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TOPIC REVIEW

Levetiracetam for seizure prevention in brain tumor patients: a systematic review

Ziad Ghantous Nasr[1] · Bridget Paravattil[1] · Kyle John Wilby[1]

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Abstract Seizures are common complications for patients with brain tumors. No clear evidence exists regarding the use of antiepileptic agents for prophylactic use yet newer agents are being favoured in many clinical settings. The objective of this systematic review was to determine the efficacy of levetiracetam for preventing seizures in patients with brain tumors. A literature search was completed using the databases PubMed (1948 to December 2015), EMBASE (1980 to December 2015), Cochrane Database of Systematic Reviews, and Google Scholar. Studies were included if they reported seizure frequency data pertaining to levetiracetam use in patients with brain tumors as either monotherapy or as an add on agent. The literature search produced 21 articles (3 randomized controlled trials, seven prospective observational studies, and 11 retrospective observational studies). All studies were found to be at high risk of bias. Overall, studies show levetiracetam decreased seizure frequency in brain tumor patients with or without craniotomy. Safety outcomes were also favourable. As such, levetiracetam appears effective for reducing seizures in patients with brain tumors and may be considered a first-line agent. However, there is an urgent need for more high quality prospective data assessing levetiracetam and other antiepileptic drugs in this population.

Keywords Levetiracetam · Brain neoplasm · Brain tumor · Seizure · Anticonvulsant

✉ Kyle John Wilby
kjw@qu.edu.qa

[1] College of Pharmacy, Qatar University, PO Box 2713, Doha, Qatar

Introduction

Brain tumors are serious medical concerns that result in significant morbidity and mortality, as well as high utilization of healthcare systems [1]. There are many different types of brain tumors, including gliomas, astrocytomas, meningiomas, and metastases, among others [2]. Some of the most serious and devastating complications of brain tumors are seizures. Seizures occur in approximately 20–45 % of brain tumor patients resulting in significant morbidity and reduction in quality of life [3]. Therefore, effective seizure prophylaxis is required to ensure the best possible patient outcomes are achieved.

One of the most important factors influencing the use of antiepileptic drugs (AEDs) in these patients is craniotomy for tumor reduction or removal. The incidence of seizures is estimated to be 15–20 % for patients undergoing non-traumatic, supratentorial craniotomy [4]. Other factors that influence development of seizures and choices of agent include extent of tumor resection in craniotomy (complete or partial), previous history of seizures, tumor location, or rate of tumor growth [5].

The limited evidence available precludes development of clinical practice guidelines or consensus statements regarding the use and choice of AEDs for brain tumor patients. However, current clinical trends show newer AEDs becoming first-line options [5]. This is likely a result of greater adverse effect and drug interaction potential from other agents, such as phenytoin [6]. Levetiracetam (LEV) is one of these new AEDs and believed to modulate synaptic neurotransmitter release by binding synaptic vesicle protein SV2A in the brain [7]. It has advantages over older agents, such as low hepatic metabolism and better tolerability in terms of adverse effects. These properties result in decreased potential for drug interactions [8].

As such, these considerations make LEV a favourable AED for use among clinicians worldwide.

To date, there is no high quality systematic review or comprehensive summary of evidence assessing the role of LEV for brain tumor patients. One systematic review applied strict inclusion criteria and only included one study [9]. Additionally, a second identified more studies but did not address study quality or critically analyze results [10]. As LEV is rapidly becoming clinicians' first choice as an AED for these patients, a comprehensive and critical review is required to guide decision-making and further research aims. Therefore, our objective was to identify, summarize, and evaluate the literature pertaining to the efficacy and safety of LEV for preventing seizures in patients with brain tumors with or without planned craniotomy.

Methods

A literature search was completed using the databases PubMed (1948 to December 2015), EMBASE (1980 to December 2015), Cochrane Database of Systematic Reviews, and Google Scholar. The search terms employed for electronic database searching were "levetiracetam" OR "anticonvulsant" OR "keppra" OR "antiepileptic drug" combined with "brain tumor" OR "brain neoplasm," using AND to combine search term categories. The search was limited to studies in humans and those published in English. Manual searching of the reference lists of identified articles and review articles were also used to capture any records not accounted for in the electronic search. The search was completed by one investigator and repeated by a second.

Studies were included in the systematic review based on predefined inclusion criteria: randomized controlled trials (RTCs) or observational studies (prospective or retrospective) that reported seizure frequency data of LEV either as monotherapy or combination therapy with other agents in patients presenting with tumors or metastases in the brain. Studies were excluded if seizure frequency could not be extracted for LEV users, or if data reported was solely from case reports. Two investigators assessed each identified study for inclusion and resolved any discrepancies through discussion.

