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Seizure Management in Adult Patients with Primary and Metastatic

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Cancer Care Alberta

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Background

Seizures are common in patients with brain tumours, and seizure management is an important part of clinical treatment. Thirty to 50% of primary brain tumour patients present with an epileptic seizure and 10 to 30% develop seizures throughout the course of their disease[1]. The incidence of seizures in patients with metastatic brain tumours ranges from 20 to 35%[1, 2]. The frequency of seizures also varies by tumour type. Among patients with primary brain tumours, seizures are more common with low-grade gliomas and other less common tumour types (e.g., dysembryoplastic neuroepithelial tumours and gangliogliomas) compared with high-grade gliomas[1, 2]. In a series of 1028 patients with low- or high-grade intracranial gliomas, the prevalence of epilepsy was 49%, 69%, and 85% for patients with glioblastomas, anaplastic gliomas, and low-grade gliomas, respectively[3]. Meningioma patients may also present with seizures both pre- and post-operatively. In a retrospective review of 626 meningioma patients, 13% presented with pre-operative seizures, and 7% continued to experience seizures 48 months post-operatively[4]. Aside from tumour type, other seizure risk factors include tumour location (cortical tumour, frontal, temporal, and parietal lobe tumours)[1] and age (> 40 years)[3].

The precise cause of seizures in brain tumour patients is unclear. Van Breemen *et al*. explain that epileptogenesis in patients with brain tumours is likely multifactorial and caused by different tumour types as well as changes in the properties of tumour-cell membranes that generate action potentials, thus affecting neuronal excitability[1, 2]. Seizures in primary or metastatic brain cancer patients may also be caused by metabolic encephalopathies, opportunistic infections, or side effects of therapy[2].

Overall, seizures are a significant source of morbidity and mortality in patients with primary and metastatic brain tumours and they require aggressive treatment with antiepileptic drugs (AEDs) or non-pharmacological therapies.

Guideline Questions

1. What is the optimal management of seizures in adult patients with primary or metastatic brain tumours?
2. What are the recommended driving guidelines for adult patients with primary or metastatic brain tumours experiencing seizures?

Search Strategy

For the 2023 guideline update, PubMed was searched (January 2011 – December 2022) for clinical trials, prospective and retrospective studies, systematic reviews, meta-analyses, and clinical practice guidelines. The Medical Subject Heading (MeSH) terms “anticonvulsants” OR “anticonvulsant drugs” OR “agents, anticonvulsant” AND “brain neoplasm” were used, and results were limited to studies in humans 19+ years of age published in English. Studies were also excluded from the final review if they did not report outcomes related to the efficacy of treatments or were not specific to brain tumour related epilepsy. Reference lists of key publications were also searched for relevant

citations. For the detailed literature search strategy, results and a summary of key evidence please refer to the accompanying evidence table.
The ECRI Guidelines Trust, well-known cancer guideline developers and Google were also searched for practice guidelines relevant to this topic. A total of five clinical practice guidelines published after 2014 were identified from the following organizations: Society for Neuro Oncology (SNO) and European Association of Neuro-Oncology (EANO), UpToDate, National Comprehensive Cancer Network (NCCN), Congress of Neurological Surgeons and the American Association of Neurological Surgeons, and BC Cancer.

Target Population

The following recommendations apply to adult cancer patients with primary or metastatic brain tumours.

Recommendations

Key Points:

- At new seizure onset, clinicians should first consider non-enzyme inducing and non-myelosuppressive anti-epileptic drugs (AEDs), such as levetiracetam.
- Primary or metastatic brain tumour patients on AEDs must be monitored closely for severe adverse side effects, especially:
    - Stevens-Johnson syndrome, which is a life-threatening skin condition and warrants the immediate discontinuation of the AED, and
    - Hepatic toxicity, can result in acute liver failure.

1. The management of seizures caused by brain tumours should be individualized *(Level of evidence: III, Strength of recommendation: C)*.

2. Prophylactic AEDs are not recommended in brain tumour patients with no history of seizures. If a surgeon chooses to give prophylactic AEDs perioperatively, then the AED should be gradually discontinued after 1 week from surgery *(Level of evidence: II, Strength of recommendation: B)*.

3. Brain tumour patients with a history of seizures should receive AED therapy; monotherapy is preferred. The following factors should be taken into consideration when choosing an AED *(Level of evidence:II , Strength of recommendation: A)*:
    - Adverse side effects
    - Drug interactions
    - Speed of titration
    - Cost/drug coverage
    - Medical/psychiatric comorbidities

- Organ function

4. The Alberta Provincial CNS Tumour Team recommends the following **non-enzyme inducing AEDs** as first line therapy *(Level of evidence:II , Strength of recommendation:B)*:

	Antiepileptic Drug (Brand Name)
Preferred	• Lamotrigine (Lamictal) • Levetiracetam (Keppra) • Topiramate (Topamax)
Other Options	• Lacosamide (Vimpat) • Perampanel (Fycompa) Others as they become available

**Note that valproic acid and divalproex are also enzyme-inhibitors and may increase the levels of certain drugs.*

Non-enzyme inducing AEDs have been chosen as first line therapy because of the reduced effectiveness of some chemotherapeutic agents and other medications while on an enzyme-inducing AED.

