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

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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. Other relevant variables

Physical& neurological exam
Exam performed includes "H/E/E/N/T, respiratory, cardiovascular, gastrointestinal, musculoskeletal, dermatologic, hematopoietic, endocrine_metabolic, genitourinary, neurologic, allergy, other exam": It can take "Yes" or "No".

Exam results: It can take" Abnormal", "Normal", "Not examined".

Labs

Sodium, potassium, chloride, carbon dioxide, bun, creatinine, glucose, calcium, AST, ALT, bilirubin, alkaline phosphatase, albumin protein, WBC, hemoglobin, hematocrit, PLT, neutrophil count, neutrophil %, lymphocyte %

Tumor type

Grade: variable "strata" will be used. can take value "Suspected HGG", "Suspected LGG", or "Metastasis".

Surgical procedure

The extent of Surgery: it can take values "Gross total", "Subtotal", and "Biopsy".

Type of Tumor/Lesion: It can take values "Newly diagnosed", "Recurrent", "Progressive", "Transformed", and "Metastasis".

The number of lesions: It can take values 1, 2, 3, 4, 5-10, and >10.

Tumor specifics: It can take values: "Left", "Right", "Midline", "Frontal Lobe", "Parietal Lobe", "Temporal Lobe", "Occipital Lobe", "Cerebellum", "Thalamus", and "Other".

WHO grade: It can take values I, II, III, IV, metastasis.

Site of primary tumor: it can take values "Lung", " Breast", "Melanoma", "GI", "Renal", and "Other".

Prior treatment for metastasis: variable "priortreat_metas" will be used. It can take "Yes" or "No".

Reason for prior treatment: It can take values "Non-resectable (cannot be surgically removed due to size of tumor/lesion, location of tumor/lesion, the spread of the tumor to distant sites, etc.", "Subject exceeded

max does or could not tolerate radiation", "Subject exceeded max does or could not tolerate chemotherapy" and "Other".

Type of previous treatment: It can take values "Craniotomy Stereotactic Radiation (SRS)", "Laser Interstitial Thermal Therapy (LITT)", "Whole Brain Radiation (WBR)", "Chemotherapy", "Local Radiation Therapy", "Corpus Callosotomy", "Hippocampectomy", "Amygdalo hippocampectomy", "Anterior temporal lobectomy", "Cortical excision", "Hemispherectomy", "Multiple subpial transections", "Vagus nerve stimulation", "Responsive Neurostimulator", "Deep Brain Simulator", "Other Brain Stimulation", "Drug Therapy and "Other".

Concomitant medication

Can take values "Acetaminophen (Tylenol)", "Ardeparin (Inderparin)", "Aspirin", "Bevacizumab (Avastin)", "Carbamazepine (Tegretol) ", "Carboplatin", "Clobazam (Onfi) ", "Clonazepam (Klonopin) ", "Clopidogrel (Plavix) ", "Dalteparin (Fragmin vial) ", "Danaparoid", "Dexamethasone (Decadron) ", "Enoxaparin", "Etoposide", "Fondaparinux (Arixtra) ", "Gabapentin (Neurontin) ", "Lacosamide (Vimpat) ", "Lamotrigine (Lamictal) ", "Leprirubin", "Levetiracetam (Keppra) ", "Lomustine", "Lorazepam", "Oxycodone", "Phenytoin", "Prednisone", "Temozolomide (Temodar) ", "Valproic acid (Valproic) ", "Warfarin", "Zonisamide (Zonegran) ", "Other"

Medication purpose: can take values "Anticoagulants", "Chemotherapy", "Steroids", "Pain", "Anticonvulsants (including Anti-epileptic drugs)", or "Other".

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11. 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).

12. Result

12.1 Demographic characteristics

There were only 4 patients who met the inclusion/exclusion criteria and enrolled in this phase II clinical trial. One patient had lacosamide (VIMPAT), two had levetriacetam (Keppra), and one patient had no anti-epileptic drug. The demographic characteristics for these 4 patients are summarized in Table 1.

