

SNO and EANO practice guideline update: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors

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Abstract

Objective. To update the 2000 American Academy of Neurology (AAN) practice parameter on anticonvulsant prophylaxis in patients with newly diagnosed brain tumors.

Methods. Following the 2017 AAN methodologies, a systematic literature review utilizing PubMed, EMBASE, Cochrane, and Web of Science databases was performed. The studies were rated based on the AAN therapeutic or causation classification of evidence (Class I-IV).

Results. Thirty-seven articles were selected for final analysis. There were limited high level, Class I studies and mostly Class II and III studies. The AAN affirmed the value of these guidelines.

Recommendations. In patients with newly diagnosed brain tumors who have not had a seizure, clinicians should not prescribe anti-epileptic drugs (AEDs) to reduce the risk of seizures (Level A). In brain tumor patients undergoing surgery, there is insufficient evidence to recommend prescribing AEDs to reduce the risk of seizures in the peri- or postoperative period (Level C). There is insufficient evidence to support prescribing valproic acid or levetiracetam with the intent to prolong progression-free or overall survival (Level C). Physicians may consider use of levetiracetam over older AEDs to reduce side effects (Level C). There is insufficient evidence to support using tumor location, histology, grade, molecular/imaging features, when deciding whether or not to prescribe prophylactic AEDs (Level U).

Key Words: Anti-epileptic drug, GBM, Glioma, Guideline, seizure

Key points

- This is the 1st update of the 2000 AAN guideline on the use of anticonvulsant prophylaxis in patients with brain tumors
- Newly diagnosed brain tumor patients without seizures should not receive AEDs (Level A)
- There is not enough evidence to recommend AEDs to reduce seizures in the peri- or postoperative period (Level C)

Importance of the Study

This article provides for the first time an update of the 2000 AAN guideline on the use of anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. A multidisciplinary panel performed a systematic literature review and rated 37 pertinent articles based on the AAN therapeutic or causation classification of evidence. In patients with newly diagnosed brain tumors who have not had a seizure, clinicians should not prescribe AEDs to reduce the risk of seizures (Level A). In brain tumor patients undergoing surgery, there is insufficient evidence to recommend prescribing AEDs to reduce the risk of seizures in the peri- or postoperative period (Level C). There is insufficient evidence to support prescribing valproic acid or levetiracetam with the intent to prolong progression-free or overall survival (Level C). There is insufficient evidence to support using tumor location, histology, grade, molecular/imaging features, when deciding whether or not to prescribe prophylactic AEDs (Level U).

INTRODUCTION

Seizures are a common and potentially devastating complication of both primary and metastatic brain tumors. Precise data are difficult to obtain, but the frequency of epileptic seizures in patients with brain tumors is reported to range from 35% to 70%.^{1,2} Seizures are described as the first symptom of brain tumors in 20-40% of all patients, while 10% of patients experience a seizure at some point during the course of their disease.^{2,3} Seizures in brain tumor patients have a significant impact on long-term disability and are associated with high symptom burden during the end-of-life phase.^{4,5}

Seizures are much more common in patients with lower grade (WHO II) glioma than patients with higher grade (WHO III/IV) glioma or brain metastases.⁶ Since brain metastases affect approximately 10-30% of patients with systemic cancer,^{7,8} management of seizures in this population is also a significant issue. While primary brain tumors are overall much rarer than brain metastases with an average annual age-adjusted incidence rate of 23.03 per 100,000, seizures in this population are estimated to cause up to 10% of all epilepsy cases.⁵

The administration of anti-epileptic drugs (AED) to patients with brain tumors who have not had seizures is common despite the lack of definitive evidence that the potential benefits might outweigh side effects of AEDs. Significant side effects include cognitive impairment, neuropsychiatric disorders, fatigue, myelosuppression, liver dysfunction, dermatologic reactions and interactions with systemic cancer treatment. Therefore, the judicious use of AEDs in the right patient to avoid unnecessary side effects and financial burden on patients is essential.

A prior American Academy of Neurology (AAN) practice parameter report systematically assessed the role of anticonvulsant prophylaxis in patients with newly diagnosed brain tumors in 2000.⁹ The guideline focused on the question of whether patients with newly diagnosed brain tumors without any history of a seizure should be treated prophylactically with AEDs to prevent first seizures. A total of four randomized trials satisfying the criteria of level I evidence at that time,¹⁰⁻¹² and eight papers describing studies of level II evidence¹³⁻¹⁸ were identified. Two of the abstracts described as level I studies at that time are excluded from this evidentiary assessment due to updated

evidence levels. The authors concluded that in patients with newly diagnosed brain tumors, anticonvulsant medications are not effective as primary seizure prophylaxis. Because of a lack of efficacy and potential side effects, they recommended that prophylactic anticonvulsants not be used routinely in patients with newly diagnosed brain tumors. In addition, they concluded that in patients with brain tumors treated surgically who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate.