5. The Alberta Provincial CNS Tumour Team recommends the following enzyme-inducing AEDs**,** if the non-enzyme inducing AEDs are not a viable option *(Level of evidence: III, Strength of recommendation: C)*.:
    - Phenytoin (brand name: Dilantin), or
    - Carbamazepine (brand name: Tegretol) or
        i. May be considered if patients don't respond to other recommended AEDs, taking into consideration myelotoxicity if the patient is receiving, or may in the future receive chemotherapy.
    - Oxcarbazepine (brand name: Trileptal),
        i. May be considered if patients don't respond to other recommended AEDs, taking into consideration myelotoxicity if the patient is receiving, or may in the future receive chemotherapy.
    - Others as they become available.

6. Brain tumour patients with recurring seizures should be evaluated for all of the following prior to a change in AED therapy *(Level of evidence: II, Strength of recommendation: B)*:
    - Patient compliance
    - New drug interactions
    - Tumour escalation and progression
    - Infections
    - Increased edema (consider starting or increasing dexamethasone; see The Use of Dexamethasone in Patients with High Grade Gliomas). Although dexamethasone is not a treatment for seizures, treating edema may decrease seizure frequency.

Note: serum levels are available for some AEDs; levels may be checked when clinically indicated (see recommendation #7). Consultation with neurology is recommended if seizures cannot be controlled.

7. Trough serum level measurements are indicated if *(Level of evidence: III, Strength of recommendation: C)*:
    - The patient is experiencing frequent seizures, or
    - There are signs of toxicity, or
    - Medication adjustments might affect AED levels (e.g., administration of dexamethasone).

It is preferable to increase the initial agent dose as opposed to adding a new AED. The frequency of serum level measurement is dependent on the half-life of the AED. Serum level measurements are currently available for the following recommended AEDs:

- Carbamazepine
- Phenytoin
- Lamotrigine
- Valproic acid

To obtain the most current information, including therapeutic ranges, please refer to the Alberta Precision Laboratories website.

8. Other AED treatment options for recurring seizures include *(Level of evidence: II, Strength of recommendation: B)*:
    - Optimizing the initial agent dose as tolerated and needed.
    - Prescribing an alternative AED, if the initial agent is not tolerated.
    - Patients who experience focal seizure may be prescribed an AED, such as lamotrigine or levetiracetam to abort a seizure before it starts. This may be particularly effective for patients who find higher doses of AEDs difficult to tolerate.
9. Non-pharmacological treatment options for recurring seizures include *(Level of evidence: III , Strength of recommendation:C)*:
    - Resection of the brain tumour or seizure focus
    - Adjuvant treatment, Radiation therapy and or chemotherapy.
10. AED therapy should stay the same unless there is a change in clinical status (chemotherapy, radiation therapy and other changes like, pregnancy, side effects) *(Level of evidence: II, Strength of recommendation: B)*.

11. Driving Guidelines

Intracranial Tumour

Patients with focal aware seizures with no deviation of head or eye are allowed to drive after 12 months. The patients are eligible to drive even if they continue to have these focal aware seizures with no head and neck deviation as long as the seizure semiology has remained unchanged for the last 12 months. The Alberta Provincial CNS Tumour Team members extrapolated from the CCMTA guidelines for patients driving with epilepsy and recommend that a patient may be eligible to drive with a Class 5 license after they have been seizure free for 6 months with the exception being the focal aware seizures with no head/eye deviation, as stated above. For brain tumour patients, Alberta Transportation also generally requires that the brain tumour be stable. The Alberta Transportation guidelines for medical conditions and driving are based on the National Safety Code of the Canadian Council of Motor Transport Administrators (Standard 6: Determining Driver Fitness in Canada). Patients must receive approval from Alberta Transportation to drive *(Level of evidence:II , Strength of recommendation:B)*.

All drivers are eligible for a license if

- movement and strength are sufficient to perform the function necessary for driving.
- cognitive and visual functions necessary for driving are not impaired.any pain associated with the condition, and any treatment for the condition, do not impair driving.
- Where required, a road test or other functional assessment indicates that driver is able to compensate for any loss of functional ability necessary for driving and the condition for maintaining a license are met.
- The conditions for maintaining license are met.