Table 1: Demographic characteristics

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	no anti-epileptic drug (N=1)	Total (N=4)
Age at consent				
Mean (SD)	41.0 (.)	51.0 (17.0)	54.0 (.)	49.3 (11.3)
Median	41.0	51.0	54.0	47.5
Q1, Q3	41.0, 41.0	39.0, 63.0	54.0, 54.0	40.0, 58.5
Range	(41.0-41.0)	(39.0-63.0)	(54.0-54.0)	(39.0-63.0)
Race				
White/Caucasian	0 (0.0%)	2 (100.0%)	1 (100.0%)	3 (75.0%)
Black/African-American	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Ethnicity				
Not Hispanic or Latino	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Gender				
Male	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Female	0 (0.0%)	1 (50.0%)	1 (100.0%)	2 (50.0%)

12.2 Medical history

The medical history for these 4 patients is summarized in Table 2.

Table 2: Medical history

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Smoking	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Heart Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral Vascular Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Coagulopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Systemic Hypertension	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Stroke/TIA?	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thromboembolic Event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal Disease	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Liver Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Kidney Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diabetes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Immune System Disease	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Other brain-related diagnoses	0 (0.0%)	0 (0.0%)	1 (100.0%)*	1 (25.0%)
Other Significant Health History not elsewhere specified	1 (100.0%)**	0 (0.0%)	0 (0.0%)	1 (25.0%)
Is the patient taking any medications?	1 (100.0%)	1 (50.0%)	1 (100.0%)	3 (75.0%)

* Brain lesion; ** Asthma, Allergic rhinitis

12.3 Tumor type, AED treatment, and surgery details

All patients had suspected LGG. Only 1 patient who had levetiracetam prophylaxis had intraoperative AED use (also levetiracetam).

Table 3: Tumor type, AED treatment, and surgery details

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Grade				
Suspected LGG	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Duration of admission stay				
Mean (SD)	1.0 (.)	1.5 (0.7)	1.0 (.)	1.3 (0.5)
Median	1.0	1.5	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 2.0	1.0, 1.0	1.0, 1.5
Range	(1.0-1.0)	(1.0-2.0)	(1.0-1.0)	(1.0-2.0)
Intra-operative AED use				
No	1 (100.0%)	1 (50.0%)	1 (100.0%)	3 (75.0%)
Yes	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Specify AED				
Levetiracetam (Keppra)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
Extent of Surgery				
Missing	1 (.%)	1 (.%)	0 (.%)	2
Gross total	0 (0.0%)	1 (100.0%)	1 (100.0%)	2 (100.0%)

Table 3: Tumor type, AED treatment, and surgery details

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Type of Tumor/Lesion				
Newly diagnosed	0 (0.0%)	1 (50.0%)	1 (100.0%)	2 (50.0%)
Progressive	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
# of lesions				
1	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Tumor/Lesion Specifics				
Left	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Right	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Midline	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Frontal Lobe	1 (100.0%)	0 (0.0%)	1 (100.0%)	2 (50.0%)
Parietal Lobe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Temporal Lobe	0 (0.0%)	2 (100.0%)	0 (0.0%)	2 (50.0%)
Occipital Lobe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cerebellum	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thalamus	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Specify WHO grade				
II	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
III	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
IV	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)
Prior Treatment				
No	0 (0.0%)	1 (50.0%)	1 (100.0%)	2 (50.0%)
Yes	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Reason for no prior treatment				
Non-resectable	.	0 (0%)	0 (0%)	0 (0%)
Subject exceeded max does or could not tolerate radiation	.	0 (0%)	0 (0%)	0 (0%)
Subject exceeded max does or could not tolerate chemotherapy	.	0 (0%)	0 (0%)	0 (0%)
Newly Diagnosed	.	1 (50.0%)	1 (100.0%)	2 (50.0%)
Type of previous treatment				
Craniotomy	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Chemotherapy	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
Specify the previous treatment				
Missing	0 (.%)	2 (.%)	0 (.%)	2
Prior craniotomy was in 2009 by Dr. Grossi Vimpat was initiated around 12 hrs prior craniotomy	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
There were no intraoperative complications. The patient tolerated the procedure well and was transferred to the neurosurgery intensive care unit in a stable condition.	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (50.0%)

Table 3: Tumor type, AED treatment, and surgery details

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
The postoperative course was unevent				

12.4 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%)
Days of hospitalization/ED visit			2	

12.5 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%)
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?	

Table 12: Ataxia

	Lacosamide (Vimpat) (N=2)
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%)
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%)

12.6 Number of contact and contact method

Within 30 days of surgery, the patients who had lacosamide contacted the providers for 5 days. He contacted the provider 2 times in each of the 2 days, 4 times in each of another 2 days, and 1 time for the left 1 day. The communication method for these 13 contacts was a phone call.