Since then, more modern, non-enzyme-inducing AEDs (ex. levetiracetam) have been approved and practice patterns in the treatment of seizures in brain tumor patients have evolved. In addition, some AEDs (ex. valproate) have been suggested to have anti-tumor activity. Building on the prior report, a multidisciplinary panel of expert neurologists, epileptologists, neurophysiologists, neurosurgeons and neuro-oncologists under the guidance of the Society for Neuro-Oncology and the European Association of Neuro-Oncology was formed to update the practice parameters on anticonvulsant prophylaxis in patients with newly diagnosed brain tumors.

METHODS

Description of Analytical Process

No institutional review board approval was obtained as only published data was used for this practice guidelines review.

This practice parameter update follows the methodologies described in the 2017 edition of the AAN's guideline development process manual.¹⁹ Conclusions and recommendations were developed in accordance with the process manual and the updated scheme for classifying therapeutic and causation articles.¹⁹ In 2017, after reviewing potential members' conflict of interest statements and curriculum vitae, a multidisciplinary panel of experts in brain tumors, neurosurgery, and epilepsy were chosen to develop this guideline. The original panel consisted of 9 neuro-oncologists (EG, TW, PW, DS, RH, MW, EL, GS, WW), 4 epileptologists (EA, JL, MC, PK), and 1 neurosurgeon (MV).

The panel developed research questions in PICO format: patient, intervention, comparison, and outcome.

The guideline panel included articles in adult patients with brain tumors related to treatment for seizures or seizure prophylaxis. The panel excluded pharmacologic treatment trials with fewer than 20 participants. The complete search strategy is presented in Appendix 1. The panel engaged a medical librarian to search the PubMed/ OVID Medline, EMBASE, Cochrane Library, and Web of Science databases from January 1999 to March 31st, 2017. An updated literature search was performed prior to starting the analysis on April 16, 2018 and again on May 14, 2021 to identify any newly published high-level evidence that might substantially change the recommendations. A total of 839 titles and abstracts were obtained (Figure 1).

Two panel members (EG, TW), working independently of each other, reviewed each of the abstracts for basic inclusion criteria: (1) article was relevant to at least one of the clinical questions; (2) article described adult brain tumor patients with or without seizures; (3) study population was greater than or equal to 20 to reduce the likelihood of spurious results due to small samples; and (4) article was not a single-patient case report, review, or editorial. Of the 839 abstracts reviewed, the 2 panelists identified 369 as possibly pertinent, for which they obtained and reviewed the full-text articles. Of the 369 reviewed articles, 86 met inclusion criteria and were reviewed and classified by 2 panel members each. Reviewers, working independently of each other, assessed the quality of evidence on the basis of the AAN therapeutic and causation study classification schemes (Appendix 2). Discrepancies in article classification between the 2 reviewers were reconciled by 2 other independent reviewers. An additional 6 articles were found by reviewing references and secondary literature.

Class III studies are discussed in the guideline text only when no Class I or limited Class II studies were identified. Class IV studies were excluded from consideration because of their high risk of bias. The panelists noted that what constituted a seizure was not always clearly defined in each article, potentially limiting accuracy of seizure occurrence. Table 1 summarizes the literature cited.

Analysis of Evidence

Clinical Question 1: In patients with newly diagnosed primary or metastatic brain tumors who have not already experienced a seizure, does anticonvulsant prophylaxis compared to no anticonvulsant prophylaxis (a.) increase seizure-free survival and (b.) reduce the frequency of first seizures at 6 months from diagnosis?

Evidence

The previous AAN practice parameter published in 2000 identified 10 published studies (4 Class I and 6 Class II studies, excluding the 2 abstracts never published as manuscripts) and the conclusion was that prophylactic anticonvulsant use did not provide a substantial benefit.^{10-18,20} Subsequent studies not included in the original AAN practice parameter were examined.

There were no Class I studies, but three Class II studies pertained to this issue.²⁰⁻²² One, examining the role of prophylactic anticonvulsants in newly diagnosed brain tumors, fulfilled all requirements of a Class I study but was terminated early.²⁰ The study population, comprised of 60% brain metastasis and 40% glioma patients, was randomized to phenytoin versus no anticonvulsant. Seizure-free survival did not differ between the two groups - 87% in the phenytoin cohort and 90% in the no anticonvulsant cohort at the primary endpoint of 3 months. The trial closed prematurely based on a feasibility analysis that found an unexpectedly low rate of first seizure in the control arm and a higher mortality rate at the 3-month time point. The authors concluded that it was unlikely that an extension of the study would change the outcomes.

