausea	Somnolence, sedation	Not reported	N-desmethylclobazam, the metabolite can be monitored for toxicity
Eslicarbazepine	Tablet, liquid/yes	Na^+ channel blocking	Hyponatremia, rash/SJS, somnolence, nausea, fatigue	Rash/TEN/SJS, hyponatremia, hepatotoxicity, blood dyscrasias, decreased T3/T4	Not reported	CYP2C9 inhibitor
Gabapentin	Tablet, liquid/yes	Binding $\alpha 2\delta$ Ca channel subunit	Dizziness, fatigue, peripheral edema, weight gain, ataxia	None	Not reported	Substrate for a protein transporter likely reducing brain availability [31]
Lacosamide	Tablet, liquid, i.v./yes	Na^+ channel blocking	Dizziness, gait instability, headache, fatigue, prolonged PR interval	PR prolongation, syncope, rash/TEN/SJS, dizziness, ataxia	6 mo seizure freedom: 55–67%	Monitor for arrhythmias
Lamotrigine	Tablet, oral dissolving tablet/yes	Na^+ channel blocking	Rash/SJS insomnia (if taken at night as b.i.d. dosing), blood dyscrasias	Rash/TEN/SJS, blood dyscrasias, angioedema, bronchospasm	Not reported	Need for slow titration May be beneficial for mood Relatively safe in pregnancy
Levetiracetam	Tablet, liquid, i.v./yes	Binds to SV2A (a synaptic vesicle glycoprotein)	Irritability, depression, anxiety, aggression, fatigue, light headedness	Suicidal ideation, depression	6 mo seizure freedom: 39–96% [30] 6 mo seizure reduction ≥ 50%: 71–100% [30]	Higher risk of psychiatric side effects in frontal lobe tumors [32] Relatively safe in pregnancy
Oxcarbazepine	Tablet, liquid/yes	Na^+ channel blocking	Hyponatremia, fatigue, light headedness, weight gain, alopecia, nausea	Hyponatremia, rash/TEN/SJS	12 mo seizure freedom: 40% 12 mo seizure reduction ≥50%: 88%	CYP2C19 inhibitor and weakly induces CYP3A4
Perampanel	Tablet, liquid/yes	AMPA antagonism	Dizziness, vertigo, fatigue, aggressiveness, agitation, irritability, anxiety, nausea	Psychiatric side effects, homicidal/suicidal ideation	No studies	
Phenobarbital	Tablet, liquid, i.v./yes	Enhancing GABA	Drowsiness, fatigue, vertigo, habit forming, blood dyscrasias, cognitive slowing, rash/SJS	Withdrawal seizures, hepatotoxicity, CNS depression, rash/TEN/SJS, blood dyscrasias	No studies	CYP1A, CYP2A6, CYP2B, CYP2C, CYP3 A, UGT inducer Increases steroid clearance [31]

Table 1 (*Continued*)