For the two patients who had levetiracetam, one patient never contacted the providers, and one contacted the providers for 5 days (1 time in each of the 4 days and 3 times in the left one day). This patient contacted the providers using a phone for 85.7% of the time (n=6) and using clinic visits for 14.3% of the time (n=1).

For the patient who had no anti-epileptic drug, he/she contacted the provider for 4 days, 1 time in each of the 3 days and 2 times in the left 1 day. This patient contacted the providers using a phone for 60% of the time (n=3) and using clinic visits for 40% of the time (n=2).

Table 15: Number of contacts

	Lacosamide (Vimpat) (N=5)	Levetiracetam (Keppra) (N=5)	No anti-epileptic drug (N=4)	Total (N=14)
How many contacts occurred?				
1	1 (20.0%)	4 (80.0%)	3 (75.0%)	8 (57.1%)
2	2 (40.0%)	0 (0.0%)	1 (25.0%)	3 (21.4%)
3	0 (0.0%)	1 (20.0%)	0 (0.0%)	1 (7.1%)
4	2 (40.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)

Table 16: Contact method

	Lacosamide (Vimpat) (N=13)	Levetiracetam (Keppra) (N=7)	No anti-epileptic drug (N=5)	Total (N=25)
Communication method				
Phone	13 (100.0%)	6 (85.7%)	3 (60.0%)	22 (88.0%)
In-person (clinic visit)	0 (0.0%)	1 (14.3%)	2 (40.0%)	3 (12.0%)

12.7 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.

12.8 Changes in dosages, type of AED, addition or discontinuation of AED after surgery

For the two patients who had levetiracetam, one patient did not have any change in AED. The other patient discontinued AED in 23.1% of the follow-up time (n=6 days). He/she had prescription modified in 3.8% of the follow-up time (n=1 day). The new dose was 500 mg/day.

For the patient who had lacosamide, he/she discontinued AED in 3.6% of the follow-up time (n=1 day). This patient was prescribed with additional AED for one day (levetiracetam 500 mg 2 times a day).

Table 17: Change in AED after surgery

	Levetiracetam (N=26)	Lacosamide (N=28)
Did you discontinue your prescribed anti-epileptic drug (AED) since the last questionnaire?		
No	20 (76.9%)	27 (96.4%)
Yes	6 (23.1%)	1 (3.6%)
Has your prescribed dose been modified since last questionnaire?		
No	25 (96.2%)	27 (96.4%)
Yes	1 (3.8%)	1 (3.6%)
What is your new prescribed dosage?		
500mg/ day	1 (100.0%)	0 (0.0%)
Discontinued usage	0 (0.0%)	1 (100.0%)

Table 17: Change in AED after surgery

	Levetiracetam (N=26)	Lacosamide (N=28)
How many times a day?		
0	0 (0.0%)	1 (100.0%)
1	1 (100.0%)	0 (0.0%)
Have you been prescribed an AED in addition to your already prescribed AED for last questionnaire?		
No	26 (100.0%)	27 (96.4%)
Yes	0 (0.0%)	1 (3.6%)
What is the name of the additional AED?		
Levetiracetam	0 (0.0%)	1 (100.0%)
What is the dose of your new AED?		
500 mg	0 (0.0%)	1 (100.0%)
How many times a day?		
2	0 (0.0%)	1 (100.0%)
Have you missed any doses since last questionnaire?		
No	20 (76.9%)	28 (100.0%)
Yes	6 (23.1%)	0 (0.0%)
Specify the detail		
Missing	24 (.%)	26 (.%)
Completed 2 ten day doses of medication according to instructions with no evidence of seizures	1 (50.0%)	0 (0.0%)
Completed prescription	1 (50.0%)	0 (0.0%)
I added that I thought I had a seizure last Saturday, but the Dr. Said I didn't have one.	0 (0.0%)	1 (50.0%)
I'm broke out in hives	0 (0.0%)	1 (50.0%)

12.9 Physical exam results

Physical exam results in the baseline period and postoperative period are summarized in Tables 18 and 19, respectively.