Data extracted included study design, population, interventions or procedures, outcomes, and findings related to the primary outcome of seizure frequency. Data was extracted by one investigator and verified by a second investigator. Data were also extracted for risk of bias assessments according to the Cochrane Collaboration's risk of bias assessment tool for RTCs [11]. Any study perceived to be at high risk of bias in any category was deemed to have an overall high risk of bias. Observational studies were assessed using the same tool, while accounting for design-specific biases within the 'other biases' category. Two investigators completed this independently. Any discrepancies were resolved through discussion.

Results

The literature search produced 2300 electronic hits and 12 hits from manual searching, as shown in Fig. 1. After title and abstract review, the full text versions of 44 articles were downloaded for review. After assessment against inclusion criteria, a total of 21 articles were included in the systematic review. Reasons for article exclusions are given in Fig. 1. The final included studies consisted of 3 RTCs [12–14], seven prospective observational studies [15–21], and 11 retrospective observational studies [22–32]. Characteristics and results from each included study are given in Tables 1 and 2.

Risk of bias assessments are given in Table 3. All studies were deemed to be at high risk of bias. Two of three RCTs were deemed to have adequate sequence generation, however all RCTs did not report adequate allocation concealment or blinding. Two of three RCTs reported complete outcome data. Other biases were largely unclear. The observational studies all scored as being at a high risk of bias. Prospective studies generally were at risk of attrition bias from incomplete outcome data. Both prospective and retrospective studies had an unclear risk of other biases, as confounding factors were not always evident or accounted for. A major point to consider is that observational studies may be confounded by interventions such as tumor

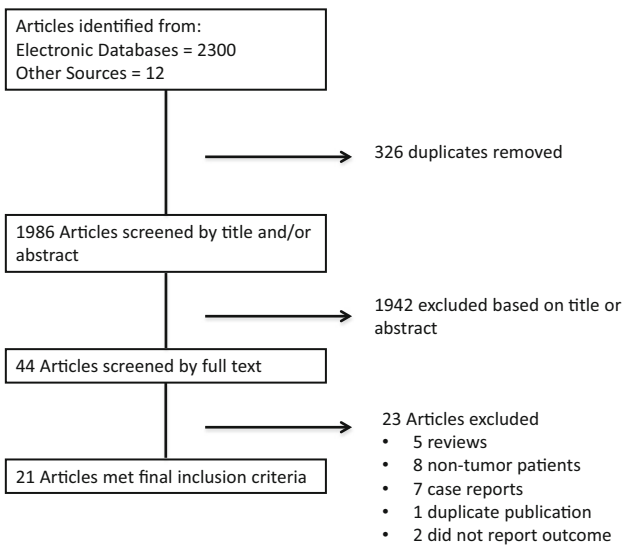

Fig. 1 Flow diagram for study selection and inclusion

Table 1 Study characteristics and results from randomized controlled trials

Study	Design	Population	Levetiracetam	Comparator	Outcomes	Results
Iuchi [13]	RCT, OL, SC	Adults ≥16 years with supratentorial tumors requiring craniotomy; adequate renal and hepatic function (n = 146)	500 mg rectally every 12 h after induction general anesthesia until oral intake available. Continued until post-op day 7 (n = 73)	Fosphenytoin 15–18 mg/kg IV after induction general anesthesia and then continued at 5–7.5 mg/kg/day until oral intake available. Then, phenytoin 250 mg/day orally until post-op day 7 (n = 73)	Seizure Occurrence of side effects	Seizure incidence 1.4 % (LEV) vs. 15.1 % (PHT) ($p < 0.005$) [OR 12.77, 95 % CI 2.39–236.71), $p = 0.001$] No difference in ADRs but PHT withdrawn due to ADR in five patients vs. 0 with LEV
Rossetti [14]	Phase II RCT, OL, MC	Adults >18 years with primary brain tumor (WHO grade II-IV) with ≥1 previous seizure and potential need for chemotherapy (n = 52)	LEV at increasing doses up to 3000 mg (initial 500 mg) in intervals of at least 24 h (n = 25)	PGB at increasing doses up to 600 mg (initial 150 mg) in intervals of at least 24 h (n = 27)	Composite: Status epilepticus, 2 seizures with consciousness impairment, need to interrupt study drug, need to add additional drug Seizure free from enrolment to last follow up Mortality	Composite met in 9 (36 %) of LEV and 12 (44 %) of PGB patients. Mostly due to need to interrupt study drug 17 (65 %) of LEV and 18 (75 %) of PGB patients remained seizure free throughout study Mortality occurred in 7 (28 %) of LEV and 5 (19 %) PGB patients.
Lim [12]	RCT	N = 29 patients (>18 years old) with supratentorial glioma with seizure history taking PHT monotherapy for prophylaxis. Patients stratified based on craniotomy. 6 month follow up period (n = 29)	Initiate LEV therapy within 24 h of surgery or continue PHT therapy. LEV dosed at 1000 mg twice daily within 24 h of surgery with phenytoin tapered off over 3 days (n = 20)	Those continuing PHT had levels confirmed between 10 and 20 mg/dl by post-op day 1 (n = 9)	Proportion of patients seizure free after 6 months ADRs	13/15 (87 %) of those switched to LEV vs. 6/8 (75 %) those maintained on PHT remained seizure free at 6 months More patients in PHT group experienced coordination difficulties