A retrospective institutional chart review study of patients with brain metastases from melanoma found that anticonvulsant prophylaxis was associated with a significantly decreased risk of new-onset seizure, with 3-month rates of 0% vs 17% in those with or without prophylaxis, respectively.²¹ A second retrospective single-center study examined patients undergoing surgery for meningioma; new-onset seizures within one week of craniotomy were not reduced in patients

receiving prophylactic levetiracetam or other anticonvulsants compared to those receiving no prophylaxis.²²

Twelve Class III studies were identified.²³⁻³⁴ Only 1 of 12 Class III studies, evaluating different tumor types with different endpoints, suggested benefit from prophylactic AEDs.³¹ That particular retrospective single-institution study with 141 relevant patients suggested a decrease of seizure frequency during the first 6 months after surgery but not thereafter.

Conclusions

Patients with newly diagnosed brain tumors who have not experienced a seizure do not appear to benefit from AED prophylaxis. Combined with the data found in the earlier AAN practice parameter, there are now 3 randomized trials providing Class I evidence,¹⁰⁻¹² 8 Class II studies^{13-18,20,22} and 11 Class III studies^{23-30,32-34} that suggest that patients do not benefit from primary prophylaxis with AEDs. Only 1 Class II²¹ and 1 Class III study³¹ support a different conclusion. This question deserves further study in patients with brain metastases from melanoma but presently there is insufficient evidence to use prophylactic AEDs in patients with metastatic melanoma to the brain.

For patients with newly diagnosed brain tumors, anticonvulsant prophylaxis compared to no anticonvulsant prophylaxis is unlikely to be effective in increasing seizure-free survival and reducing the frequency of first seizures at 6 months from diagnosis.

Recommendation

In patients with newly diagnosed brain tumors who have not had a seizure, clinicians should not prescribe AEDs to reduce the risk of seizures (Level A).

Clinical Question 2: In patients with newly diagnosed primary or metastatic brain tumors who have not already experienced a seizure and who undergo a neurosurgical procedure (craniotomy or biopsy) for initial treatment or diagnosis of their tumor does perioperative anticonvulsant prophylaxis compared to no perioperative anticonvulsant prophylaxis (a.) prolong time to seizure occurrence and (b.) reduce the frequency of first seizure at 14 days following surgery?

Evidence

There were no Class I or Class II studies, but 3 relevant Class III studies assessed the impact on prolongation of time to seizure occurrence (question 2a).^{23,29,34} All found that prophylactic AEDs did not prolong postoperative time to seizure occurrence, and none of the studies showed improved overall time to seizure occurrence with prophylaxis.

There were no Class I trials, but 1 prospective, randomized Class II trial examined the role of 7-day phenytoin prophylaxis in patients undergoing craniotomy for supratentorial brain tumors (question 2b).³⁵ Phenytoin was loaded prior to craniotomy, given for 7 days with dose adjustments for therapeutic levels, and then tapered off. Seizures were determined on clinical grounds or with electroencephalogram (EEG) if an event in question was not felt to be definitive. The study was powered to detect a reduction in clinically significant seizures from 30% to 10%. The incidence of seizures within 30 days of surgery was 8% in the observation group and 10% in the prophylaxis group. The incidence of clinically significant seizures was 2% in the prophylaxis group and 3% in the observation group, while adverse effects of AED were seen in 18% of patients in the prophylaxis group. After enrolling 123 of the planned 142 patients, however, the study was closed early as an interim analysis indicated a probability of 0.003 that prophylaxis would be superior to observation at the end of the study. Given the stringent criteria used for this guideline, this trial is rated as a Class II study rather than Class I evidence due to early closure.

Two Class III studies found reduced seizure frequency with prophylaxis within 14 days of surgery.^{31,36} Five Class III studies found there was no impact of prophylaxis on seizures within this postoperative period.^{23,29,32,37,38}

Conclusion

There are 3 Class III studies^{23,29,34} all showing that postoperative prophylaxis does not result in prolongation of time to seizure occurrence (question 2a). There is 1 prospective randomized Class II trial³⁵ and 5 Class III studies^{23,29,32,37,38} indicating that perioperative therapy with an AED has no impact on seizure outcomes within 14 days of surgery. While 2 Class III studies^{31,36} showed reduced seizure activity (question 2b), the collective findings did support perioperative therapy with AEDs.

For patients with newly diagnosed primary or metastatic brain tumors who never had a seizure and who undergo a neurosurgical procedure (craniotomy or biopsy) for initial treatment or diagnosis of their tumor, perioperative anticonvulsant prophylaxis is possibly not effective in reducing seizures overall and during the first 14 days following surgery.