Table 18: Physical exam in the baseline period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
H/E/E/N/T				
Abnormal	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Normal	0 (0.0%)	1 (50.0%)	1 (100.0%)	2 (50.0%)
Finding Description				
Hearing impairment (mild hearing loss - no	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)

Table 18: Physical exam in the baseline period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
hearing aid)				
visual disturbance	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
Respiratory				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Cardiovascular				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Gastrointestinal				
Abnormal	0 (0.0%)	1 (50.0%)	1 (100.0%)	2 (50.0%)
Normal	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Finding Description				
Positive for constipation.	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (50.0%)
diarrhea, nausea and vomiting	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
Musculoskeletal				
Abnormal	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Normal	0 (0.0%)	2 (100.0%)	1 (100.0%)	3 (75.0%)
Finding Description				
back pain (cervical spine bulging disc - back brace and has order for PT (service related injury))	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Dermatologic				
No	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)
Yes	1 (100.0%)	2 (100.0%)	0 (0.0%)	3 (75.0%)
Result				
Normal	1 (100.0%)	2 (100.0%)	0 (0.0%)	3 (100.0%)
Hematopoietic/lymph				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Endocrine/Metabolic				
Abnormal	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Normal	0 (0.0%)	2 (100.0%)	1 (100.0%)	3 (75.0%)
Finding Description				
Obesity (BMI 35)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Genitourinary				
No	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Yes	1 (100.0%)	1 (50.0%)	1 (100.0%)	3 (75.0%)
Result				
Normal	1 (100.0%)	1 (100.0%)	1 (100.0%)	3 (100.0%)
Neurologic				

Table 18: Physical exam in the baseline period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Abnormal	1 (100.0%)	1 (50.0%)	1 (100.0%)	3 (75.0%)
Normal	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Finding Description				
Dizziness (intermittently with weight lifting) and Chronic headache since 2009	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Positive for dizziness	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (33.3%)
tremors	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (33.3%)
Allergy/Sensitivity				
No	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (25.0%)
Yes	1 (100.0%)	1 (50.0%)	1 (100.0%)	3 (75.0%)
Result				
Abnormal	1 (100.0%)	1 (100.0%)	0 (0.0%)	2 (66.7%)
Normal	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (33.3%)
Finding Description				
Ciprofloxacin, Lisinopril, Sulfamethoxazole-Trimethoprim, Codeine, Venlafaxine	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
Yellow Fever Vaccine Live (rash)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Other				
No	0 (0.0%)	1 (50.0%)	1 (100.0%)	2 (50.0%)
Yes	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Specify Other Exam				
Psychiatric/Behavioral	1 (100.0%)	1 (100.0%)	0 (0.0%)	2 (100.0%)
Result				
Abnormal	1 (100.0%)	1 (100.0%)	0 (0.0%)	2 (100.0%)
Finding Description				
Anxiety	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
confusion and sleep disturbance	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (50.0%)

Table 19: Physical exam in the postoperative period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
H/E/E/N/T				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Respiratory				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Cardiovascular				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)

Table 19: Physical exam in the postoperative period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Gastrointestinal				
No	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)
Yes	1 (100.0%)	2 (100.0%)	0 (0.0%)	3 (75.0%)
Result				
Normal	1 (100.0%)	2 (100.0%)	0 (0.0%)	3 (100.0%)
Musculoskeletal				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Dermatologic				
No	0 (0.0%)	1 (50.0%)	1 (100.0%)	2 (50.0%)
Yes	1 (100.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
Result				
Normal	1 (100.0%)	1 (100.0%)	0 (0.0%)	2 (100.0%)
Hematopoietic/lymph				
No	1 (100.0%)	2 (100.0%)	0 (0.0%)	3 (75.0%)
Yes	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)
Result				
Normal	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Endocrine/Metabolic				
No	0 (0.0%)	2 (100.0%)	1 (100.0%)	3 (75.0%)
Yes	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Result				
Normal	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Genitourinary				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Neurologic				
Normal	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Finding Description				
Missing	1 (.%)	2 (.%)	1 (.%)	4
Allergy/Sensitivity				
No	1 (100.0%)	0 (0.0%)	1 (100.0%)	2 (50.0%)
Yes	0 (0.0%)	2 (100.0%)	0 (0.0%)	2 (50.0%)
Result				
Normal	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
Other				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)

12.10 Lab test results

Lab test results in the baseline period and postoperative period are summarized in Tables 20 and 21, respectively.