Seizures and epilepsy

All drivers are eligible for license if

- They undergone a neurological assessment to determine the cause of seizure, epilepsy is not diagnosed. This recommendation would not apply to brain tumour patients as they do have epilepsy related to brain.
- It has been 6 months since the provoking factor stabilized, resolved or was corrected with or without treatment and they have not had a seizure during that time.
- The treating neurologist or neurosurgeon indicated that further seizures are unlikely.

Recommendations for non-commercial drivers

- If it has been 6 months since the seizures occurred with or without medication.
- Reassessment in one year if the seizure occurred within the past 12 months.
- Brain tumour patients who have seizures should be on AED if they wish to drive.

Epilepsy with medication change

- Non-commercial drivers eligible for license if it has been 6 months since the prescribed change or withdrawal and they have not had a seizure during that time and conditions for maintaining the license are met. Brain tumour patients who have seizures should be on AED if they wish to drive.

12. In Alberta, seizure disorder to physician reporting is discretionary, not mandatory. However, it is recommended that patients who hold a professional license (Class 1–4) be reported. Patients should also be advised to notify their insurance company of their seizure status *(Level of evidence: I, Strength of recommendation: A)*.

13. If a patient is driving, then it is strongly recommended they continue taking AEDs *(Level of evidence: I, Strength of recommendation: A)*.
    - Exception: patients with a surgically curable tumour (e.g., some grade I tumours) who are seizure free for > 1 year may be considered for AED withdrawal.

14. Women of childbearing age or pregnant women should be counseled regarding possible teratogenic effects of anti-seizure management. Lamotrigine and levetiracetam are the most widely used due to their known safety during pregnancy and valproate is contraindicated in pregnancy.

Discussion

Despite the frequency of seizures in patients with brain tumours, prospective studies on the medical treatment of seizures in this population are scarce. Furthermore, existing studies have limitations, such as being retrospective with small patient numbers and heterogeneous regarding patient characteristics[5].

Seizure management in patients with brain tumours needs a multidisciplinary approach and should be individualized, taking into consideration a number of different patient-centred factors. Although the use of AEDs is the most common form of seizure management in this patient population, non-pharmacological therapies, such as surgery or RT, may also be considered.

AED Therapy

Brain tumour patients who have experienced a seizure should be treated with a standard first-line AED monotherapy. In the last two decades, several new AEDs have been approved for use in patients with epilepsy; however, clinicians still commonly prescribe the older AEDs. The most common older drugs used in Alberta are: phenytoin, and carbamazepine. The newer drugs used in Alberta are: lamotrigine, topiramate, levetiracetam, oxcarbazepine, clobazam, and lacosamide. Unfortunately, there is a lack of large prospective studies and randomized trials comparing the efficacy of old versus new AEDs, specifically in the brain tumour patient population, and therefore, the superiority of one agent over others has not been established.[5] In general, findings from the literature suggest that newer AEDs are better tolerated than older AEDs. However, newer AEDs are also more

expensive than the older drugs. Given the inconclusive state of the evidence, clinicians should take into consideration the following factors when choosing an AED: adverse side effects, drug interactions, speed of titration, cost/drug coverage, medical/psychiatric comorbidities, and organ function.

Non-enzyme Inducing AEDs: Many AEDs have significant effects on the cytochrome P450 system, which may increase the metabolism of numerous chemotherapeutic agents and supportive care agents, such as dexamethasone[6]. As a result, AEDs that induce the P450 system can significantly reduce serum levels of antitumour agents. Given these clinically significant drug interactions, the National Comprehensive Cancer Network suggest the use of non-enzyme inducing AEDs, where possible, over the use of enzyme inducing AEDs[6]. The Alberta Provincial CNS Tumour Team recommends the following non-enzyme inducing AEDs: levetiracetam, or lamotrigine, or topiramate, or valproic acid, or clobazam, or lacosamide, or perampanel.

A prospective observational study of 176 glioma patients evaluated the efficacy and safety of levetiracetam in the management of seizures[7]. Eighty-two patients (47%) received levetiracetam at a dose that ranged from 1500 to 3000 mg/day; nine patients required an increase in dosage to 4000 mg/day to become seizure free. At the last evaluation, 91% were seizure free (two of these patients discontinued the drug because of intolerable side effects). The authors of the study concluded that levetiracetam is efficacious and safe in patients with seizures due to glioma. Maschio and colleagues conducted a prospective observational study to investigate the efficacy and tolerability of topiramate in brain tumour patients with seizures (n=47)[8]. Follow-up ranged from 3 to 48 months (mean 16.5 months) and at final follow-up 56% were seizure free, 20% had a seizure frequency reduction higher than 50%, and 24% were stable. The response rate to topiramate was 76%; three patients discontinued the drug due to severe side effects.

