



The effect of lacosamide on psychiatric comorbidities in patients with epilepsy

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ABSTRACT

We investigated the efficacy of lacosamide (LCM) polytherapy in improving seizure outcomes and psychiatric symptoms in patients with epilepsy with psychiatric comorbidities. We retrospectively collected data from medical records of outpatients of the Department of Psychiatry of Nishiniigata Chuo Hospital Epilepsy Center in Japan. We extracted data from all patients with epilepsy and psychiatric comorbidities who had been treated with LCM. We evaluated seizure prognosis and changes in psychiatric symptoms after LCM polytherapy. After LCM administration, 19 (47.5%) patients had improvements in seizure outcomes. The other 18 (45%) patients experienced no changes in seizure outcomes, and the remaining 3 (7.5%) patients experienced worse seizure outcomes after LCM polytherapy. LCM administration improved psychiatric symptoms in 21 (52.5%) of the 40 patients; psychiatric symptoms did not change in 14 (35%) patients and worsened in 5 patients (12.5%). There was no significant association between psychiatric and seizure prognoses. LCM polytherapy may have less negative influence on psychiatric comorbidities in patients with epilepsy compared with other antiseizure medications, and may also improve seizure severity. While LCM polytherapy might improve psychiatric symptoms as seizures improve, a small number of patients experienced worsening of psychiatric symptoms despite seizure improvement.

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1. Introduction

An estimated one third of patients with epilepsy have experienced a psychiatric disorder during the course of their life [1], and psychiatric comorbidities have major impact on patients' quality of life. Indeed, some authors have reported that psychiatric comorbidities lower the quality of life of patients with epilepsy more so than does seizure frequency [2]. Furthermore, epileptic seizures can directly worsen some psychiatric symptoms in these patients [3]. Conversely, treatments to suppress seizures can sometimes worsen psychiatric symptoms [4]. In addition, psychiatric comorbidities are associated with an increased risk of premature death by external causes in patients with epilepsy [5]. Therefore, it is important to treat psychiatric symptoms in the comprehensive care of patients with epilepsy.

Antiseizure medications (ASMs) play a major role in controlling psychiatric comorbidities in patients with epilepsy. Some ASMs, such as mood stabilizers, are known to improve psychiatric symptoms, whereas others can themselves have psychiatric side effects [6]. Lacosamide (LCM) is a new-generation ASM that selectively enhances slow sodium-channel inactivation [7]. In Japan, it is indicated as monotherapy at doses of up to 400 mg/day and as adjunctive therapy in patients with focal onset seizures. LCM is generally well tolerated by people with intellectual disabilities and mental health disorders, and can aid seizure control in adult patients with epilepsy [8]. However, there have been very few reports regarding the effects of LCM on psychiatric comorbidities; one study reported that LCM was effective and well tolerated in patients with epilepsy with psychiatric comorbidities, which mainly included depression and anxiety [9]. However, there have been no comprehensive reports on the effect of LCM in patients with severe comorbidities, such as irritability and psychosis.

In the present study, we investigated the clinical characteristics of patients who had epilepsy with psychiatric comorbidities that were treated with LCM in the psychiatry department of our epilepsy center. The purpose of our study was to clarify the effects

Abbreviations: ASMs, antiseizure medications; LCM, lacosamide; LEV, levetiracetam; SD, standard deviation.

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of LCM in patients with epilepsy with relatively severe psychiatric comorbidities.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the medical records of outpatients of the Department of Psychiatry of Nishiniigata Chuo National Hospital Epilepsy Center. We extracted data from all patients with epilepsy and psychiatric comorbidities who had been treated with LCM. We extracted data from medical records on the diagnoses of psychiatric comorbidities, including psychosis, irritability, depression, anxiety, psychogenic non-epileptic attacks (PNEA), amnesia, personality change due to epilepsy, and obsessive-compulsive symptoms. Intellectual disabilities and developmental disorders, such as autism spectrum disorder, were assessed separately from psychiatric comorbidity. Intellectual disability was diagnosed based on intelligence tests, such as the Wechsler Adult Intelligence Scale and Tanaka-Binet test, or by their developmental history if intelligence test scores were not available. All patients were older than 18 years and were under the care of a single clinical epilepsy specialist who was certified by the Japan Epilepsy Society and a psychiatrist certified by the Japanese Board of Psychiatry. All patients were diagnosed with focal epilepsy based on a comprehensive assessment of seizure symptoms, electroencephalography, magnetic resonance imaging, and other laboratory findings. We

recruited patients who were followed as outpatients and had been observed for at least 3 months after LCM administration. Regarding the method of LCM administration, the starting dose was 100 mg/day, and this was gradually increased by 100 mg over a period of at least 4 weeks. A retrospective analysis of electronic and paper-based medical records was conducted for each patient to establish detailed demographic information.