RCT randomized controlled trial, *OL* open label, *SC* single center, *IV* intravenous, *LEV* levetiracetam, *PHT* phenytoin, *OR* odds ratio, *ADR* adverse drug reaction, *MC* multi center, *PGB* pregabalin

reduction or removal and the typical decline in seizure activity over time after craniotomy.

Data from randomized controlled trials

Three RTCs were identified that assessed efficacy and safety of LEV in the target population. In 2009, Lim et al. reported results from a phase II pilot study assessing the feasibility of switching patients from phenytoin (PHT) to LEV monotherapy following craniotomy for glioma-related seizure control [12]. A total of 29 patients were randomized in a 2:1 fashion (LEV:PHT) and followed for 6 months. Upon follow up, data was only available for 15/20 patients in the LEV group and 8/9 in the PHT group. Of these patients, 13/15 (87 %) receiving LEV and 6/8 (75 %) receiving PHT remained seizure free at 6 months. Adverse effects were similar between groups, with coordination difficulties reported more commonly in the PHT group.

Table 2 Study characteristics and results from observational trials

Study	Design	Population	Procedures	Outcomes	Main Findings
Bahr [15]	Prospective, OL, single-arm cohort	Patients >18 years with suspected primary brain tumor with ≥1 tumor-related seizure undergoing neurosurgery (n = 30)	Initial oral LEV dose of 500 mg twice daily escalated to 1000 mg twice daily after 72 h. If further seizures, dose increased up to 1500 mg twice daily. Treatment received up to 4 weeks in advance of surgery. On the day of surgery, patients received an oral dose in the morning and IV dose in evening and until oral doses could be resumed. Patients were followed for seizure activity for 4 weeks	Seizure occurrence before surgery, within 48 h of surgery, and from 48 h to 4 weeks post-surgery	N = 25 patients fully evaluable. 25/25 (100 %) were seizure free in pre-surgery phase (3 days to 4 weeks), 22/25 (88 %) in 48 h post-surgery phase, and 21/25 (84 %) in 48 h to 4 week phase
Maschio [18]	Prospective cohort	Patients >18 years with tumor-related epilepsy characterized by simple or complex partial seizures and at least two seizures per month prior to referral (n = 29)	Patients started on LEV monotherapy (250 mg twice daily) or converted from other AED to LEV monotherapy and escalated to 1000–3000 mg LEV per day. Other AEDs were tapered over 3 weeks. Patients followed for 1 year	Seizure occurrence	N = 15 patients fully evaluable at 12 month follow up. 1 (6.7 %) had seizure frequency reduction of ≥50 % and 14/15 (93.3 %) were seizure free. Before after comparisons were significant ($p < 0.001$). For the ITT population (n = 29), 21 (72.4 %) were seizure free, 7 (24.1 %) had seizure frequency reduction of ≥50 %, and 1 (3.5 %) had stationary seizure frequency over a mean duration of 8.6 months. Before and after testing in the ITT population was significant ($p < 0.001$)
Maschio [21]	Prospective cohort	Patients with brain metastases and seizures within 1 month prior to study period (n = 30 evaluable patients)	Patients received one of LEV, oxcarbazepine, or topiramate at first visit according to usual clinical practice. Six patients took LEV (500 mg twice daily up to 3000 mg per day), 16 patients took oxcarbazepine (300 mg twice daily up to 1800 mg per day), and 8 patients took topiramate (25 mg twice daily up to 300 mg daily). Patients followed until death	Seizure frequency before and after starting AED	Mean duration follow up was 6.1 months All groups had significant change in mean monthly seizure frequency: LEV 12.2 ± 21.73 SD before vs. 5.33 ± 12.1 SD after, $p = 0.027$ Oxcarbazepine: 5.69 ± 8.19 SD before vs. 0.43 ± 0.93 SD after, $p = 0.003$ Topiramate: 3.75 ± 3.24 SD before vs. 0.08 ± 0.24 SD after, $p = 0.011$