A randomized phase II trial investigated the safety and feasibility of switching from phenytoin (an enzyme inducing AED) to levetiracetam monotherapy for postoperative control of glioma-related seizures[10]. Twenty patients were randomized to receive levetiracetam and nine patients were randomized to continue receiving phenytoin. At six months follow-up, 87% of patients receiving levetiracetam and 75% of patients receiving phenytoin were seizure free. Reported side effects included (% levetiracetam/% phenytoin): dizziness (0/14), difficulty with coordination (0/29), depression (7/14) lack of energy or strength (20/43), insomnia (40/43), and mood instability (7/0). The results of this phase II study suggest that it is safe to switch patients from phenytoin to levetiracetam monotherapy following craniotomy for supratentorial glioma.

Enzyme Inducing AEDs: Although enzyme inducing AEDs increase the metabolism of concurrent chemotherapeutic agents, it is unclear whether this impacts patient outcomes. In particular two studies compared the use of enzyme inducing AEDs to non-enzyme inducing AEDs and reported conflicting results in the glioblastoma patient population[11, 12]. Oberndorfer *et al*. retrospectively analyzed survival in 168 glioblastoma patients treated with either no AED (n=88), an enzyme inducing AED (n=43), or a non-enzyme inducing AED (n=37)[11]. Carbamazepine (81%) was the most frequently

administered enzyme inducing AED; valproic acid (85%) was the most frequently administered non-enzyme inducing AED. The authors of the study found a significant difference in survival between the two groups; those patients who received a non-enzyme inducing AED survived 13.9 months compared to 10.8 months in the enzyme inducing AED group. The authors concluded that it was uncertain whether the difference in survival was due to a decrease of efficacy of chemotherapeutic agents by the enzyme inducing AED, or due to increased efficacy of chemotherapeutic agents caused by the enzyme inhibiting properties of valproic acid. Valproic acid has been shown to prolong survival in patients receiving temozolomide and radiotherapy[13]. Conversely, in a similar study of 620 newly diagnosed glioblastoma patients Jaeckle *et al*. found that the median overall survival was longer for patients who received an enzyme inducing AED compared with a non-enzyme inducing AED (12.3 versus 10.7 months, p=0.0002)[12]. The study authors suggest that in comparative clinical trials that test agents metabolized by the P450 system, treatment arms may need stratification for the proportion of patients receiving enzyme inducing AEDs.

A retrospective observational study of 70 brain tumour patients found that oxcarbazepine showed a similar efficacy to valproic acid, a non-enzyme inducing AED, as well as other older enzyme inducing AEDs (carbamazepine, phenobarbital, and phenytoin)[14]. However, the older AEDs had significantly more side effects, both serious and non-serious. Similarly, a prospective observational study of 70 patients with brain metastases found that oxcarbazepine was equally as effective as levetiracetam and topiramate, significantly reducing seizure frequency and producing few side effects[15]. A prospective, randomized, single-centre study of 81 patients found that both levetiracetam (n=36) and phenytoin (n=38) are well-tolerated perioperatively[16].

Given the inconclusive evidence on the impact of enzyme inducing AEDs on patient outcomes and the common prescription of these drugs by clinicians, the Alberta Provincial CNS Tumour Team recommends the following enzyme inducing AEDs as an alternative to non-enzyme inducing AEDs: phenytoin. Oxcarbazepine and Carbamazepine may be considered if patients don't respond to other recommended AEDs, taking into consideration myelotoxicity if the patient is receiving, or may in the future receive chemotherapy.

Prophylactic AEDs: There is general consensus amongst a number of guideline developers that AED therapy in patients without a history of seizures is not recommended because of a lack of efficacy and the potential for serious side effects[6, 17-21]. Despite the recommendations, many clinicians still prescribe prophylactic AEDs, and this is particularly true for prophylactic AEDs that are given perioperatively. A survey of 386 neurosurgeons found that more than 70% of respondents reported routine use of AED prophylaxis for patients with primary or metastatic brain tumours[22]. Given this reality, the Alberta Provincial CNS Tumour Team recommend that if a clinician chooses to give prophylactic AEDs perioperatively, then the AED should be discontinued after one week from surgery as quickly and safely as possible, which is in agreement with the American Academy of Neurology recommendation[21].

Several observational studies and small randomized trials have shown a lower risk of early postoperative seizures in patients treated with prophylactic AEDs perioperatively[23-25]. Lwu *et al*. present Alberta-specific retrospective data on the use of perioperative AEDs in patients with newly diagnosed high-grade glioma[24]. In their study, 27% of patients were given prophylactic AEDs and of these, none experienced perioperative seizures (within one week). Perioperative seizures occurred in two patients without prophylactic AEDs. Of those patients taking AED prophylaxis, 18% were continued on the drug beyond the first perioperative week, which contradicts the American Academy of Neurology guidelines. The authors suggest that increased awareness of practice guidelines may help modify AED prescription patterns in brain tumour patients.