Table 20: Lab test in the baseline period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Sodium (mmol/L)				
Mean (SD)	137.0 (.)	137.0 (1.4)	135.0 (.)	136.5 (1.3)
Median	137.0	137.0	135.0	136.5
Q1, Q3	137.0, 137.0	136.0, 138.0	135.0, 135.0	135.5, 137.5
Range	(137.0-137.0)	(136.0-138.0)	(135.0-135.0)	(135.0-138.0)
Potassium (mmol/L)				
Mean (SD)	3.9 (.)	3.9 (0.7)	4.4 (.)	4.0 (0.5)
Median	3.9	3.9	4.4	4.2
Q1, Q3	3.9, 3.9	3.4, 4.4	4.4, 4.4	3.7, 4.4
Range	(3.9-3.9)	(3.4-4.4)	(4.4-4.4)	(3.4-4.4)
Chloride (mmol/L)				
Mean (SD)	102.0 (.)	102.0 (7.1)	100.0 (.)	101.5 (4.2)
Median	102.0	102.0	100.0	101.0
Q1, Q3	102.0, 102.0	97.0, 107.0	100.0, 100.0	98.5, 104.5
Range	(102.0-102.0)	(97.0-107.0)	(100.0-100.0)	(97.0-107.0)
Carbon Dioxide (mmol/L)				
Mean (SD)	26.0 (.)	23.0 (2.8)	28.0 (.)	25.0 (2.9)
Median	26.0	23.0	28.0	25.5
Q1, Q3	26.0, 26.0	21.0, 25.0	28.0, 28.0	23.0, 27.0
Range	(26.0-26.0)	(21.0-25.0)	(28.0-28.0)	(21.0-28.0)
Urea Nitrogen (mg/dL)				
Mean (SD)	14.0 (.)	16.0 (4.2)	17.0 (.)	15.8 (2.8)
Median	14.0	16.0	17.0	15.5
Q1, Q3	14.0, 14.0	13.0, 19.0	17.0, 17.0	13.5, 18.0
Range	(14.0-14.0)	(13.0-19.0)	(17.0-17.0)	(13.0-19.0)
Creatinine (mg/dL)				
Mean (SD)	1.2 (.)	0.9 (0.2)	0.7 (.)	0.9 (0.2)
Median	1.2	0.9	0.7	0.9
Q1, Q3	1.2, 1.2	0.7, 1.0	0.7, 0.7	0.7, 1.1
Range	(1.2-1.2)	(0.7-1.0)	(0.7-0.7)	(0.7-1.2)
Glucose				
Mean (SD)	91.0 (.)	128.0 (35.4)	98.0 (.)	111.3 (28.3)
Median	91.0	128.0	98.0	100.5
Q1, Q3	91.0, 91.0	103.0, 153.0	98.0, 98.0	94.5, 128.0
Range	(91.0-91.0)	(103.0-153.0)	(98.0-98.0)	(91.0-153.0)
UOM				
mg/dL	1 (100.0%)	2 (100.0%)	0 (0.0%)	3 (75.0%)
g/dL	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)
Calcium (mg/dL)				
Mean (SD)	9.2 (.)	9.3 (0.3)	9.1 (.)	9.2 (0.2)