Recommendation

In patients with brain tumors undergoing surgery, there is insufficient evidence to recommend prescribing AEDs to reduce the risk of seizures in the peri- or postoperative period (Level C).

Clinical Question 3: In patients with newly diagnosed primary or metastatic brain tumors, does treatment with valproic acid or other AEDs (either prophylactic or following a seizure) compared to treatment with any other anticonvulsant medication increase progression-free or overall survival?

Evidence

There were no Class I or Class II studies, but 6 Class III studies³⁹⁻⁴⁴ were identified as pertinent to this question. Five Class III studies evaluated the effect of valproic acid on seizure control and survival in patients with glioblastoma (GBM).^{39,40,42-44} One Class III study analyzing a subgroup of patients who received an AED while undergoing treatment in a large randomized clinical chemotherapy trial⁴⁵ was the first study to find a possible survival benefit when adding valproic acid to the treatment of radiation therapy and temozolomide in GBM patients.⁴⁴ A positive impact on patient survival was also found in 2 other subsequent single-center retrospective Class III studies focusing on valproic acid in GBM treatment^{40,42} while the same protective effect was not detected in patients with grade II/ III gliomas.⁴⁰

The positive results of valproic acid were not replicated by 2 other Class III studies,^{39,43} one being a pooled analysis of 4 randomized clinical trials with a total of 1,869 patients.³⁹ The findings indicated that there was no improvement in progression-free or overall survival with the use of valproic acid or levetiracetam in patients with GBM. In the second retrospective study with 102 GBM patients treated with valproic acid, a stratified analysis did not show any significant association with overall survival.⁴³

Two retrospective Class III studies evaluated the survival benefit of levetiracetam in patients undergoing standard treatment with radiotherapy and temozolomide for newly diagnosed GBM.^{39,41} While 1 single center study with 103 patients showed a survival benefit of 2.7 months,⁴¹ the above-mentioned analysis of 1,869 clinical trial patients did not show any survival benefit associated with levetiracetam³⁹ (Table 1).

Conclusion

There are 3 Class III studies⁴²⁻⁴⁴ indicating that there is a possible survival benefit of valproic acid and 2 Class III studies^{40,41} showing a positive effect of levetiracetam on overall survival in GBM patients. All of these studies are retrospective or based on post-hoc analysis. A larger Class III study based on a pooled analysis of participants of multiple clinical trials did not show any survival benefit for patients

who were on valproic acid or levetiracetam in addition to chemotherapy. This study included more patients than all other reviewed studies combined and did not reveal any impact on survival.³⁹

While there is a lack of high-level evidence, in patients with newly diagnosed primary or metastatic brain tumors treatment with valproic acid or levetiracetam does not appear to increase progression-free or overall survival. Use of valproic acid has also been associated with complications such as thrombocytopenia and hepatotoxicity.

Recommendation

In patients with newly diagnosed primary or metastatic brain tumors, there is insufficient evidence to support prescribing valproic acid or levetiracetam with the intent to prolong progression-free or overall survival (Level C).

Clinical Question 3a: In patients with newly diagnosed primary or metastatic brain tumors, does treatment with a non-enzyme-inducing antiepileptic drug (EIAED) or more “modern” AED (either prophylactic or following a seizure) compared to treatment with a EIAED (either prophylactic or following a seizure) have a more favorable side effect profile?

Evidence

There were no Class I trials, one Class II,⁴⁶ and 8 Class III studies^{28,34,36,44,47-50} identified as pertinent to this question.

Of the newer non-EIAEDs, levetiracetam was the AED most studied in brain tumor patients with 1 Class II⁴⁶ and 7 Class III studies^{28,34,36,47-50} evaluating the efficacy and side effect profile. Levetiracetam was well tolerated and perioperative seizure frequency was low in the first 7 days postcraniotomy in all studies. One Class II study⁴⁶ and 2 Class III^{47,50} studies compared the efficacy

and tolerability of levetiracetam versus phenytoin and carbamazepine after supratentorial brain tumor surgery.⁵⁰ There was no difference in postoperative seizure outcomes; however, levetiracetam was associated with fewer adverse drug reactions and a higher retention rate in both studies. A second Class III study comparing valproic acid with EIAEDs found that GBM patients starting adjuvant temozolomide while taking valproic acid were at significantly higher risk for grade 3 and grade 4 hematologic toxicities.⁴⁴

There was 1 retrospective Class III study evaluating the use of valproic acid or levetiracetam for the prevention of postoperative seizures.⁴⁸ The study evaluated 282 patients on either levetiracetam or valproic acid and the primary end points were seizure outcome and tolerability. Seizure outcome for the prevention of early postoperative seizures and the development of long-term epilepsy was similar in both groups. However, adverse effects were statistically significantly higher in the valproic acid group leading to changes in AED therapy.