Wu *et al*. conducted a prospective randomized trial of perioperative seizure prophylaxis in patients with primary (n=46) or metastatic (n=77) brain tumours[26]. Sixty-two patients received seven-day phenytoin and 61 patients received no prophylactic AED. The incidence of seizures was 18% versus 24% (p=0.51), in the observation and prophylaxis group, respectively. The prophylaxis group also experienced significantly more adverse events (18% versus 0%, p<0.01). In this trial, the incidence of clinically significant seizures was only 3%. As a result of these findings, the study authors conclude that the routine use of prophylactic phenytoin in brain tumour patients is concerning. Similarly, a retrospective cohort study to assess the effectiveness of perioperative seizure prophylaxis (levetiracetam) in high-grade glioma patients found that levetiracetam prophylaxis was not a significant predictor of seizure occurrence; younger age, however, was a significant predictor of greater seizure occurrence[27].

A meta-analysis of randomized controlled trials evaluated the efficacy of AED prophylaxis versus no treatment or placebo in patients with brain tumours and found no evidence to support the administration of prophylactic AEDs (phenobarbital, phenytoin, or valproic acid)[28]. Similarly, a systematic analysis of the efficacy of prophylactic AEDs across 19 studies found that there were no significant differences in the extent of resection, perioperative mortality, or recurrence between the AED and non-AED cohorts[29]. The study authors conclude that prophylactic administration of AEDs during resection provide no benefit in the prevention of either early or late postoperative seizures. A recent Cochrane review of AEDs as prophylaxis for post-craniotomy seizures also concluded that there is little evidence to suggest that AED treatment administered prophylactically is effective in preventing post-craniotomy seizures[30]. An older Cochrane review concluded that the decision to start an AED for seizure prophylaxis should ultimately be guided by assessment of individual risk factors and careful discussion with patients regarding predicted risk of seizure, which tends to be low[31], cost, and potential side effects[32].

Recurring Seizures: The efficacy of AEDs in neuro-oncology patients is dependent on a number of variables; approximately 60% to 70% of patients will experience recurrent seizures[33]. Wick *et al*. reported that in their study, 70%, 51%, and 44% of patients on carbamazepine, phenytoin, and valproic acid, respectively, had recurrent seizures[34].

It is important to investigate the cause of recurrence prior to a change in AED therapy. The Alberta Provincial CNS Tumour Team recommends that clinicians evaluate the following as potential causes of recurrence: patient compliance, new drug interactions, tumour progression, recurrence, and infections. If possible, serum level concentrations may also be verified before prescribing an alternative AED or adding a second agent.

If a patient is experiencing recurrent seizures, the first treatment option is to optimize the initial agent dose as tolerated and needed. Table 1 below provides the minimum and maximum daily doses for the old and newer AEDs, although it should be noted that there are many possibilities and variables to consider when escalating the initial dose. (see Appendix A)

If a patient continues to experience recurrent seizures and the initial agent is not tolerated, then the clinician should either prescribe an alternative AED or add-on another AED, such as clobazam or any other agent at the discretion of the treating clinician. Lorazepam could be used in patients with focal seizures, to prevent the evolution to a bilateral tonic clonic seizure.

Clobazam as an add-on treatment may reduce seizure frequency and may be most effective in focal-onset seizures[35]. A retrospective analysis was performed on 181 glioblastoma patients with seizures to examine the efficacy of valproic acid given either with or without levetiracetam on seizure control and survival[36]. At the end of follow-up (minimum 6 months), 78% of patients on valproic acid and 70% of patients on levetiracetam were seizure free with monotherapy. Of those patients with recurrent seizures who received polytherapy with valproic acid and levetiracetam, 60% achieved seizure freedom. Patients on valproic acid and temozolomide had a median survival of 69 weeks compared to 61 weeks in the group without valproic acid after adjusting for various factors. The authors of the study conclude that polytherapy with valproic acid and levetiracetam more strongly contributes to seizure control than does either as monotherapy.

Another retrospective observational study of 140 brain tumour patients (99 with seizures), of whom 24% had a low-grade glioma, 54% had a high-grade glioma, and 23% had either ependymoma, meningioma, or brain metastasis, found that patients treated with a combination of valproic acid and levetiracetam showed the highest percentage of responders (82%) compared to other AED monotherapy[36]. In this group 59% of patients achieved seizure freedom. The authors of the study suggest that rather than administering sequential trials of AED monotherapy, add-on levetiracetam might be more effective than valproic acid alone or levetiracetam alone.

Several studies have assessed levetiracetam as an add-on treatment and found that it is well tolerated. One prospective study[37] and two retrospective studies[38, 39] found that the rate of response to add-on levetiracetam ranges between 65 and 90% and the percentage of seizure free patients ranges from 20 to 59%. A small prospective study of add-on gabapentin found that 100% of patients had seizure reduction and 57% achieved seizure freedom[40]. It should be noted that all of these studies are limited by small sample sizes and heterogeneous patient tumour characteristics.

