Phase II Trial of Seizure Prophylaxis in Brain Tumor Patients Undergoing Neurosurgical Procedure

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Investigator:

Lead Investigator: Claudia Pamanes

Mentors: Annick Desjardins, MD, FRCPC

Co-authors (if known):

Biostatistician(s): Beiyu Liu

Supervising Biostatistician: Sin-Ho Jung

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1. Study Overview

Seizures are a debilitating complication of brain tumors. Aberrant and repetitive neuronal firing leads to the generation of seizures. Approximately 75% of patients with low-grade tumors and 25% with high-grade tumors suffer from seizures compared to 0.5-1% of the general population. Slower growing, low-grade tumors are associated with higher epileptogenicity, while faster-growing, high-grade tumors are associated with seizures secondary to mass effect. Higher seizure frequency has been associated with reduced cognitive function and Health-Related Quality of Life (HRQOL) and strips patients of driving privileges for 6 months on average in the US, thus affecting daily functional activities of living. While surgery can be potentially curative of tumor-related seizures by resecting the nidus of seizure activity, it could also cause seizures due to irritation of the cortex, hemorrhage at the surgical site, and cerebral hypoxia and acidosis during surgery.

The current guidelines recommend against peri-operative seizure prophylaxis in patients who have never had a seizure, and to taper Anti-Epileptic Drug (AED) therapy after the first post-procedure week. However, these guidelines were based on older generation AEDs [(Phenytoin (PHT), Phenobarbitol (PBT), and Valproic Acid (VPA)] that were associated with significant side effects and drug-drug interactions. Since these guidelines were published in 2000 and reaffirmed in 2003 and 2008, newer generation AEDs have emerged with more favorable side effect profiles. Lacosamide (LCM), a third-generation AED, and Levetiracetam (LEV), a second-generation AED, are both well tolerated with unique mechanisms of action.

Given the reduced risk of adverse event occurrence with newer AEDs, the clinical use of AEDs as prophylaxis has increased; however, there have been no updated guidelines and there is a lack of clinical trial data to reflect this practice. LCM is US Food and Drug Administration (FDA) approved as adjunctive and monotherapy for partial-onset seizures and LEV is approved as adjunctive therapy. Their promising roles in brain tumor patients continue to be explored.

2. Primary Objectives:

To assess the impact of LCM, LEV, or no AED in patients with suspected glioma (WHO Gr I-IV) or brain metastasis on ED visits and readmissions within 30 days of maximum safe resection (MSR).

3. Secondary Objectives:

1. Assess the safety and tolerability profile of LCM and LEV.
2. Describe the duration of admission stays among patients treated prophylactically with LCM, LEV, or no AED.
3. Describe the number of provider communications (email, telephone, or additional clinical visits) among patients treated prophylactically with LCM, LEV, or no AED
4. Describe the usage of intraoperative AED
5. Describe the frequency of changes in AED dosage, type of AED, addition or discontinuation of AED
6. Assess the impact of LCM, LEV, or no AED on post-procedure seizure occurrence

4. Study Design & Procedures:

The protocol assessed the need for AED prophylaxis during the post-procedure period in patients undergoing MSR for a suspected diagnosis of glioma (WHO grade I-IV) or brain metastasis. There will be three arms to the study – patients were randomized to LCM, LEV, or control (no AED). The AED can be initiated anytime within 48 hours before an MSR incision. Subjects were followed for seizure-related healthcare encounters. Adverse events were collected and recorded for the first 30 days post-procedure.