Table 20: Lab test in the baseline period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Median	9.2	9.3	9.1	9.2
Q1, Q3	9.2, 9.2	9.1, 9.5	9.1, 9.1	9.1, 9.4
Range	(9.2-9.2)	(9.1-9.5)	(9.1-9.1)	(9.1-9.5)
Aspartate Aminotransferase (AST, unit?)				
Mean (SD)	20.0 (.)	22.5 (3.5)	22.0 (.)	21.8 (2.4)
Median	20.0	22.5	22.0	21.0
Q1, Q3	20.0, 20.0	20.0, 25.0	22.0, 22.0	20.0, 23.5
Range	(20.0-20.0)	(20.0-25.0)	(22.0-22.0)	(20.0-25.0)
ALT (Alanine Aminotransferase, u/L**)**				
Mean (SD)	33.0 (.)	27.0 (9.9)	27.0 (.)	28.5 (6.5)
Median	33.0	27.0	27.0	30.0
Q1, Q3	33.0, 33.0	20.0, 34.0	27.0, 27.0	23.5, 33.5
Range	(33.0-33.0)	(20.0-34.0)	(27.0-27.0)	(20.0-34.0)
Bilirubin, Total (mg/dL)				
Mean (SD)	0.6 (.)	0.8 (0.1)	0.6 (.)	0.7 (0.1)
Median	0.6	0.8	0.6	0.7
Q1, Q3	0.6, 0.6	0.7, 0.9	0.6, 0.6	0.6, 0.8
Range	(0.6-0.6)	(0.7-0.9)	(0.6-0.6)	(0.6-0.9)
Alkaline Phosphatase				
Mean (SD)	73.0 (.)	75.0 (15.6)	37.0 (.)	65.0 (20.7)
Median	73.0	75.0	37.0	68.5
Q1, Q3	73.0, 73.0	64.0, 86.0	37.0, 37.0	50.5, 79.5
Range	(73.0-73.0)	(64.0-86.0)	(37.0-37.0)	(37.0-86.0)
UOM				
mg/dL	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)
U/L	1 (100.0%)	2 (100.0%)	0 (0.0%)	3 (75.0%)
Albumin (g/dL)				
Mean (SD)	4.3 (.)	4.2 (0.3)	3.7 (.)	4.1 (0.3)
Median	4.3	4.2	3.7	4.2
Q1, Q3	4.3, 4.3	4.0, 4.4	3.7, 3.7	3.9, 4.4
Range	(4.3-4.3)	(4.0-4.4)	(3.7-3.7)	(3.7-4.4)
Protein, Total (g/dL)				
Mean (SD)	7.2 (.)	7.4 (0.8)	6.2 (.)	7.0 (0.7)
Median	7.2	7.4	6.2	7.0
Q1, Q3	7.2, 7.2	6.8, 7.9	6.2, 6.2	6.5, 7.6
Range	(7.2-7.2)	(6.8-7.9)	(6.2-6.2)	(6.2-7.9)
White Blood Cell Count (10^9/L)				
Mean (SD)	3.3 (.)	7.1 (0.8)	10.0 (.)	6.9 (2.8)
Median	3.3	7.1	10.0	7.1
Q1, Q3	3.3, 3.3	6.5, 7.6	10.0, 10.0	4.9, 8.8
Range	(3.3-3.3)	(6.5-7.6)	(10.0-10.0)	(3.3-10.0)

Table 20: Lab test in the baseline period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	No anti-epileptic drug (N=1)	Total (N=4)
Hemoglobin (g/dL)				
Mean (SD)	15.1 (.)	15.8 (0.1)	14.1 (.)	15.2 (0.8)
Median	15.1	15.8	14.1	15.4
Q1, Q3	15.1, 15.1	15.7, 15.9	14.1, 14.1	14.6, 15.8
Range	(15.1-15.1)	(15.7-15.9)	(14.1-14.1)	(14.1-15.9)
Hematocrit (%)				
Mean (SD)	46.8 (.)	46.8 (0.7)	42.4 (.)	45.7 (2.2)
Median	46.8	46.8	42.4	46.6
Q1, Q3	46.8, 46.8	46.3, 47.3	42.4, 42.4	44.3, 47.1
Range	(46.8-46.8)	(46.3-47.3)	(42.4-42.4)	(42.4-47.3)
Platelets (10^9/L)				
Mean (SD)	236.0 (.)	280.0 (53.7)	309.0 (.)	276.3 (43.2)
Median	236.0	280.0	309.0	275.5
Q1, Q3	236.0, 236.0	242.0, 318.0	309.0, 309.0	239.0, 313.5
Range	(236.0-236.0)	(242.0-318.0)	(309.0-309.0)	(236.0-318.0)
Neutrophil Count (109/L)				
N	0	2	1	3
Mean (SD)		4.8 (1.1)	7.8 (.)	5.8 (1.9)
Median	.	4.8	7.8	5.6
Q1, Q3		4.0, 5.6	7.8, 7.8	4.0, 7.8
Range		(4.0-5.6)	(7.8-7.8)	(4.0-7.8)
Neutrophil %				
N	0	2	1	3
Mean (SD)		67.3 (8.7)	78.0 (.)	70.8 (8.7)
Median	.	67.3	78.0	73.4
Q1, Q3		61.1, 73.4	78.0, 78.0	61.1, 78.0
Range		(61.1-73.4)	(78.0-78.0)	(61.1-78.0)
Lymphocyte Count (10^9/L)				
N	0	2	1	3
Mean (SD)		1.4 (0.3)	1.2 (.)	1.3 (0.2)
Median	.	1.4	1.2	1.2
Q1, Q3		1.2, 1.6	1.2, 1.2	1.2, 1.6
Range		(1.2-1.6)	(1.2-1.2)	(1.2-1.6)
Lymphocyte %				
N	0	2	1	3
Mean (SD)		20.3 (6.2)	12.5 (.)	17.7 (6.2)
Median	.	20.3	12.5	15.9
Q1, Q3		15.9, 24.6	12.5, 12.5	12.5, 24.6
Range		(15.9-24.6)	(12.5-12.5)	(12.5-24.6)