This study was performed in compliance with the Declaration of Helsinki, and the study protocol was approved by Nishiniigata Chuo Hospital Ethics Committee. Informed consent of individual patients was waived given that personal information was encrypted.

2.2. Seizure outcomes and psychiatric symptoms

Seizure prognosis and changes in psychiatric symptoms after LCM polytherapy were evaluated using data from medical records. The seizure prognosis was judged according to seizure frequency before LCM administration and during the last follow-up visit, according to which patients were classified into the three following groups: “improvement” was defined as a $\geq 50\%$ reduction in seizure frequency after LCM administration; “unchanged” was defined as a seizure frequency reduction $< 50\%$; and “worsened” was defined as a seizure frequency that increased after LCM administration. Psychiatric changes were also used to classify patients into “improved,” “unchanged,” and “worsened” groups. Psychiatric symptoms were assessed according to patients’ complaints or

Table 1
Demographic and clinical data of patients.

N	45
Sex (male/female)	25/20
Age, mean \pm SD (range)	46.2 \pm 17.2 years (22–80 years)
Age at epilepsy onset, mean \pm SD (range)	20.4 \pm 19.7 years (0–67 years)
Duration of epilepsy, mean \pm SD (range)	25.8 \pm 17.6 years (1–54)
Seizure frequency at initiation of LCM (per month)	20.2 \pm 54.0 (0–335)
Epilepsy diagnosis	
Temporal lobe epilepsy (including mesial temporal lobe epilepsy)	14 (31.1%)
Frontal lobe epilepsy	2 (4.4%)
Occipital lobe epilepsy	1 (2.2%)
Focal epilepsy with undetermined focus area	28 (62.2%)
No. of patients with intellectual disability (IQ < 70)	23 (51.1%)
No. of patients with developmental disorders	9 (20%)
Psychiatric comorbidities, No. (%)	
Irritability	17 (37.8%)
Psychosis	13 (28.9%)
Anxiety	5 (11.1%)
Psychogenic non-epileptic seizures	4 (8.9%)
Amnesia	2 (4.4%)
Personality change	2 (4.4%)
Obsessive-compulsive symptoms	1 (2.2%)
Depression	1 (2.2%)
Maintenance dose of LCM, mean \pm SD (range)	328 \pm 92.5 mg/day (200–400 mg/day)
Follow-up period after initiation of LCM, mean \pm SD (range)	542 \pm 301 days (28–1084 days)
ASMs	
No. of concomitant ASMs at initiation of LCM, mean \pm SD (range)	1.89 \pm 1.5 (0–6)
Discontinuation of other ASMs after initiation of LCM	25 (55.6%)
Addition of ASMs after initiation of LCM	8 (17.8%)
Seizure-free status	
Seizure-free before LCM initiation	9 (20.0%)
Seizure-free after LCM initiation	11 (24.4%)
Seizure outcomes after administration of LCM, No. of patients (%)	
Improvement of seizures (including achievement of seizure-free status)	19 (42.2%)
No change in seizures (including original seizure-free status)	18 (40%)
Worsening of seizures	3 (6.7%)
Discontinuation of LCM, No. of patients (%)	5 (11.1%)
Adverse effects/complaints	2/5
Ineffective seizure control	1/5
Economic issues	1/5
Adverse effects of worsening psychiatric symptoms	1/5

ASM: antiseizure medicine; LCM: lacosamide; SD: standard deviation.

Table 2
List of patients whose psychiatric symptoms improved after initiation of lacosamide.