Table 2 continued

Study	Design	Population	Procedures	Outcomes	Main Findings
Rosati [17]	Prospective cohort	Patients with a first diagnosis of glioma and seizures who were not taking AEDs at time of first encounter (n = 176)	Patients underwent screening to determine seizure status and were diagnosed with epilepsy if (1) recurrent seizures with or without interictal epileptiform abnormalities, (2) single focal or convulsive seizure in presence of interictal epileptiform abnormalities, (3) single convulsive seizure and history of episodes suggestive of focal seizures with or without interictal epileptiform abnormalities, or (4) seizures occurring for the first time during follow up with or without interictal epileptiform abnormalities. These patients (n = 82) were treated with LEV started at 250 or 500 mg twice daily and increased up to 3000 or 4000 mg per day	Seizure frequency	Mean follow up time of 13.1 months At last evaluation, 75/82 (91 %) of patients treated with LEV were seizure free (2 of these patients had LEV withdrawn due to ADRs and treated with alternative agents). 9/82 (11 %) of treated patients required dose of 4000 mg/day to become seizure free
Usery [16]	Prospective OL cohort	Patients ≥18 years with a diagnosis of a brain tumor that was operable and a history of at least 1 witnessed seizure (n = 20)	Seizure frequency assessed at baseline from 1-month prior to study enrolment. Patients initiated or converted to LEV monotherapy with all other agents discontinued before surgery. Those previously untreated with LEV given 500 mg IV LEV twice daily within 6 h of surgery for at least 48 h. Patients receiving prior to surgery received same preoperative regimen as above. Doses titrated based on response and seizure frequency to max 3000 mg/day. Oral conversion occurred after 48 h of IV therapy. Patients were followed for 4 weeks	Seizure frequency	12 patients completed 4 week follow up. 11/12 (91.7 %) achieved ≥50 % reduction in seizure activity and 10/12 (83 %) achieved seizure freedom

Table 2 continued

Study	Design	Population	Procedures	Outcomes	Main Findings
Maschio [19]	Prospective cohort	N = 19 patients (>18 years old) with brain tumor-related epilepsy being treated with AEDs other than LEV with daily monthly seizure frequency	LEV 1000 mg/day (titrated to max 3000 mg/day) added to AED treatment regimen in all patients. Therapeutic drug monitoring occurred for other baseline agents. Patients followed for mean 25 months (range 7–50)	Seizure frequency	At last follow up, 9 (47.4 %) patients were seizure free (7 to 33 months). Five (25 %) patients reported improvement with daily to weekly (n = 1), daily to monthly (n = 1), or weekly to monthly (n = 3). Four (21 %) patients did not improve or worsen and 1 (5.2 %) patient worsened from monthly to weekly
Wagner [20]	Prospective cohort	N = 26 patients with primary brain tumors with persisting seizures, ADRs of other AEDs and/or potential for drug interactions	LEV given at dose of 2000 mg/day for patients with potential drug interactions and no seizures. LEV was raised to 3000–4000 mg/day in presence of seizures. Median follow up time was 9.3 months	Seizure frequency	In 20 patients with persisting seizures, a reduction of >50 % was found in 13 (65 %) over a mean period of 11.8 months. Four of these patients became seizure free. The other 6 patients received LEV for other indications
Garbossa [22]	Retrospective cohort, MC	N = 91 patients with newly diagnosed and untreated supratentorial high-grade gliomas without seizures. Patients must have had total or subtotal resection of the tumor	Group A (n = 43): Received LEV 1000 mg/day for 3–5 days pre-surgery and up to 6 months post-surgery. Dose increased to 2000 mg/day if seizures occurred Group B (n = 48): Did not receive prophylactic AED	Occurrence of seizures at 1, 3 and 6 months post-surgery	Seizure occurrence 1 month: Group A: 1 (2.3 %) Group B: 0 (0 %) 3 months: Group A: 5 (13.9 %) Group B: 3 (6.2 %) 6 months: Group A: 2 (18.5 %) Group B: 6 (18.75 %) LEV use not predictor of seizure occurrence (OR 0.869, p = 0.818)
Lee [23]	Retrospective cohort	N = 282 patients with supratentorial tumors treated with LEV or VPA as monotherapy prior to craniotomy and were followed 1 month after surgery	VPA (n = 231): 600 mg IV VPA infused over 12 h 1 day prior to surgery and then continued for 24 h (50 mg/h) on day of surgery. Postoperatively, VPA given as 600 mg orally twice daily and then adjusted using therapeutic drug monitoring LEV (n = 51): Infusion of 500 mg/12 h given 1 day prior to surgery and day of surgery. Postoperatively, LEV 500 mg orally twice daily and increased to maximum of 3000 mg/day	Seizure occurrence at 1 month	Total postoperative seizures: LEV: 4 (7.8 %) VPA: 15 (6.5 %) (p = 0.728) Majority of seizures occurred in first 0–7 days post-surgery