Table 21: Lab test in the postoperative period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	no anti-epileptic drug (N=1)	Total (N=4)
Sodium (mmol/L)				
Mean (SD)	138.0 (.)	138.5 (3.5)	136.0 (.)	137.8 (2.4)
Median	138.0	138.5	136.0	137.0
Q1, Q3	138.0, 138.0	136.0, 141.0	136.0, 136.0	136.0, 139.5
Range	(138.0-138.0)	(136.0-141.0)	(136.0-136.0)	(136.0-141.0)
Potassium (mmol/L)				
N	1	1	1	3
Mean (SD)	3.8 (.)	4.4 (.)	3.8 (.)	4.0 (0.3)
Median	3.8	4.4	3.8	3.8
Q1, Q3	3.8, 3.8	4.4, 4.4	3.8, 3.8	3.8, 4.4
Range	(3.8-3.8)	(4.4-4.4)	(3.8-3.8)	(3.8-4.4)
Chloride (mmol/L)				
Mean (SD)	106.0 (.)	104.5 (3.5)	105.0 (.)	105.0 (2.2)
Median	106.0	104.5	105.0	105.5
Q1, Q3	106.0, 106.0	102.0, 107.0	105.0, 105.0	103.5, 106.5
Range	(106.0-106.0)	(102.0-107.0)	(105.0-105.0)	(102.0-107.0)
Carbon Dioxide (mmol/L)				
Mean (SD)	25.0 (.)	23.0 (1.4)	23.0 (.)	23.5 (1.3)
Median	25.0	23.0	23.0	23.5
Q1, Q3	25.0, 25.0	22.0, 24.0	23.0, 23.0	22.5, 24.5
Range	(25.0-25.0)	(22.0-24.0)	(23.0-23.0)	(22.0-25.0)
Urea Nitrogen (mg/dL)				
Mean (SD)	13.0 (.)	15.0 (0.0)	11.0 (.)	13.5 (1.9)
Median	13.0	15.0	11.0	14.0
Q1, Q3	13.0, 13.0	15.0, 15.0	11.0, 11.0	12.0, 15.0
Range	(13.0-13.0)	(15.0-15.0)	(11.0-11.0)	(11.0-15.0)
Creatinine (mg/dL)				
Mean (SD)	1.4 (.)	0.9 (0.2)	0.6 (.)	0.9 (0.4)
Median	1.4	0.9	0.6	0.9
Q1, Q3	1.4, 1.4	0.7, 1.0	0.6, 0.6	0.7, 1.2
Range	(1.4-1.4)	(0.7-1.0)	(0.6-0.6)	(0.6-1.4)
Glucose (mg/dL)				
Mean (SD)	143.0 (.)	152.5 (7.8)	116.0 (.)	141.0 (17.8)
Median	143.0	152.5	116.0	145.0
Q1, Q3	143.0, 143.0	147.0, 158.0	116.0, 116.0	129.5, 152.5
Range	(143.0-143.0)	(147.0-158.0)	(116.0-116.0)	(116.0-158.0)
Calcium (mg/dL)				
Mean (SD)	8.9 (.)	9.1 (0.5)	8.5 (.)	8.9 (0.4)
Median	8.9	9.1	8.5	8.8
Q1, Q3	8.9, 8.9	8.7, 9.4	8.5, 8.5	8.6, 9.2
Range	(8.9-8.9)	(8.7-9.4)	(8.5-8.5)	(8.5-9.4)
Aspartate Aminotransferase (AST, unit?)				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)