Unfortunately, certain brain tumour patients are resistant to AEDs and will continue to experience seizures despite the use of AEDs and adequate serum concentrations. Ruda *et al*. explain that the major cause of resistance to AEDs is over-expression of proteins belonging to the ATP-binding cassette transporter family, which have been reported in tumour cells of glioma patients, and can lead to diminished drug transport into the brain parenchyma[41]. AEDs may also fail to control seizures because of a loss of receptor sensitivity. For these patients, it is important to consider non-pharmacological treatment therapies to manage recurrent seizures (please see *Non-pharmacological Treatment* section below).

Adverse Side Effects of AEDs

AEDs can have serious side effects that may affect a patient's quality of life. Brain tumour patients also experience a higher incidence of adverse effects, ranging from 30 to 40%, than that observed in seizure patients without brain tumours[42]. Of those brain tumour patients that experience adverse effects as a result of AEDs, 24% are severe enough to warrant a change or discontinuation of AED therapy[42].

Common Side Effects: The most common side effects of AEDs are listed in Table 2 below. Cognitive impairment, bone-marrow suppression, liver dysfunction, and dermatological reactions are some of the more commonly experienced side effects of AEDs[2]. Long term therapy with the older AEDs can also have an adverse effect on bone metabolism, which is pertinent for low grade glioma patients.

Mild Skin Rashes: Mild skin rashes are frequently observed in patients taking AEDs; brain tumour patients compared to those without have a higher likelihood of drug rash with AEDs. A retrospective review of 289 patients that received radiotherapy found that 18% experienced mild rashes, compared with the expected rate of 5 to 10%[43]. The study authors noted that mild drug rashes among brain tumour patients did not appear to be related to the radiotherapy. Cross-sensitivity rash has also been reported between various AEDs, such as phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and lamotrigine, especially between carbamazepine and phenytoin[44]. Arif *et al*. investigated predictors of AED-related rash in 1,890 patients and found that the risk of developing a rash increased three- to four-fold if the patient had a rash to one or more AED, or an allergy to another medication[45].

Stevens-Johnson Syndrome: Severe skin reactions, such as Stevens-Johnson syndrome, may occur in a small percentage of patients during the first four to eight weeks on carbamazepine, phenobarbital, phenytoin, or lamotrigine, especially in patients who have received cranial radiotherapy[46-50]. Patients who exhibit signs of Stevens-Johnson syndrome must discontinue the use of the AED immediately.

Chemotherapeutic Drug Interactions: In addition to direct adverse side effects, some AEDs also have clinically significant interactions with chemotherapeutic agents used to treat brain tumour patients. As previously mentioned, the enzyme inducing AEDs, such as phenytoin, carbamazepine,

and oxcarbazepine, may significantly reduce serum levels of chemotherapeutic agents, including nitrosoureas, cyclophosphamide, ifosfamide, procarbazine, vincristine, paclitaxel, irinotecan, topotecan, 9-aminocampthetecin, doxorubicin, teniposide, thiotepa, methotrexate, and busulfan[51, 52]. In addition, certain chemotherapeutic agents, such as methotrexate, doxorubicin, adriamycin, and cisplatin have been shown to decrease serum levels of valproic acid, carbamazepine, and phenytoin, as well[33]. Fortunately, the most common chemotherapeutic agent used to treat brain tumour patients, temozolomide, has no clinically significant drug interactions with AEDs.

Other Drug Interactions: AEDs may also interact with the metabolism of various steroids, including cortisol, prednisone, and dexamethasone, which is commonly used in brain tumour patients to control peritumoral edema. For example, phenytoin induces the hepatic metabolism of dexamethasone, reducing its half-life and bioavailability[2]. Valproic acid, specifically, has distinct enzyme-inhibiting properties, which may reduce the metabolism of another drug by raising plasma concentrations. This may result in an increase in bone marrow toxic effects of concomitant chemotherapeutic agents[5].

Cognitive Function: Several AEDs also significantly impact the patient's cognitive function and quality of life. Klein *et al*. compared 156 patients with low-grade gliomas and seizures to healthy controls. Compared with the healthy controls, glioma patients had significant reductions in information processing speed, psychomotor function, attentional functioning, verbal and working memory, executive functioning, and health-related quality of life, most of which were attributed to the use of AEDs[53].

Generally speaking, newer AEDs that are non-enzyme inducing have significant advantages over older agents when it comes to adverse side effects.

Non-Pharmacological Treatment

Some patients are resistant to AED therapy and in these cases, non-pharmacological treatment approaches should be considered.