Table 2 continued

Study	Design	Population	Procedures	Outcomes	Main Findings
Kerkhof [24]	Retrospective cohort	N = 291 patients with glioblastoma multiforme following biopsy or surgical resection. N = 181 of these patients had epilepsy	Most commonly prescribed first AED was VPA (n = 100), then LEV (n = 37), and other (n = 8). N = 59 patients needed no change in AED therapy choice. In 49 patients LEV was added to VPA, VPA discontinued in 10 and LEV given as an alternative	Seizure frequency in patients followed for 6 months	Initial seizure freedom achieved in 41/100 (41 %) on VPA, 16/37 (43.3 %) on LEV, and 89/116 (76.7 %) on subsequent VPA/LEV combination At end of follow up (median, 9 months), freedom of seizures achieved in 28/36 (77.8 %) on VPA, 25/36 (69.5 %) on LEV, and 38/63 (60.3 %) on VPA/LEV combination
Kern [25]	Retrospective cohort	N = 235 patients without seizures given prophylactic AED on day of and after craniotomy for intracranial tumors	N = 154 given PHT infused 750 mg for 1 h before entering operating room and then continued for 24 h (30 mg/h). On day after surgery, PHT 100 mg IV three times daily. On day 2 after surgery, PHT 50 mg IV or orally three times daily. On day 3 after surgery, PHT 50 mg twice daily and on day 4 50 mg of PHT given once N = 81 given LEV 1000 mg before entering operating room and again after surgery. On day after surgery, LEV 1000 mg IV twice daily. On day 2 after surgery, LEV 500 mg IV or orally given twice daily. On days 3 and 4, LEV 500 mg orally given once	Seizures within 7 days of craniotomy	Seizures occurred in 7 (4.5 %) of PHT patients and 2 (2.5 %) of LEV patients (p = 0.66)
Zachenhofer [26]	Retrospective cohort	N = 78 patients with supratentorial brain tumors given peri-operative treatment with LEV as monotherapy whether or not presenting with seizures. Time between hospital admission and 7 days after operation defined as perioperative period	LEV given 1000–1500 mg perioperatively and could be increased up to 3000 mg/day. LEV started 1–7 days preoperatively. If no seizures before or after surgery, LEV tapered 1 week after surgery. If new or withdrawal seizures occurred, LEV continued. In those initially presenting with seizures or newly developed seizures, LEV continued till follow up 3 months post-surgery	Seizure occurrence	Preoperatively: 30 (38.5 %) had experienced seizures but no seizures in any patient receiving LEV 1000–3000 mg daily Postoperatively: 7 (9.0 %) Within 1 week: 2 (2.6 %) Late (mean 10.5 months): 5 (6.4 %)

Table 2 continued

Study	Design	Population	Procedures	Outcomes	Main Findings
Chaichana [31]	Retrospective cohort	N = 648 adult patients undergoing primary resection of a supratentorial malignant astrocytoma with (n = 153) or without (n = 495) pre-operative seizures	No defined standard for use of AEDs Of 153 patients presenting with seizures, 88 % given AED. 42 (27 %) given combination therapy, 102 (67 %) PHT, 13 (8 %) LEV, 12 (8 %) divalproex, 5 (3 %) CBZ, 7 (5 %) VPA, 4 (3 %) lamotrigine, and 3 (2 %) phenobarbital Of 495 patients presenting without seizures, 51 (10 %) given AED. N = 36 (PHT), 6 (LEV), 5 (divalproex), 3 (CBZ), and 1 (VPA) Patients followed for 12 months	AED comparisons for seizure frequency	No differences existed between AED drug regimens
van Breeman [32]	Retrospective cohort	N = 140 patients with brain tumors (n = 99 developed seizures during course of disease)	VPA most common 1st line therapy (80.1 %) followed by CBZ (12.1 %). LEV most common 2nd line (65.1 % of 1st line patients needing 2nd line therapy). Two agent combination therapy also used, if needed	Seizure frequency	Combination of VPA and LEV showed highest response with 81.5 % decline in seizure frequency and 59 % becoming seizure free Seizure freedom occurred in 31 % of patients receiving LEV without VPA ± other AEDs
Milligan [27]	Retrospective cohort	Patients without seizures but with brain tumors who underwent supratentorial neurosurgery and had at least 7 day follow up (n = 105 LEV monotherapy, n = 210 PHT monotherapy)	All records of patients receiving LEV between Jan 1999 and Dec 2004) were reviewed and compared to a group of patients receiving PHT (2:1 LEV) identified by taking every 10th patient on PHT during study dates	Seizure frequency	Prior to surgery, 33 patients on LEV and 45 patients on PHT had experienced seizure 7 day follow up showed 1/105 (1.0 %) LEV patients had seizure vs. 9/210 (4.3 %) PHT patients (p = 0.17) 30 day follow up showed 1.9 % LEV patients had seizure vs. 5.2 % PHT patients (p = 0.23) 12 month follow up showed 26 % LEV patients developed epilepsy vs. 36 % PHT patients (p = 0.34)