Conclusion

One Class II⁴⁶ and 8 Class III studies^{28,34,36,44,47-50} evaluated the safety and tolerability of newer AEDs, mostly levetiracetam. The use of levetiracetam is well tolerated in patients with brain tumors. The prevention of early postoperative seizures within 7 days of surgery is comparable to previous trials with first generation antiepileptic drugs but associated with fewer side effects. The use of valproic acid in brain tumor patients on chemotherapy has also been associated with higher hematologic toxicities.

Recommendation

In patients with newly diagnosed primary or metastatic brain tumors, physicians may choose to prescribe levetiracetam rather than older AEDs to reduce side effects (Level C).

Clinical Question 4: In patients with newly diagnosed supratentorial primary or metastatic brain tumors who have not had a seizure, should aggressive tumor characteristics such as histology (primary vs. metastatic), grade, molecular pathology (e.g., O(6)-methylguanine-DNA methyltransferase promoter methylation, isocitrate dehydrogenase mutation (IDH), epidermal growth factor receptor amplification) or imaging (e.g., tumor location, number of tumors, edema, enhancement, vascularity) compared to tumors considered to be less aggressive, in less epileptogenic regions influence prophylactic anticonvulsant use?

Evidence

There were no Class I trials identified as pertinent to this question, and 2 Class II^{22,51} and 9 Class III studies^{29-31,34,52-56} were identified as pertinent to this question. While several studies correlated specific brain locations with seizure risk, none of the studies investigated how the use of AEDs should be adjusted according to these associations.

One Class II study of GBM patients found that tumors in the superior frontal, inferior occipital, and inferior-posterior temporal regions were associated with higher seizure risk whereas patients with GBM in the medial and inferior-anterior temporal areas had significantly lower risk of developing seizures.⁵¹ One Class III study found that the incidence of postoperative seizures in patients with GBM was highest with frontal lobe lesions.³¹ Three other Class III studies supported the epileptogenic potential of both low- and high-grade gliomas located in the temporal and insular regions.^{34,52,53} In meningiomas, 1 Class II study and 1 Class III study found that a non-skull base tumor location was a significant risk factor for postoperative seizures.^{22,56}

In 2 Class III studies, extent of resection had an inconclusive impact on seizure occurrence.^{54,55} Gross total resection was a risk factor for early postoperative seizures (within the first week after surgery)⁵⁵ but subtotal resection and biopsy were also associated with seizures within the first 30 days of surgery.⁵⁴

Only Class III studies could be found to suggest an association between seizure occurrence and IDH mutation status,⁵⁵ tumor size/edema,⁵⁵ younger age,²⁹ male gender,²⁹ and leptomeningeal dissemination.³⁰

Conclusion

The evidence for tumor location as being an important factor for prescribing AEDs for primary seizure prophylaxis was limited to 2 Class II^{22,51} studies and 4 Class III studies.^{31,34,52,53} Different locations were identified as epileptogenic without answering the question how location should influence the use of prophylactic AEDs. Therefore, interpretation of these studies is limited. Based on 4 Class III studies,^{29,30,54,55} the current data do not support extent of resection, histology (primary vs. metastatic), grade, molecular pathology or imaging factors as predictors of seizure risk and, thus, these parameters also should not influence prophylactic anticonvulsant use. Recent updates in the WHO classification of brain tumors are not reflected in these prior studies but should be a focus of future research.

Recommendation

In patients with brain tumors who have not had seizures, there is insufficient evidence to support using tumor location, histology (primary vs. metastatic), grade, molecular features, or imaging characteristics when deciding whether or not to prescribe prophylactic AEDs (Level U).

SUMMARY

This document updates the 2000 AAN guideline “Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors”⁹ and extends it to questions related to selection of AEDs and the impact intrinsic tumor characteristics may have on seizure risk. The conclusions from this update confirm that prophylactic AED use in a brain tumor patient who has never had a seizure is not warranted. SNO and EANO approved these guidelines and the AAN affirmed the value of the guidelines.

The data for patients undergoing brain tumor surgery suggested that there may be no need to prescribe prophylactic AED treatment but the limited data were inconclusive. Several systematic reviews and meta-analyses have attempted to clarify the benefit of perioperative seizure prophylaxis.^{2,9,57-61} Given the limited number of randomized trials and lack of high level evidence on this topic, it is not surprising that the majority of these reviews were either unable to answer the underlying question⁵⁸ or did not see a benefit in prescribing AEDs.² The exception is one recent meta-analysis that found that peri-operative AED use might result in decreased short-term seizure occurrence but this was not seen in long-term prevention of seizures.⁵⁷ We noted a lack of literature evaluating newer surgical approaches such as motor mapping where there may be a higher risk of provoking seizures or awake craniotomies in which a seizure might result in urgent intubation and associated risks. Future guidelines would benefit from more Neurosurgeon input regarding peri-operative seizure management and these novel approaches.