5. Study Population:

Inclusion criteria

1. Patients with a suspected diagnosis of new, recurrent, or transformed glioma (WHO grade I-IV) or brain metastasis scheduled for MSR at DUMC;
2. Safe for surgery per treating neurosurgeon;
3. Due to the potential implications of the treatment on the developing CNS, all patients must be ≥ 18 years of age at the time of entry into the study;
4. Laboratory Studies:
    a. Total bilirubin, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Alkaline Phosphatase (ALK) ≤ 1.5 x upper limit of normal (ULN)
    b. Creatinine ≤ 1.5
5. A signed informed consent form approved by the Duke University Institutional Review Board (IRB) will be required for patient enrollment into the study. Patients or their Legally Authorized Representative (LAR) must be able to read and understand the informed consent document and must sign the informed consent indicating that they are aware of the investigational nature of this study. Treating physicians at the time the protocol is presented can determine based on their clinical judgment whether patients lack the capacity and require a LAR to sign the consent form.
6. Patients of childbearing potential or with partners of child-bearing potential must agree to practice recommended contraceptive methods to prevent pregnancy during treatment and for 1 month after the last dose of AED for women and men.

Exclusion criteria

1. Pregnant or need to breastfeed during the study period (Negative urine β-HCG test required), or unable to maintain use of contraception while on the study and for 1 month after the last dose of AED;
2. Patients already on AED(s) specifically to treat seizures will be excluded. Those patients taking AEDs for any diagnosis other than seizures will be included (e.g. Gabapentin for neuropathic pain, Topiramate for migraine, benzodiazepines as a sleeping aid, etc). Patients taking AEDs for seizure prophylaxis and without a clear history of seizures will be included;
3. Known history of epilepsy/seizure disorder;
4. Known history of dependency/abuse of psychopharmaceuticals, alcohol, illicit drugs, or narcotics;
5. Any significant medical or psychiatric illness that cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate therapy, per the discretion of the treating investigator;
6. Known allergy to LCM or LEV.

6. Primary Outcome:

ED visit or hospital readmission within 30 days of MSR: Variable "admitted_ed" and "hospitalized" will be used. It can take values "Yes' or "No".

7. Secondary outcomes:

1. Adverse event of special interest within the first 30 days after MSR: Adverse event includes:
   - Dizziness: It can take values "Yes' or "No".
     Dizziness severity: It can take values "Mild", "Limit daily activities", or "Limit self-care".
     Seek attention for dizziness: Did you seek medical attention? It can take values "Yes' or "No".
     Feeling after treatment of dizziness: It can take values "Better", "Same", or "Worse".
   - Somnolence: It can take values "Yes' or "No".
     Somnolence severity: it can take values "Relieved by rest", "Not relieved by rest", or "Limit self-care".
     Seek attention for somnolence: It can take values "Yes' or "No".
     Feeling after treatment of somnolence: It can take values "Better", "Same", or "Worse".
   - Cognitive disturbance: It can take values "Yes' or "No".
     Cognitive disturbance severity: It can take values "Mild, not interfering with life", "Interfering with life, but independent", "Severe impairment of life".
     Seek attention for cognitive disturbance: It can take values "Yes' or "No".
     Feeling after treatment of cognitive disturbance: It can take values "Better", "Same", or "Worse".
   - nausea: It can take values "Yes' or "No".
     nausea severity: It can take values "Loss of appetite", "Unable to eat enough, no weight loss", "Severe, need to be in the hospital".
     Seek attention for nausea: It can take values "Yes' or "No".
     Feeling after treatment of nausea: It can take values "Better", "Same", or "Worse".
   - vomiting: It can take values "Yes' or "No".
     vomiting severity: It can take values "1-2 times/day", "3-5 times/day", "More than 6 times/day".

     Seek attention for vomiting: It can take values "Yes' or "No".
     Feeling after treatment of vomiting: It can take values "Better", "Same", or "Worse".
   - ataxia: It can take values "Yes' or "No".
     ataxia severity: It can take values "Mild", "Limit daily life", "Need a cane or walker".
     Seek attention for ataxia: It can take values "Yes' or "No".
     Feeling after treatment of ataxia: It can take values "Better", "Same", or "Worse".
   - Suicide thought: It can take values "Yes' or "No".
     suicide thought severity: It can take values "No wish to die", "No plan", "Plan".
     Seek attention for suicide thought: It can take values "Yes' or "No".
     Feeling after treatment of suicide thought: It can take values "Better", "Same", or "Worse".
   - Attempted suicide: It can take values "Yes' or "No".
     Seek attention for suicide attempts: It can take values "Yes' or "No".
     Feeling after treatment of suicide attempt: It can take values "Better", "Same", or "Worse".
   - anxiety: It can take values "Yes' or "No".
     anxiety severity: It can take values "Mild, not interfering with life", "Moderate impairment of life", "Severe impairment of life".
     Seek attention for anxiety: It can take values "Yes' or "No".