Antiseizure medication	Formulation/approved for children	Primary mechanism of action	Most commonly reported side effects	Serious side effects	Reported efficacy for use as monotherapy in TRE	Additional considerations
Phenytoin	Tablet, liquid, i.v./yes	Na^+ channel blocking	Transaminitis, rash/SJS ataxia, dysarthria	Rash/TEN/SJS, hepatotoxicity, blood dyscrasias, gingival hyperplasia, lymphadenopathy, arrhythmias	12 mo seizure freedom: 49–64% [30]	Enzyme-inducing agent Increases steroid clearance [31] Risk of birth defects
Pregabalin	Tablet, liquid/yes	Binding α2δ Ca channel subunit	Drowsiness, sedation, weight gain, blood dyscrasias	Peripheral edema, angioedema, hypersensitivity reactions	12 mo seizure freedom: 75% [30]	–
Primidone	Tablet/yes	Enhancing GABA	N/A	Hypersensitivity reaction, thrombocytopenia, megaloblastic anemia	N/A	Not recommended due to similar SEs as phenobarbital and more difficult to monitor
Tiagabine	Tablet/yes, >12 years old	Enhancing GABA	Lightheadedness, fatigue, anxiety, tremor, diarrhea, depression	CNS depression, rash	No studies	Side effects are commonly reported
Topiramate	Tablet, sprinkles/yes	Na^+ channel blocking, enhancing GABA, AMPA antagonism	Weight loss, word-finding difficulty, psychomotor slowing, metabolic acidosis, parasthesias, glaucoma	Acute angle closure glaucoma, nephrolithiasis, rash/TEN/SJS, oligohydrosis with heat stroke	6 mo seizure freedom: 59% 12 mo seizure freedom: 57–71% [30]	CYP3A4 inducer
Valproic acid	Tablet, liquid, i.v./yes >10 years old	Na^+ channel blocking, enhancing GABA, blocking T-type Ca channels	Weight gain, hair loss, fatigue, hyperammonemia, transaminitis, tremor, thrombocytopenia, rash/SJS	Hyperammonemia, hepatotoxicity, rash/TEN/SJS thrombocytopenia	6 mo seizure freedom: 65% 6 mo seizure reduction ≥50%: 77% 12 mo seizure freedom: 30–57% 12 mo seizure reduction ≥ 50%: 75–86% [30]	CYP2C9, UGT1A4 inhibitor (and weak inhibitor of CYP2C19 and CYP3A4) Significant risk of birth defects
Zonisamide	Tablet/yes >16 years old	Na^+ channel blocking, blocking T-type Ca channels	Somnolence, weight loss, lightheadedness, word-finding difficulty, renal calculi, oligohydrosis, rash	Rash/TEN/SJS, glaucoma, nephrolithiasis	No studies	Avoid in patients with history of nephrolithiasis Avoid in patients with sulfa allergies

Reported response rates are for patients with tumor-related epilepsy and may include tumors other than gliomas including meningiomas and brain metastases. CNS, central nervous system; CYP, cytochrome; Mo, month; SE, side effect; SJS, Stevens–Johnson syndrome. Reprinted with permission from Avila *et al.* [16▪].

[30]. This is due to both a lack of efficacy in preventing seizure as well as potential toxicity of ASM. A joint practice guideline of the Society for Neuro-Oncology (SNO) and European Association of Neuro-Oncology (EANO) in 2021 re-affirmed this recommendation [33]. Moreover, they noted insufficient evidence to recommend ASM during the perioperative and early postoperative period in patients who have never had a seizure, although this remains common in clinical practice.

In patients with brain tumors after a first lifetime seizure, secondary prophylaxis with an ASM is recommended [33]. Levetiracetam is the most common agent of choice as it does not induce hepatic enzymes and is well tolerated [34]. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor blockers such as perampanel, have also gained interest in the management of brain tumor-related epilepsy, as gliomas were shown to have AMPA receptor-dependent neuron–glioma synapses [35]. However, trials of telempanel, another AMPA receptor blocker, did not show a survival benefit in newly diagnosed and recurrent glioblastoma [36,37]. A metanalysis of 18 studies examining new ASM found 72% of patients experienced a reduction in seizure burden greater than 50% and 34% of patients' seizure freedom [38]. Ultimately, the choice of medication is influenced by available formulations, patients' comorbidities, adverse effects, and potential for interaction with other medications. Commonly used medications in patients with brain tumors are detailed in Table 1 and a 2024 SNO consensus review provides further details [16▪].

In patients with gliomas, surgical resection of the tumor has been shown to reduce seizure burden, although the extent of resection required for seizure control differs across studies [39,40]. Similarly, radiotherapy and alkylating chemotherapy have been shown to decrease seizure burden [41]. Finally, discontinuation of ASM after a period of seizure freedom can be considered in some patients, although there is conflicting evidence on the risk of recurrent seizures [42,43]. One study on 83 patients with low-grade gliomas who were seizure free for over a year, found that 26% of those who withdrew ASM had a seizure versus 8% of patients who had continued medications [44]. In clinical practice, factors to consider when assessing discontinuation include tumor histology, history of seizures and status epilepticus, extent of resection, disease status (stable or progressive), electroencephalographic findings, seizure free-duration, medication side effects, and other risks (i.e. driving) should a seizure occur [45▪]. In general, ASM monotherapy at the lowest effective dose is preferred to reduce side effects.