Table 2 continued

Study	Design	Population	Procedures	Outcomes	Main Findings
Newton [29]	Retrospective cohort	N = 13 patients with metastatic brain tumors receiving LEV for seizure control and had at least 1 follow up visit after receiving LEV (median 15 month follow up)	LEV used as add on agent in 7 (54 %) of patients and as monotherapy in 6 (46 %) of patients (median dose 1000 mg/day)	Seizure frequency	Baseline frequency was one event every other day After LEV initiation, median seizure frequency = 0 per week (range 0–2 per month). 100 % of patients reduced seizure frequency to less than 50 % baseline (p = 0.0002) and 10 (77 %) patients had complete seizure control
Newton [30]	Retrospective cohort	N = 41 patients with brain tumors that received LEV for seizure control with at least 4 week follow up	LEV used as add on in 33 (80 %) of patients and as monotherapy in 8 (20 %) patients (median dose of 1500 mg/day)	Seizure frequency	Prior to LEV therapy, median frequency was 1 per week with range from 20 per day to 1 per month After LEV initiation, median seizure frequency = 0 per week. 90 % had frequency reduced to <50 % baseline (p < 0.0001) and 59 % had complete seizure control. two patients (5 %) had an increase in seizure frequency (both patients on concomitant PHT)
Gokhale [28]	Retrospective cohort	N = 165 adult patients undergoing brain tumor surgery at higher risk of seizures (pre-operative seizure, supratentorial meningioma, supratentorial low grade glioma)	LEV given in dose of 1000–3000 mg/day in immediate postoperative period	Seizure frequency	12/165 (7.3 %) patients developed seizures within 7 days post-op

OL open label, *LEV* levetiracetam, *IV* intravenous, *ITT* intention to treat, *AED* antiepileptic drug, *SD* = standard deviation, *ADR* adverse drug reaction, *MC* multi center, *VPA* valproic acid, *PHT* phenytoin, *CBZ* carbamazepine

A second study evaluated LEV versus PHT during and after craniotomy for brain tumors (glioma, metastasis, meningioma, others) [13]. A total of 147 patients were randomized to receive LEV (n = 74) or PHT (n = 73) until postoperative day 7. The primary outcome was occurrence of seizures. No seizures occurred in any patient during surgery. Twelve patients developed seizures after surgery (1.4 % of those taking LEV vs. 15.1 % of those taking PHT, p = 0.005). However, due to the small sample size and seizure frequency, the odds ratio of postoperative seizures with LEV versus PHT was difficult to interpret [OR 12.77, 95 % CI 2.39–236.71]. Therapy was withdrawn due to adverse events in 5 (6.8 %) of PHT patients yet none of the LEV patients.

The third RCT evaluated LEV against pregabalin monotherapy in patients with gliomas [14]. Patients were eligible if they had at least one previous seizure and were randomized to receive either LEV (n = 25) or pregabalin (n = 27). The primary endpoint was survival free of a composite endpoint that included status epilepticus, 2 seizures with impaired consciousness, need of a second agent, or need to discontinue study drug. At 1 year follow up, 9/25 (36 %) of those taking LEV and 12/27 (44 %) of those taking pregabalin failed therapy. The composite endpoint was driven by the need to interrupt study drug (7/9 in LEV group and 7/12 in pregabalin group) and this was mostly due to adverse effects.

Data from prospective observational studies

Seven prospective observational studies were identified that reported seizure frequency as an outcome with LEV

Table 3 Risk of bias assessments for identified studies

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other biases	Overall
Iuchi [13]	Low	Unclear	High	Low	Low	Unclear	High
Rossetti [14]	Low	Unclear	High	Low	Low	Unclear	High
Lim [12]	Unclear	Unclear	High	High	Low	Unclear	High
Bahr [5]	High	High	High	High	Low	Unclear	High
Maschio [18]	High	High	High	High	Low	Unclear	High
Maschio [21]	High	High	High	High	Low	Unclear	High
Rosati [17]	High	High	High	Low	Low	Unclear	High
Usery [16]	High	High	High	Low	Low	Unclear	High
Maschio [19]	High	High	High	Low	Low	Unclear	High
Wagner [20]	High	High	High	Low	Unclear	Unclear	High
Garbossa [22]	High	High	High	Low	Low	Unclear	High
Lee [23]	High	High	High	Low	Low	Unclear	High
Kerkhof [24]	High	High	High	Low	Unclear	Unclear	High
Kern [25]	High	High	High	Low	Unclear	Unclear	High
Zachenhofer [26]	High	High	High	Low	Low	Unclear	High
Chaichana [31]	High	High	High	Low	Low	Unclear	High
van Breeman [32]	High	High	High	Low	Unclear	Unclear	High
Milligan [27]	High	High	High	Low	Low	Unclear	High
Newton [29]	High	High	High	Low	Low	Unclear	High
Newton [30]	High	High	High	Low	Low	Unclear	High
Gokhale [28]	High	High	High	Low	Unclear	Unclear	High

therapy. Six studies included comparisons between baseline and follow up seizure frequencies. Six studies reported data for up to 30 patients, while one study enrolled 176 patients (Table 2).