Feeling after treatment of anxiety: It can take values “Better”, “Same”, or “Worse”.

- depression: It can take values “Yes’ or “No”.
  depression severity: It can take values “Mild, not interfering with life”, “Moderate impairment of life”, “Severe impairment of life”.
  Seek attention for depression: It can take values “Yes’ or “No”.
  Feeling after treatment of depression: It can take values “Better”, “Same”, or “Worse”.
- irritability: It can take values “Yes’ or “No”.
  irritability severity: It can take values “Able to control”, “Moderate”, “Severe and unable to control”.
  Seek attention for irritability: It can take values “Yes’ or “No”.
  Feeling after treatment of irritability: It can take values “Better”, “Same”, or “Worse”.
- Psychosis: It can take the values “Yes’ or “No”.
  Psychosis severity: It can take values “Mild”, “Moderate”, “Severe”.
  Seek attention for psychosis: It can take values “Yes’ or “No”.
  Feeling after treatment of psychosis: It can take values “Better”, “Same”, or “Worse”.
- Personality change: It can take values “Yes’ or “No”.
  Personality change severity: It can take values “Mild”, “Moderate”, “Severe”.
  Seek attention for personality change: It can take values “Yes’ or “No”.
  Feeling after treatment of personality change: It can take values “Better”, “Same”, or “Worse”.

2. Duration of initial admission stay for MSR: variable “duration_stay” will be used. It is a continuous variable.

3. Intra-operative AED use: variable “aed_use” will be used. It can take “Yes” or “No”.
   AED specification: variable “spef_aed” will be used. it can take values “Lacosamide (VIMPAT)” or “Levetiracetam (Keppra)”.

4. Provider communications (email, telephone, or additional clinical visits) that occurred within 30 days of MSR. It includes:
   Contacted provider: It can take values “Yes’ or “No”.
   number of contacts: it can take values 1-5.
   Communication method: It can take values “E-mail”, “Phone”, “In-person (clinic visit)” or “Other”.

5. Changes in dosages, type of AED, addition or discontinuation of AED that occur within 30 days of MSR
   - Discontinued AED: Did you discontinue your prescribed anti-epileptic drug (AED) since the last questionnaire? It can take values “Yes’ or “No”.
   - Prescription modified: It can take values “Yes’ or “No”.
   - Additional AED prescription: Have you been prescribed an AED in addition to your already prescribed AED since the last questionnaire? It can take values “Yes’ or “No”.
   - Missed doses: Have you missed any doses since the last questionnaire? It can take values “Yes’ or “No”.
6. Patients experiencing post-procedure seizures during the 30-day postoperative phase.
   Have you experienced a seizure since the last questionnaire? It can take values “Yes’ or “No”.
   Number of seizures: It can take values 1-5 and >5.

8. Exposures

Patients were randomized into 3 treatment groups: 1) Arm A - Lacosamide (Vimpat) 100mg twice a day; 2) Arm B - Levetiracetam (Keppra) 1000mg twice a day; 3) Arm C - or no anti-epileptic (anti-seizure) drug. Variable "treatment" will be used.

9. Demographics

Age at consent: variable "consent_age" will be used, It is a continuous variable.

Race: A categorical variable. It can take values: "White/Caucasian", "Black/African-American", "Asian" "Native American", "Native Hawaiian or Other Pacific Islander", "Other", or "Unknown".