FATIGUE

Fatigue is the most frequently reported symptom in patients with brain tumors [46]. A high percentage of patients with brain tumors report moderate-to-severe fatigue and this is correlated with worsening quality of life [47].

Pharmacological interventions with CNS stimulants have shown little effectiveness. A randomized clinical trial (RCT) examining the effect of modafinil on fatigue, motivation, physical health, and working memory in 37 patients showed no difference compared with placebo [48]. Dexamphetamine resulted in increased psychiatric side effects with no difference in fatigue [49]. A recent double-blinded RCT of methylphenidate for cancer fatigue also showed no benefit [50]. A placebo-controlled phase II trial of armodafinil did not improve radiation-related fatigue in glioma patients [51]. Most recently, a phase 3 RCT of two doses of armodafinil over 8 weeks in 328 patients with high-grade glioma found no difference in fatigue, quality of life, or neurocognitive function when compared with placebo [52].

In the absence of efficacious medications, the best available interventions for fatigue are nonpharmacological and centered around exercise, management of insomnia, and minimizing the use of medications that contribute to fatigue [53–55,56▪].

DEPRESSION AND ANXIETY

Patients with primary brain tumor and brain metastases are especially susceptible to mood disorders because of psychological distress related to the diagnosis and prognosis and additionally because of potential direct effect of the tumor and treatment itself on brain function [57]. One metanalysis found the pooled prevalence of depression to be 21.7% in patients with brain tumors, however, others have reported up to 42% of patients, and results vary greatly across studies as mood disorders are underdiagnosed in this population [58,59]. Furthermore, depression and anxiety have been shown to be independent predictors of worsening neurocognitive function and quality of life [42,60]. Unfortunately, psychological interventions for patients with brain tumors are quite scarce [61].

Although there is no specific recommendations for pharmacological therapy to address mood disorders in patients with brain tumors, there has been recent interest in fluoxetine, owing to preclinical evidence of an increase in glioblastoma cell death with fluoxetine that is augmented when combined with temozolomide [62]. This effect is mediated by inhibition of sphingomyelin phosphodiesterase 1 and is actively being evaluated in a phase 1 surgical window of opportunity trial (NCT05634707).

Although most antidepressants have the potential to lower seizure threshold, buproprion poses the highest risk and should be avoided in patients with brain tumors, if possible.

COGNITIVE DECLINE

Cognitive deficits are common in patients with brain tumors because of the effects of the tumor itself, ASM, and radiotherapy, and exacerbated by the fatigue that patients frequently experience.

Radiation remains a cornerstone of treatment for brain tumors and whole-brain radiotherapy has long been used to treat brain metastases. However, it results in significant neurocognitive deterioration, which manifests as decreased attention, executive function, and verbal memory 6 months or later after radiation [63]. Due to this, several approaches have been evaluated to minimize the cognitive deficits induced by radiation.

Although clinical deterioration is better appreciated with time, acute microstructural damage occurs at the time of radiation and includes decreased tyrosine phosphorylation and a loss of *N*-methyl-D-aspartate (NMDA) receptors at the neuronal cell surface, and these changes can be abrogated with the use of NMDA receptor antagonists such as memantine [64]. This finding led to the RTOG 0614 trial, which examined the effect of memantine in 504 patients with brain metastases receiving whole brain radiation (WBRT) [65]. Although, the trial did not find a significant difference in its primary endpoint of delayed recall at 24 weeks, this may have been impacted by patient loss, which was almost 70% at 24 weeks. In subgroup analyses, patients in the memantine arm had significant differences in time to cognitive decline, processing speed and delayed recognition. These results have led to the frequent use of memantine in patients receiving WBRT with a good prognosis.