Studies reporting outcomes from prospective observational studies before and/or after surgical procedures

Bahr et al. enrolled 30 brain tumor patients with at least one seizure and planned neurosurgery (resection or biopsy) in a single-arm prospective study [15]. Patients received oral LEV up to 4 weeks before surgery and then IV LEV (with step down to oral therapy when indicated) for up to 4 weeks after surgery. A total of 25 patients were fully evaluable with 100 % having no seizures during pre-surgical phase, 88 % in the 48 h period post-surgery phase, and 84 % between 48 h post-surgery up to 4 weeks. No major safety concerns were noted.

Usery et al. enrolled 17 patients with operable brain tumors and a history of at least one witnessed seizure [16]. Patients were continued, converted to, or started on LEV monotherapy within 6 h following surgery for up to a minimum of 48 h. Patients had an average of 3.5 (range 1–22) seizures preoperatively. Post-operatively 16/17 (94.1 %) of patients had complete seizure control while in hospital and 11/12 (91.7 %) post-discharge. Five patients were lost to follow up and no outcome data post-discharge was available.

Rosati et al. evaluated seizure outcomes in 176 patients with glioma presenting to a neurosurgery clinic for follow up procedures [17]. Of the 176 patients, 82 had been diagnosed as having epilepsy with durations ranging from 13 months to 4.2 years. After mean follow up of 13.1 months (range 10 months to 2.9 years), 75 of 82 patients (91 %) were seizure free. Seventy-three of these patients were taking LEV. In patients experiencing recurrent seizures, dosage increases of LEV were given to achieve seizure relief. Only transient somnolence was documented as an adverse effect in four patients.

Studies reporting outcomes from prospective observational studies without clear surgical intervention for all patients

Maschio et al. completed a prospective case series of 29 patients with brain tumors referred to a specialized tumor-related epilepsy center with at least two seizures per month [18]. All patients were initiated or converted to LEV monotherapy and followed for 12 months of follow up. At

12 months, 15 evaluable patients remained with 1 having ≥50 % reduction in seizure frequency and 14 (93.3 %) remaining seizure free. An intention-to-treat population (n = 29, mean follow-up of 8.6 months) analysis found 21 patients seizure free (72.4 %), 7 (24.1 %) patients with ≥50 % reduction in seizure frequency and 1 (3.5 %) with stable seizure frequency. One patient developed a side effect (restlessness) that warranted discontinuation of LEV therapy.

Maschio et al. reported results from a prospective cohort assessing 19 patients with brain tumors and seizures [19]. At baseline, patients were experiencing seizures at daily to monthly frequencies. LEV was added to AED regimens in all patients and median follow up occurred over 20 months (range 7–50). At the end of follow up, 9 (47.4 %) of patients were seizure free (seizure free period range 7–33 months), 5 (25 %) reported improvement from daily to weekly. Seizure frequency did not change in 4 (21 %) of the patients and increased in 1 patient. No adverse effects related to LEV were noted.

Wagner et al. reported results from a study assessing the efficacy of LEV in 26 patients with primary brain tumors who had persisting seizures, adverse effects from other AEDs, and/or potential drug interactions with chemotherapy regimens [20]. LEV was added as combination therapy in 25 patients. For 20 patients with persisting seizures, ≥50 % reduction in seizure frequency was achieved in 13 (65 %) of patients over a mean follow up period of 11.8 months. Four of these patients became completely seizure free. The remaining 6 patients using LEV for indications of adverse effects from other agents or drug interactions became seizure free at the end of follow up. Adverse effects occurred in 9 (35 %) of the patients and most frequently were fatigue, somnolence, and dizziness.

Studies reporting outcomes from prospective observations studies assessing patients with brain metastases

Maschio et al. completed a prospective observational study of 48 patients with seizures related to brain metastases but only 30 returned to study site and had outcome data available [21]. At first visit, patients received LEV (n = 6), oxcarbazepine (n = 16), or topiramate (n = 8) according to usual practices and then followed until death (mean duration of follow up was 6.1 months). Baseline mean seizure frequency in the LEV group was 12.2 (±21.73 SD) and was reduced to 5.33 (±12.1 SD) at the last visit preceding patient's death (p = 0.027). The oxcarbazepine and topiramate groups also had significant reductions in seizure frequencies. No severe adverse effects were noted. In the LEV group, 1 patient experienced rash and 1 patient experienced restlessness.