Ethnicity: A categorical variable. It can take values: "Hispanic or Latino", "Not Hispanic or Latino", "Unknown", "Not Reported".

Gender: A categorical variable. It can take values "Male" or "Female".

Medical history

Medical history: Medical history includes smoking, heart disease, vascular disease, coagulopathy, hypertension, stroke, thromboembolic event, pulmonary disease, gastrointestinal disease, liver disease, kidney disease, diabetes, immune system disease, other brain-related diagnoses, other Significant Health history not elsewhere specified, steroid medications. They are binary variables. They can take value "Yes" or "No".

10. Statistical Analysis:

ED visit or hospital readmission within 30 days of surgery, the occurrence of adverse effects, and other relevant variables are summarized using descriptive statistics. Continuous variables are reported with mean/standard deviation/median/IQR/minimum/maximum and categorical variables are summarized with frequency counts and percentages for non-missing values. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

11. Primary outcome: 30-day ED visit/hospital readmission after surgery

Only the patient who had no anti-epileptic drug had hospital readmission within 30 days of surgery. The reason for hospital readmission is to have surgery to remove two brain tumors. The length of stay was 2 days.

Table 4: ED visit or hospital readmission within 30 days after surgery

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
ED visit	0 (0%)	0 (0%)	0 (0%)	0 (0%)
hospital readmission	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)

Table 4: ED visit or hospital readmission within 30 days after surgery

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Days of hospitalization/ED visit			2	

11.1 30-day adverse effects

For the patient who had lacosamide, he/she had at least one event of dizziness, somnolence, cognitive disturbance, nausea, vomiting, ataxia, anxiety, and irritability. For the two patients who had levetiracetam, both had at least one event of somnolence, one had dizziness and irritability, and the other one had nausea. For the patient who had no anti-epileptic drug, he/she had at least one event of dizziness, somnolence, and cognitive disturbance.

Table 5: adverse events occurred within 30 days after surgery

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Dizziness	1 (100.0%)	1 (50.0%)	1 (100.0%)	3 (75.0%)
Somnolence	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Cognitive disturbance	1 (100.0%)	0 (0.0%)	1 (100.0%)	2 (50.0%)
Nausea	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Vomiting	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Ataxia	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Suicide thought	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Suicide attempt	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anxiety	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Depression	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Irritability	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Psychosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Personality change	0 (0%)	0 (0%)	0 (0%)	0 (0%)

The frequency number of each adverse effect within 30 days of surgery is summarized in Table 6.

Table 6: Number of adverse events that occurred 30 days after surgery

Treatment	Dizziness	somnolence	Cognitive disturbance	Nausea	vomiting	ataxia	anxiety	irritability
Levetiracetam (Keppra), patient 1	0	25	0	24	0	0	23	0
Levetiracetam (Keppra), patient 2	1	1	0	0	0	0	0	1
Lacosamide (Vimpat)	8	4	1	4	1	2	3	4
No anti-epileptic drug	3	8	4	0	0	0	0	0

Severity and treatment of adverse effects

The severity and treatment of each adverse event are summarized in Table 7-14.

Table 7: Dizziness

	Lacosamide (Vimpat) (N=8)	Levetiracetam (Keppra) (N=1)	No anti-epileptic drug (N=3)
How bad is it?			
Mild	7 (87.5%)	1 (100.0%)	3 (100.0%)
Limit daily activities	1 (12.5%)	0 (0.0%)	0 (0.0%)

Table 7: Dizziness

	Lacosamide (Vimpat) (N=8)	Levetiracetam (Keppra) (N=1)	No anti-epileptic drug (N=3)
Did you seek medical attention?			
No	8 (100.0%)	1 (100.0%)	2 (66.7%)
Yes	0 (0.0%)	0 (0.0%)	1 (33.3%)
What kind of treatment did you get?			
We asked the Duke resident neurologist for a call back to discuss but we never received a call back. This is the second time we have called and never received a callback	0 (0.0%)	0 (0.0%)	1 (100.0%)
Are you...			
Better	4 (50.0%)	0 (0.0%)	1 (33.3%)
Same	4 (50.0%)	1 (100.0%)	2 (66.7%)