Surgery: Tumour resection may remove the seizure focus and therefore control seizures. However, the seizure focus in brain tumour patients may be located outside the main tumour mass and in this situation even a gross total resection will not control the seizures. The percentage of seizure free patients after tumour surgery ranges from 65 to 82%; the most significant prognostic factors associated with seizure freedom are completeness of tumour resection and short preoperative duration of tumour-associated seizures[5]. Englot *et al*. conducted a systematic review of seizure outcomes after surgical resection of low-grade brain tumours in 910 patients from 39 studies[54]. The study authors found that 80% of patients were seizure free after surgery. Higher rates of seizure freedom were achieved in patients with ≤ 1 year duration of seizures compared to patients with > 1 year of seizures (OR 9.48, 95% CI 2.26–39.66) and in patients with gross-total resection compared to subtotal lesionectomy (OR 5.34, 95% CI 3.61–7.89). Similarly, a retrospective study of 269 patients with low-grade gliomas who underwent initial surgery found that 89% of patients were seizure free at six months following gross total resection versus 57% following subtotal resection[55]. Van Breemen *et*

al. note that in the majority of series reporting high rates of seizure freedom after surgery, the epileptogenic zone was excised together with the tumour, whereas general surgery for brain tumours typically resects part or all of the tumour without special attention to the epileptogenic zone[2].

Radiotherapy: There is limited data on the effect of radiotherapy on tumour-related seizures, although some studies have found that radiotherapy can result in improved seizure control. A phase III trial compared 157 patients receiving adjuvant postoperative radiotherapy (54 Gy in fractions of 1.8 Gy) versus observation (n=157) in low-grade glioma patients and found that at one year, 25% of treated patients had seizures compared to 41% in the observation group[56]. In a retrospective study of 43 glioma patients with medically intractable seizures, 76% of patients achieved a significant reduction in seizures and 32% were seizure free at 12 months following RT[57]. The study authors observed that seizure reduction occurred more often in patients displaying an objective tumour response on MRI; however, patients with no change on MRI also had a significant seizure reduction, suggesting that ionizing radiation on seizure control include damage to epileptogenic neurons or metabolic changes of the microenvironment[5]. The study authors also found that timing of radiotherapy and duration of seizures prior to radiation was significantly associated with seizure reduction[57].

Driving Guidelines

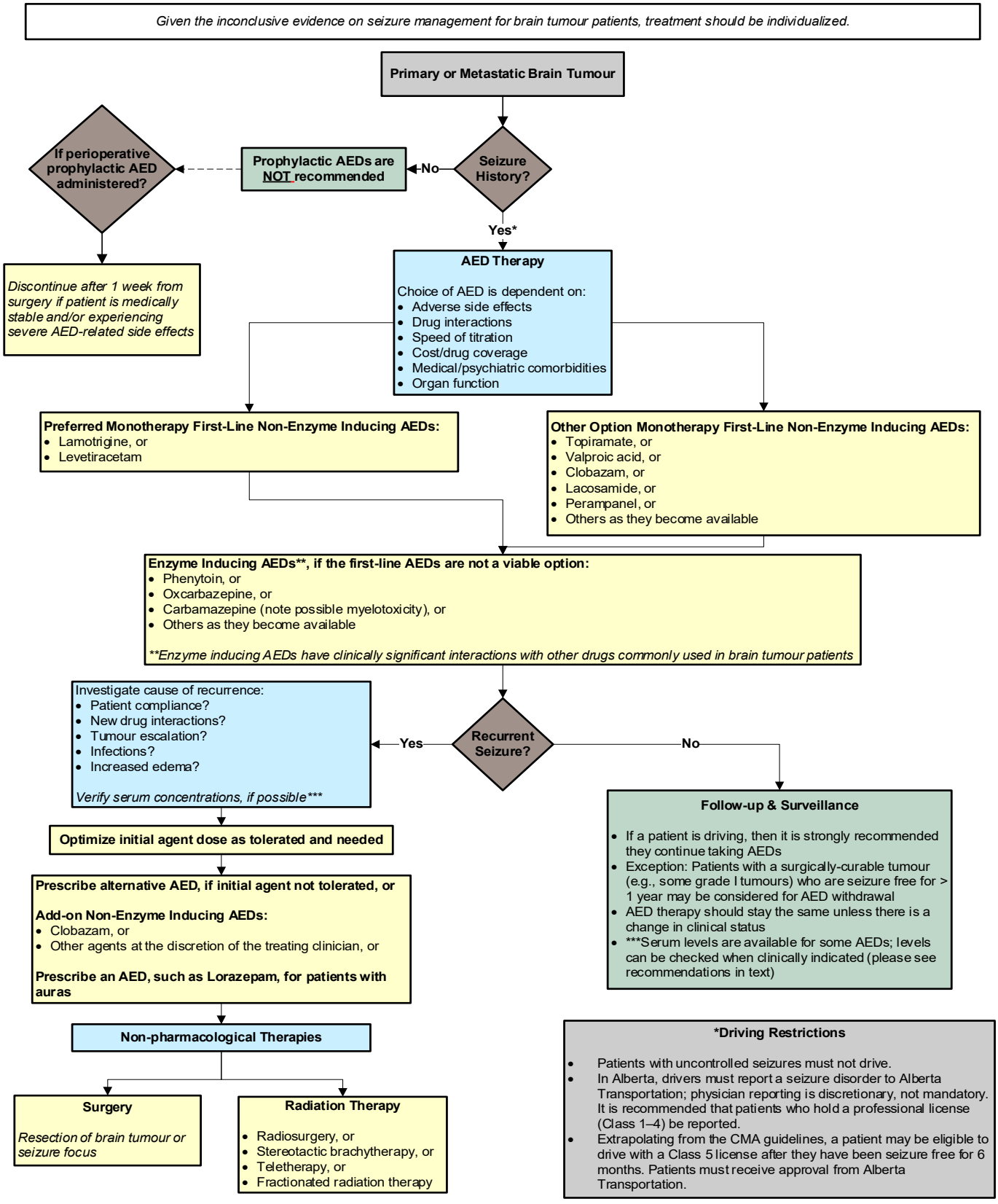
The Alberta Provincial CNS Tumour Team recommends that patients with focal aware seizures with no deviation of head or eye are allowed to drive after 12 months. The patients are eligible to drive even if they continue to have these focal aware seizures with no head and neck deviation as long as the seizure semiology has remained unchanged for the last 12 months. Patients with brain tumours who have not had a seizure and who are driving should not be placed on prophylactic AEDs. In Alberta, drivers are required by law to report any health condition, including seizures, that may affect their ability to drive safely; physician reporting to Alberta Transportation is discretionary, not mandatory. However, if a patient has been instructed not to drive, it is important to document this in their medical record. Patients should be advised of the risk of seizure activity and the potential for driving restrictions that may occur while on AEDs. Patients are also required to advise their insurance company of their condition to ensure that their policy is valid in the event of an accident.