Attempts to identify higher risk subpopulations were fraught with methodological limitations in the published evidence, so we were unable to pinpoint subpopulations based on tumor location or molecular features that might benefit from prophylactic AED treatment. While one study⁶ suggested seizures are more common in low-grade tumors, the data are insufficient to suggest *prophylactic* AED treatment is needed in these patients.

Based on the studies identified, choice of AED favored the newer generation of agents because of the side effect profile but efficacy seemed equivalent in preventing seizures and convincing data favoring valproic acid or levetiracetam as an anti-tumor agent were lacking. One important factor missing from the studies we identified was the pharmacology of the newer AEDs such as levetiracetam which may have less interaction with other medications. As non-enzyme inducing AEDs, there is limited interaction with other drugs and cancer therapies, in particular where dose is important for efficacy. Also, newer AEDs have less teratogenicity and less long-term impact on bone health.^{62,63}

The panel noted methodological weaknesses across studies that hindered the practice of evidence-based medicine, leading ultimately to a crucial lack in scientific evidence that has persisted since the previous AAN guideline. Very few randomized controlled trials were found and most were closed early before accruing the planned patient population.^{20,35,64} In addition, data from at least one more recent trial that was also terminated have not yet been published (NCT01432171: Lacosamide in Preventing Seizures in Participants With Malignant Glioma), highlighting the need for more definitive randomized trials. One particular methodical challenge was seizure ascertainment in retrospective studies, particularly the assessment of subclinical and partial seizures, resulting in a significant limitation as correctly identifying a seizure event is critical to understanding seizure frequency.

While substantive progress has been made to define patient populations by combining molecular markers with histopathology, there is no conclusive knowledge about how these new definitions might be applied to managing patients without seizures. Anti-seizure prophylaxis based on molecular findings or histology remains elusive and studies included here often documented contradictory findings.^{22,29,30,54,55} Thus, important clinical questions such as the impact of molecular markers on the risk of developing seizures cannot be answered at this point and need to be addressed by future studies.

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Figure 1: Literature search strategy.

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Pico Questions	Conclusion	Recommendation	Level of Evidence	Rating of Evidence	
PICO 1: In patients with newly diagnosed primary or metastatic brain tumors who have not already experienced a seizure: Does anticonvulsant prophylaxis compared to no anticonvulsant prophylaxis (a.) increase seizure-free survival and (b.) reduce the frequency of first seizures at 6 months from diagnosis	For patients with newly diagnosed brain tumors, anticonvulsant prophylaxis compared to no anticonvulsant prophylaxis is unlikely to be effective in increasing seizure-free survival and reducing the frequency of first seizures at 6 months from diagnosis.	In patients with newly diagnosed brain tumors who have not had a seizure, clinicians should not prescribe AEDs to reduce the risk of seizures.	Level A	II	Forsyth PA, et al. ²⁰
				II	Goldlust SA, et al. ²¹
				II	Skardelly M, et al. ²²
				III	Al-Dorzi HM, et al. ²³
				III	Ansari SF, et al. ²⁴
				III	Chaichana KL, et al. ²⁵
				III	de Oliveira JA, et al. ²⁶
				III	Garbossa D, et al. ²⁷
				III	Gokhale S, et al. ²⁸
				III	Lapointe S, et al. ²⁹
				III	Liang SL, et al. ³¹
				III	Lee MH, et al. ³⁰
III	Lwu S, et al. ³²				
III	Riva M, et al. ³³				
III	Wychowski T, et al. ³⁴				
PICO 2a: In patients with newly diagnosed primary or metastatic brain tumors who have not already experienced a seizure and who undergo a neurosurgical procedure (craniotomy or biopsy) for initial treatment or diagnosis of their tumor does perioperative anticonvulsant	For patients with newly diagnosed primary or metastatic brain tumors who never had a seizure and who undergo a neurosurgical procedure (craniotomy or biopsy) for initial treatment or diagnosis of their tumor, perioperative anticonvulsant prophylaxis is possibly	In patients with brain tumors who have never had a seizure and are undergoing surgery, there is insufficient evidence to recommend prescribing AEDs to reduce the risk of seizures in the peri- or postoperative period	Level C	III	Al-Dorzi HM, et al. ²³
				III	Lapointe S, et al. ²⁹
				III	Wychowski T et al. ³⁴