Furthermore, preclinical models revealed hippocampal dysfunction and reduced neurogenesis had a mechanistic role in the development of cognitive decline after radiation leading to the development of radiotherapy techniques avoiding the hippocampus [66–68]. The NRG CC001 trial investigated the role of WBRT with memantine with or without hippocampal avoidance in 518 patients with brain metastases [69]. Toxicity, overall survival, and progression-free survival were similar across both arms and hippocampal avoidance resulted in improved cognitive outcomes, owing to a reduction in deterioration of executive function, learning, and memory.

Similarly, radiation results in a reduction of cholinergic neurons in the hippocampus, leading to interest in acetyl cholinesterase inhibitors such as donepezil in the management of cognitive decline after radiotherapy [70,71]. A study compared the efficacy of donepezil vs. placebo in 198 patients who had received partial or whole brain radiation more than 6 months ago and compared them at 24 weeks [72]. Overall, treatment with donepezil did not improve cognitive composite score. However, in subgroup analysis, there was a modest improvement in memory, dexterity, and motor speed in the patients who had greater pretreatment cognitive impairment.

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Cancer has long been recognized as a risk factor for VTE, and importantly the risk is among the highest in patients with primary brain tumors [73]. In patients with gliomas, the risk increases with increasing WHO grade, being the highest in those with glioblastoma [74,75]. Interestingly, this difference compared with IDH-mutant tumors appears to be mediated by a downregulation of tissue factor and podoplanin caused by the IDH mutation. Moreover, the risk of VTE is greater in the first 2 months after diagnosis but remains elevated throughout a patient's lifetime [76–78]. ASCO guidelines for the treatment of VTE in patients with cancer recommend the use of low-molecular-weight heparin (LMWH) as first-line treatment, with direct oral anticoagulants (DOACS) considered an alternative [79]. However, the guidelines note a higher risk of bleeding with DOACS in those with gastrointestinal and genitourinary cancers. Importantly, the guidelines also highlight the low evidence available in those with CNS malignancies, and clinical decision-making is complicated in CNS malignancies by the risk of intracranial hemorrhage.

Due to the scarcity of data from RCTs of DOACS in patients with brain tumors, a 2021 joint EANO-European Society of medical Oncology (ESMO) clinical practice guideline recommended the use of LMWH (level II evidence) for the treatment of VTE in those with CNS malignancies [80]. However, several recent retrospective studies and metanalyses have suggested similar or decreased rates of intracranial hemorrhage in those with DOACS compared with LMWH in this patient population [81–86]. Thus, despite the absence of clinical trial data, many consider the use of either agent [75]. In patients who are considered to have a high risk of intracranial hemorrhage, unfractionated heparin without a bolus can be utilized initially because of is short half-life and reversibility and then transitioned to a longer agent [87▪].

For patients with VTE, our practice is to obtain a head computed tomography (CT) prior to starting

anticoagulation to exclude acute hemorrhage and to have a baseline for comparison in case of clinical deterioration. After which we consider the use of LMWH or DOACS for most patients. However, when considering the use of a DOAC, it is important to account for hepatic enzyme CYP inhibitors such as antiepileptics [88]. Moreover, it is important to consider other factors including concurrent use of bevacizumab, which increases the risk of bleeding and the need for procedures for which practical recommendations for the clinician are available [87▪,89].

CONCLUSION

Patients with brain tumors will present with a variety of medical and neurological complications throughout the disease course, which require multidisciplinary collaboration and expertise. Moreover, as molecular characterization redefines previous tumor types, there is an increasing number of possibilities for research and development of novel interventions for complications of brain tumors. However, a recent analysis of glioblastoma patients did not find any genomic predictors of the complications that have been discussed [90].

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- ▪ of special interest
- ▪▪ of outstanding interest

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