Table 21: Lab test in the postoperative period

	Lacosamide (Vimpat) (N=1)	Levetiracetam (Keppra) (N=2)	no anti-epileptic drug (N=1)	Total (N=4)
ALT (Alanine Aminotransferase, u/L)				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Bilirubin, Total (mg/dL)				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Alkaline Phosphatase				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Albumin (g/dL)				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Protein, Total (g/dL)				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
White Blood Cell Count (10^9/L)				
Mean (SD)	11.6 (.)	15.3 (3.9)	21.8 (.)	16.0 (4.8)
Median	11.6	15.3	21.8	15.3
Q1, Q3	11.6, 11.6	12.5, 18.0	21.8, 21.8	12.1, 19.9
Range	(11.6-11.6)	(12.5-18.0)	(21.8-21.8)	(11.6-21.8)
Hemoglobin (g/dL)				
Mean (SD)	13.8 (.)	12.8 (2.1)	11.6 (.)	12.7 (1.5)
Median	13.8	12.8	11.6	12.7
Q1, Q3	13.8, 13.8	11.3, 14.2	11.6, 11.6	11.5, 14.0
Range	(13.8-13.8)	(11.3-14.2)	(11.6-11.6)	(11.3-14.2)
Hematocrit (%)				
Mean (SD)	40.2 (.)	36.9 (6.5)	33.6 (.)	36.9 (4.6)
Median	40.2	36.9	33.6	36.9
Q1, Q3	40.2, 40.2	32.3, 41.5	33.6, 33.6	33.0, 40.9
Range	(40.2-40.2)	(32.3-41.5)	(33.6-33.6)	(32.3-41.5)
Platelets (10^9/L)				
Mean (SD)	236.0 (.)	246.5 (12.0)	265.0 (.)	248.5 (13.9)
Median	236.0	246.5	265.0	246.5
Q1, Q3	236.0, 236.0	238.0, 255.0	265.0, 265.0	237.0, 260.0
Range	(236.0-236.0)	(238.0-255.0)	(265.0-265.0)	(236.0-265.0)
Neutrophil Count (109/L)				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Neutrophil %				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Lymphocyte Count (10^9/L)				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)
Lymphocyte %				
No	1 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)

12.11 Concomitant medications

Concomitant medications used in the baseline period and postoperative period are summarized in Tables 22 and 23, respectively. In the baseline period, one of the two patients who had levetiracetam did not have any concomitant medications.

Table 22: Concomitant medications used in the baseline period		
Treatment	**Concomitant medication**	**Purpose for use**
Levetiracetam (Keppra)	Ondansetron (zofran-odt)	Nausea and vomiting
	Olanzapine	Sleep aid
	Dronabinol (marinol)	Nausea and vomiting
	Valacyclovir (valtrex)	Antiviral
	Promethazine (Phenergan)	Antihistamine
	Pantoprazole	GERD
Lacosamide (Vimpat) 100 mg twice a day;	Montelukast	Asthma
	Fluticasone	Steroids
	Dextromethorphan-guaifenesin	Cough suppressant/expectorant
	Albuterol	Asthma
	Cannabidiol, CBD, extract orally	At night to help him sleep
No anti-epileptic drug	Cefuroxime	Antibiotic
	Acetaminophen (tylenol)	Pain
	Zofran	Anti-nausea
	Pantoprazole	Pain
	Sennosides	Constipation
	Levetiracetam (Keppra)	Anticonvulsants (including anti-epileptic drugs)
	Oxycodone	Pain
	Dexamethasone (Decadron)	Steroids

Treatment	**Concomitant medication**	**Purpose for use**
Levetiracetam (Keppra), patient 1	Acetaminophen (tylenol)	Pain
	Fluticasone	Steroids
	Promethazine	Antihistamine
	Diphenoxylate-atropine	Antidiarrheal

Treatment	Concomitant medication	Purpose for use
	Dronabinol	Nausea and vomiting
	Bacitracin ointment	Antibiotic
	Ondansetron (ZOFRAN-ODT)	Nausea and vomiting
	Polyethylene glycol (MIRALAX) packet	Laxative
	Valacyclovir (VALTREX)	Antiviral
	Olanzapine	Depression
	Lorazepam	Anxiety
	Dexamethasone (decadron)	Steroids
	Pantoprazol	Erge
Levetiracetam (Keppra), patient 2	Sennosides-docusate	Laxative
	Polyethylene glycol	Laxative
	Pantoprazole	Antiacid
	Levetiracetam (Keppra)	Anticonvulsants (including Anti-epileptic drugs)
	Dexamethasone (decadron)	Steroids
	Butalbital-acetaminophen-caffeine	Pain
	Acetaminophen (tylenol)	Pain
Lacosamide (Vimpat)	Polyethylene glycol	Osmotic laxative
	Dexamethasone (decadron)	Steroids
	Bacitracin ointment	Antibiotic
	Lacosamide (vimpat)	Anticonvulsants (including Anti-epileptic drugs)
	Pantoprazole	Edge
No anti-epileptic drug.	Acetaminophen (tylenol)	Pain
	Cefuroxime	Antibiotic
	Dexamethasone (decadron)	Steroids
	Ondansetron	Antiemetic
	Oxycodone	Pain

13. 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.