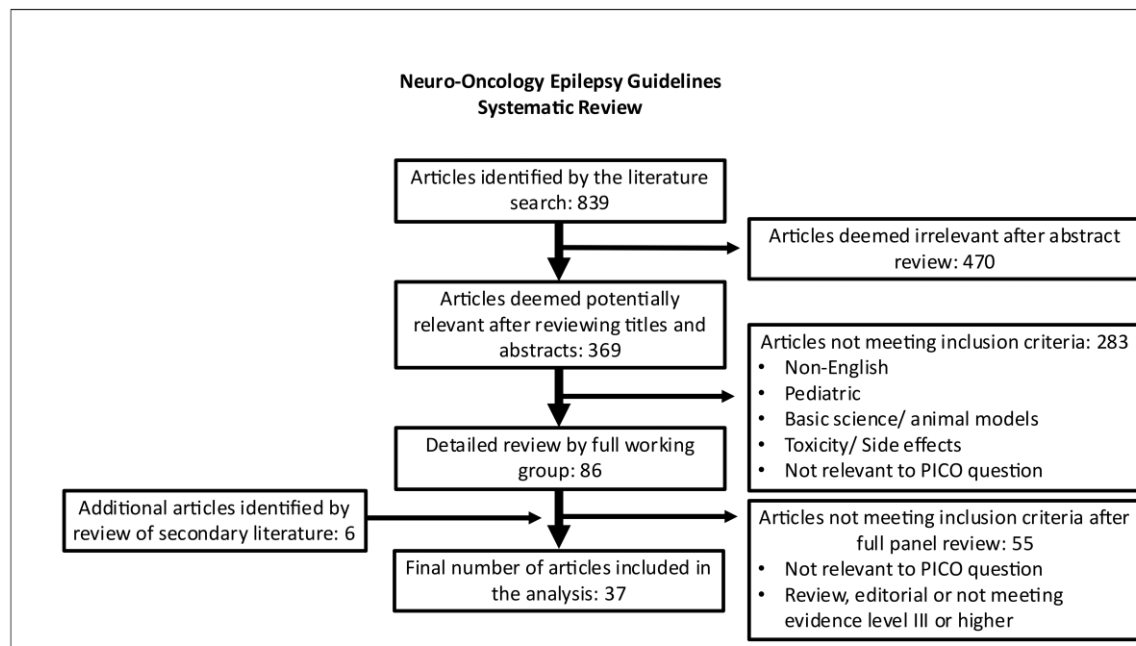
prophylaxis compared to no perioperative anticonvulsant prophylaxis prolong time to seizure occurrence	not effective in reducing seizures overall.				
PICO 3a: In patients with newly diagnosed primary or metastatic brain tumors, does treatment with valproic acid or other AEDs (either prophylactic or following a seizure) compared to treatment with any other anticonvulsant medication increase progression-free or overall survival.	While there is a lack of high-level evidence, in patients with newly diagnosed primary or metastatic brain tumors, treatment with valproic acid or levetiracetam does not appear to increase progression-free or overall survival. Use of valproic acid has also been associated with complications such as thrombocytopenia and hepatotoxicity.	In patients with newly diagnosed primary or metastatic brain tumors, there is insufficient evidence to support prescribing valproic acid or levetiracetam with the intent to prolong progression-free or overall survival	Level C	III	Happold C, et al. ³⁹
				III	Kerkhof M, et al. ⁴⁰
				III	Kim YH, et al. ⁴¹
				III	Redjal N, et al. ⁴²
				III	Tsai HC, et al. ⁴³
				III	Weller M, et al. ⁴⁴
PICO 2b: In patients with newly diagnosed primary or metastatic brain tumors who have not already experienced a seizure and who undergo a neurosurgical procedure (craniotomy or biopsy) for initial treatment or diagnosis of their tumor does perioperative anticonvulsant prophylaxis compared to	For patients with newly diagnosed primary or metastatic brain tumors who never had a seizure and who undergo a neurosurgical procedure (craniotomy or biopsy) for initial treatment or diagnosis of their tumor, perioperative anticonvulsant	In patients with brain tumors who have never had a seizure and are undergoing surgery, there is insufficient evidence to recommend prescribing AEDs to reduce the risk of seizures in the peri- or postoperative period	Level C	II	Wu et al. ³⁵
				III	Al-Dorzi HM, et al. ²³
				III	Lapointe S, et al. ²⁹
				III	Liang SL, et al. ³¹
				III	Lockney D et al. ³⁷
				III	Lwu S, et al. ³²
				III	Sughrue ME, et al. ³⁸
				III	Zachenhofer I et al. ³⁶