Data from retrospective observational studies

Eleven retrospective studies were identified that reported seizure frequency associated with LEV therapy [22–32]. Study data and results are given in Table 2.

Data from studies assessing LEV use in patients undergoing surgical tumor resection or biopsy was generally in favor of LEV as a first-line agent. Seven studies directly assessed surgical outcomes [22–28]. Two studies found no differences between LEV and PHT in terms of seizure frequency post-surgery [25, 27]. One study found similar post-surgical seizure rates between LEV and valproic acid [23], while another reported the combination of these two agents to be highly effective (although no statistical comparisons were completed) [24]. In high-risk patients undergoing surgery (pre-existing seizures, supratentorial meningioma, supratentorial low grade glioma), one study reported a 7-day post surgical seizure rate of 7.3 % associated with LEV use [28]. Finally, two studies assessed LEV use in patients with no planned surgical interventions and found statistically significant reductions in seizure frequency after LEV initiation [29, 30].

Reporting of safety outcomes was variable. One study showed significant reductions in adverse effect rates with LEV when compared to valproic acid [23]. Additionally, another study reported significant decreases in adverse effects requiring discontinuation of therapy with LEV versus PHT [27]. Finally, two studies reported the most common adverse effect with LEV to be somnolence, which was deemed to be mild and occurred in 23–37 % of patients [29, 30].

Discussion

This systematic review identified 21 studies that reported seizure frequency outcomes associated with LEV use in patients with brain tumors. The data obtained from RCTs is encouraging but must be interpreted cautiously. However, this is the best evidence available to date and interpretations can guide clinical decision-making. The study by Iuchi et al. provides strong evidence that LEV is likely effective and safe up to 7 days post-craniotomy, as compared to PHT [13]. The study was limited by sample size and outcome frequency (as demonstrated by the very wide confidence interval) and so conclusions regarding better efficacy compared to PHT are only speculative. Subsequent studies should include a longer follow up duration (6 months to 1 year) to better assess the long-term efficacy and safety of LEV. The two other smaller RCTs demonstrated that LEV was no worse than study comparators, although data should be considered preliminary only [12,

14]. Outcome rates across all RCTs differed greatly, suggesting high heterogeneity between study settings, populations, and designs.

While observational studies are prone to bias and confounding, both the prospective and retrospective studies reported efficacy outcomes in favour of LEV. Although positive, these finding must be interpreted cautiously as it is possible that confounders such as tumor reduction or removal and decreases in seizure activity over time may have influenced results in favour of LEV. Therefore, long-term benefits of LEV in this population are still unknown.

No major safety concerns were noted across all studies. The most common adverse effect noted was somnolence and was typically mild in nature. Discontinuations due to LEV adverse effects were uncommon, especially when compared to studies reporting the same outcome with PHT and valproic acid [12, 13, 23, 27]. These findings are not surprising, as it is well known that LEV is better tolerated than other, older agents [8].

Practice implications of our findings are relevant to the use of newer AEDs such as LEV for seizure prophylaxis in brain tumor patients, as compared to older, traditional agents. Consensus statements and clinical practice guidelines should consider the evidence presented in this review to direct future decision-making. Specifically, LEV was found to be a suitable therapeutic alternative in terms of efficacy, as compared to other agents. Additionally, enhanced tolerability and lack of drug interactions and need for therapeutic drug monitoring support its use as a valid option for these patients.

The major limitation of this review was the poor quality of identified studies. Every article was found to be at a high risk of bias. This was not surprising, due to the challenges designing studies in this population in terms of obtaining enough patients for adequate power and highly individualized nature of treatments and medication responses. Future studies can limit bias by adhering to good randomization, allocation concealment, and blinding principles. Additionally, prospective observational studies can make greater attempts to avoid attrition bias.

Conclusions

Efficacy data reviewed for LEV supports its use as a first line agent for patients with brain tumors. No worsening efficacy was noted against any other agent and seizure frequencies were commonly reduced with its use. This conclusion is supported by clear benefits in safety outcomes with LEV versus other agents. A future well-designed RCT or prospective observational study is warranted to further evaluate the role of LEV and other AEDs in brain tumor patients despite difficulties and limitations proposed by the disease/population. Finally, clinicians caring for patients with brain tumors should use the evidence presented in this review, along with strict patient monitoring and reassessment, to optimize seizure prophylaxis therapy and achieve the best possible patient outcomes.

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Compliance with ethical standards

Conflict of Interest All authors report no conflicts of interest.

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