Table 8: Somnolence

	Lacosamide (Vimpat) (N=4)	Levetiracetam (Keppra) (N=26)	No anti-epileptic drug (N=8)
How bad is it?			
Relieved by rest	3 (75.0%)	25 (96.2%)	8 (100.0%)
Not relieved by rest	1 (25.0%)	0 (0.0%)	0 (0.0%)
Limit self-care	0 (0.0%)	1 (3.8%)	0 (0.0%)
Did you seek medical attention?			
Missing	0 (.%)	1 (.%)	0 (.%)
No	4 (100.0%)	25 (100.0%)	8 (100.0%)
Are you...			
Missing	0 (.%)	1 (.%)	1 (.%)
Better	1 (25.0%)	0 (0.0%)	2 (28.6%)
Same	3 (75.0%)	25 (100.0%)	5 (71.4%)

Table 9: Cognitive disturbance

	Lacosamide (Vimpat) (N=1)	no anti-epileptic drug (N=4)
How bad is it?		
Mild, not interfering with life	1 (100.0%)	4 (100.0%)
Did you seek medical attention?		
No	1 (100.0%)	4 (100.0%)
Are you...		
Better	1 (100.0%)	0 (0.0%)
Same	0 (0.0%)	4 (100.0%)

Table 10: Nausea

	Lacosamide (Vimpat) (N=4)	Levetiracetam (Keppra) (N=24)
How bad is it?		
Loss of appetite	2 (50.0%)	3 (12.5%)
Unable to eat enough, no weight loss	2 (50.0%)	21 (87.5%)
Did you seek medical attention?		
Missing	0 (.%)	1 (.%)
No	4 (100.0%)	23 (100.0%)
Are you...		
Better	1 (25.0%)	0 (0.0%)
Same	3 (75.0%)	24 (100.0%)

Table 11: Vomited

	Lacosamide (Vimpat) (N=1)
How bad is it?	
1-2 times/day	1 (100.0%)
Did you seek medical attention?	
No	1 (100.0%)
Are you...	
Same	1 (100.0%)

Table 12: Ataxia

	Lacosamide (Vimpat) (N=2)
How bad is it?	
Mild	2 (100.0%)
Did you seek medical attention?	
No	2 (100.0%)
Are you...	
Better	2 (100.0%)

Table 13: Anxiety

	Lacosamide (Vimpat) (N=3)	Levetiracetam (Keppra) (N=23)
How bad is it?		
Mild, not interfering with life	3 (100.0%)	23 (100.0%)
Did you seek medical attention?		
Missing	0 (.%)	1 (.%)
No	3 (100.0%)	22 (100.0%)

Table 13: Anxiety

	Lacosamide (Vimpat) (N=3)	Levetiracetam (Keppra) (N=23)
Are you...		
Missing	0 (.%)	1 (.%)
Better	2 (66.7%)	2 (9.1%)
Same	1 (33.3%)	20 (90.9%)

Table 14: Irritability

	Lacosamide (Vimpat) (N=4)	Levetiracetam (Keppra) (N=1)
How bad is it?		
Able to control	4 (100.0%)	1 (100.0%)
Did you seek medical attention?		
No	4 (100.0%)	1 (100.0%)
Are you...		
Better	2 (50.0%)	0 (0.0%)
Same	2 (50.0%)	1 (100.0%)

11.2 Number of seizures that occurred within 30 days of surgery

Only the patient who had lacosamide experienced one event of seizure within 30 days of surgery.

12.Conclusions:

The number of ED visits/hospital readmission, the occurrence of adverse effects, and other clinical characteristics within 30 days of MSR for patients who had and who did not have AED are summarized. This study was limited by the small sample size, and a dataset with a larger sample size should be used to further evaluate the impact of LCM and LEV on ED visits and readmissions in the future.