no perioperative anticonvulsant prophylaxis reduce the frequency of first seizure at 14 days following surgery	prophylaxis is possibly not effective in reducing seizures during the first 14 days following surgery.																									
PICO 3b: In patients with newly diagnosed primary or metastatic brain tumors, does treatment with a non-EIAED or more “modern” AED (either prophylactic or following a seizure) compared to treatment with an EIAED (either prophylactic or following a seizure) have a more favorable side effect profile.	The use of levetiracetam is well tolerated in patients with brain tumors. The prevention of early postoperative seizures, within 7 days of surgery, is comparable to previous trials with first generation AEDs. The use of valproic acid in brain tumor patients on chemotherapy may be associated with higher hematologic toxicities.	In patients with newly diagnosed primary or metastatic brain tumors, physicians may choose to prescribe levetiracetam rather than older AEDs to reduce side effects	Level C	<table border="1"> <tr><td>II</td><td>Iuchi T, et al.⁴⁶</td></tr> <tr><td>III</td><td>Gokhale S, et al.²⁸</td></tr> <tr><td>III</td><td>Iuchi T, et al.⁴⁷</td></tr> <tr><td>III</td><td>Lee YJ, et al.⁴⁸</td></tr> <tr><td>III</td><td>Merrell RT, et al.⁴⁹</td></tr> <tr><td>III</td><td>Milligan TA, et al.⁵⁰</td></tr> <tr><td>III</td><td>Weller M, et al.⁴⁴</td></tr> <tr><td>III</td><td>Wychoswski T et al.³⁴</td></tr> <tr><td>III</td><td>Zachenhofer I et al.³⁶</td></tr> </table>	II	Iuchi T, et al. ⁴⁶	III	Gokhale S, et al. ²⁸	III	Iuchi T, et al. ⁴⁷	III	Lee YJ, et al. ⁴⁸	III	Merrell RT, et al. ⁴⁹	III	Milligan TA, et al. ⁵⁰	III	Weller M, et al. ⁴⁴	III	Wychoswski T et al. ³⁴	III	Zachenhofer I et al. ³⁶				
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III	Wychoswski T et al. ³⁴																									
III	Zachenhofer I et al. ³⁶																									
PICO 4: In patients with newly diagnosed supratentorial primary or metastatic brain tumors who have not had a seizure, should aggressive tumor characteristics such as histology (primary vs. metastatic), grade, molecular pathology (e.g. O(6)-methylguanine-DNA methyltransferase promoter methylation, isocitrate	The current data do not support extent of resection, histology (primary vs. metastatic), grade, molecular pathology or imaging factors as predictors of seizure risk and, thus, these parameters also should not influence prophylactic anticonvulsant use.	In patients with brain tumors who have not had seizures, there is insufficient evidence to support using tumor location, histology (primary vs. metastatic), grade, molecular features, or imaging characteristics when deciding whether or not to prescribe prophylactic AEDs.	Level U	<table border="1"> <tr><td>II</td><td>Cayuela N, et al.⁵¹</td></tr> <tr><td>II</td><td>Skardelly M, et al.²²</td></tr> <tr><td>III</td><td>Das RR, et al.⁵²</td></tr> <tr><td>III</td><td>Lapointe S, et al.²⁹</td></tr> <tr><td>III</td><td>Lee JW, et al.⁵³</td></tr> <tr><td>III</td><td>Lee MH, et al.³⁰</td></tr> <tr><td>III</td><td>Liang SL, et al.³¹</td></tr> <tr><td>III</td><td>Oushy S, et al.⁵⁴</td></tr> <tr><td>III</td><td>Skardelly M, et al.⁵⁵</td></tr> <tr><td>III</td><td>Wirsching HG, et al.⁵⁶</td></tr> <tr><td>III</td><td>Wychoswski T et al.³⁴</td></tr> </table>	II	Cayuela N, et al. ⁵¹	II	Skardelly M, et al. ²²	III	Das RR, et al. ⁵²	III	Lapointe S, et al. ²⁹	III	Lee JW, et al. ⁵³	III	Lee MH, et al. ³⁰	III	Liang SL, et al. ³¹	III	Oushy S, et al. ⁵⁴	III	Skardelly M, et al. ⁵⁵	III	Wirsching HG, et al. ⁵⁶	III	Wychoswski T et al. ³⁴
II	Cayuela N, et al. ⁵¹																									
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III	Wychoswski T et al. ³⁴																									

dehydrogenase mutation (IDH), epidermal growth factor receptor amplification) or imaging (e.g. tumor location, number of tumors, edema, enhancement, vascularity) compared to tumors considered to be less aggressive, in less epileptogenic regions influence prophylactic anticonvulsant use.					
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Anti-epileptic drug – AED; Non-enzyme-inducing anti-epileptic drug – EIAED; Isocitrate dehydrogenase mutation – IDH

Figure 1



Accer