In accordance with the Canadian Medical Association (CMA) guidelines for driving with epilepsy, a patient may be eligible to drive with a Class 5 license after they have been seizure free for six months and with a favourable recommendation from their treating clinician[58]. However, the CMA suggests that each case be evaluated individually by the treating clinician(s)[58]. Patients may obtain more information about the license reinstatement process from Alberta Transportation, Driver Fitness & Monitoring Department at (780) 427-8230 or https://www.alberta.ca/driver-fitness-and-suspensions.

Follow-up & Surveillance

The Alberta Provincial CNS Tumour Team recommends that AED therapy stay the same unless there is a change in clinical status. The continuation of AEDs is recommended because of the absence of data for seizure outcome after withdrawal, and high seizure recurrence in adults[2]. To add, if a patient is driving, then they are strongly recommended to continue taking AEDs due to the high risk of fatal outcomes if a seizure were to recur. The exception to AED withdrawal is for patients with a surgically-curable tumour, such as some grade I tumours, who are seizure free for > 1 year; in this patient population, AED withdrawal may be considered. These patients still have a risk of seizures six months post-surgery, and there is minimal evidence between the six-month to one-year range; therefore, most experts agree that AEDs may be weaned one year post-surgery[55].

Treatment Algorithm



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Appendix A:

Table 1. Minimum and maximum daily doses for AEDs*

AED (Brand Name)	Daily Dose Range (mg)**	Notes
Phenytoin (Dilantin)	200–600	Either at bedtime or split twice a day, enzyme inducing
Levetiracetam (Keppra)	500–3000	Twice a day, non-enzyme inducing, can be used during pregnancy
Lamotrigine (Lamictal)	100–500	Twice a day; strict titration guidelines, non-enzyme inducing, can be used during pregnancy
Clobazam (Frisium)	10–40	Either at bedtime or split twice a day
Carbamazepine (Tegretol)	400–1600	Twice a day; controlled release tablets, enzyme inducing
Lacosamide (Vimpat)	100–400	Twice a day, non-enzyme inducing
Valproic acid/Divalproex Depakene/Epival)	500–2000	Twice a day, non-enzyme inducing
Topiramate (Topamax)	100–400	Twice a day, non-enzyme inducing
Oxcarbazepine (Trileptal)	300–2400	Twice a day

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial CNS Tumour Team. Members include neurosurgeons, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial CNS Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2014 and updated in 2023.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AED, antiepileptic drug; CBC complete blood count; CI, confidence interval, CMA, Canadian Medical Association, CNS, central nervous system, LFT, liver function test; OR, odds ratio

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Alexandra Hanson has nothing to disclose.
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Egiroh Omene has nothing to disclose.
Frances Folkman* has nothing to disclose.
Jay Easaw* has nothing to disclose.
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Paula De Robles has nothing to disclose.
Roland Coppens has nothing to disclose.
Ritu Sharma has nothing to disclose.
Wilson Roa has nothing to disclose.

*** Working group leads**