No	Age	Sex	Epilepsy syndrome	Etiology	Types of psychiatric comorbidities	LCM dose (mg/day)	Seizure prognosis	Concomitant ASMs	ASMs terminated after LCM initiation	ASMs added after LCM initiation	Psychiatric medication	Changes in psychiatric medication after LCM initiation
1	29	F	Focal epilepsy	Unknown	PNEA	400	Improved	VPA, CZP	CBZ			
2	25	F	Focal epilepsy	Autoimmunity	PNEA	200	Improved	VPA, LEV	ZNS,CLB		quetiapine, olanzapine	Added immunotherapy
3	70	F	Temporal epilepsy	Unknown	Amnesia	300	Improved	None	LEV			
4	69	F	Temporal epilepsy	Unknown	Amnesia	200	Improved	None				
5	27	M	Focal epilepsy	Unknown	Irritability	400	Improved	PHT, VPA, CZP, TPM, LTG, PER			levomepromazine, risperidone	discontinue risperidone
6	34	F	Focal epilepsy	Unknown	Psychosis	400	Improved	LTG, PER	VPA	PER	blonanserin, risperidone	discontinue blonanserin and risperidone, add brexpiprazole
7	43	M	Focal epilepsy	Unknown	Irritability	400	Improved	VPA, LEV	PER		risperidone	
8	37	M	Focal epilepsy	Unknown	Irritability	400	Improved	VPA	PB			
9	68	M	Focal epilepsy	Post cerebral hemorrhage	Irritability	400	Improved	CLB, LTG, PER	ZNS	LTG	risperidone	
10	43	M	Temporal epilepsy	Unknown	Anxiety	300	Improved	None				add sertraline
11	27	F	Focal epilepsy	Brain contusion	Irritability	200	Improved	CLB, VPA, LEV	ZNS,CLB			
12	58	F	Temporal epilepsy	Unknown	Anxiety	300	Unchanged	LEV			paroxetine	discontinue paroxetine
13	68	F	Mesial temporal epilepsy	Amygdala enlargement	Anxiety	200	Unchanged	CZP, PER	LEV	PER		
14	62	F	Temporal epilepsy	Unknown	Psychosis	400	Unchanged	PER	CBZ		risperidone, haloperidol	discontinue haloperidol
15	24	M	Frontal epilepsy	Unknown	Irritability	300	Unchanged	None	LEV			
16	39	M	Focal epilepsy	Lissencephaly	Irritability	200	Unchanged	PB, VPA, LEV			risperidone	
17	26	F	Temporal epilepsy	Unknown	Irritability	400	Unchanged	VPA, LEV	LEV		risperidone	discontinue risperidone
18	40	F	Focal epilepsy	Unknown	PNEA	250	Unchanged	None	ZNS,PER			
19	39	F	Focal epilepsy	Unknown	PNEA	200	Unchanged	None	PER			
20	27	F	Focal epilepsy	Unknown	Irritability	400	Unchanged	PER	PHT		risperidone, sertraline	
21	28	F	Focal epilepsy	Autoimmunity	Irritability	400	Unchanged	PB, VPA, LEV			risperidone	Added immunotherapy

ASM: antiseizure medicine; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; PB: phenobarbital; PER: perampanel; PHT: phenytoin; TPM: topiramate; VPA: sodium valproate; ZNS: zonisamide.

observations of their families or caregivers. We also investigated which ASMs were added or discontinued after LCM administration in each patient.

2.3. Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics 24 (IBM Corp., Armonk, NY, US). We used the chi-squared test to assess whether changes in psychiatric symptoms were associated with seizure prognosis. Significance was defined as a $p \leq 0.05$.

3. Results

3.1. Patient characteristics

A total of 45 patients with psychiatric comorbidities prescribed LCM were included in this study. Demographic and clinical data for the patients are shown in Table 1. A relatively large number of patients had drug-resistant epilepsy, had a long disease duration, and were prescribed LCM as polytherapy. Forty out of 45 patients were able to continue LCM for more than 3 months, and nine patients achieved seizure free status. Only one of the five patients who discontinued LCM discontinued LCM because of worsening psychiatric symptoms. This patient had mesial temporal lobe epilepsy, had been treated with both levetiracetam (LEV) and perampanel, and had a psychiatric comorbidity of irritability. Irritability

worsened immediately after LCM administration; LCM was therefore discontinued, after which irritability immediately improved. In this patient, the exacerbation of psychiatric symptoms was likely to have been an adverse effect of LCM itself.

Twenty-five (55.6%) patients had already been prescribed psychiatric medication. All patients had been on chronic psychiatric medication for at least 6 months before being prescribed LCM. Twenty of the 25 patients had been prescribed antipsychotics, four patients had been prescribed antidepressants, and one patient had received both antipsychotics and antidepressants. All patients or their families had received supportive psychotherapy from a psychiatrist. None of the patients had received insight-oriented psychotherapy, attempted suicide, or performed other acts of self-harm.

3.2. Outcomes of psychiatric symptoms

Five patients who had discontinued LCM within 3 months were excluded, and changes in psychiatric symptoms were investigated in the remaining 40 patients.

After LCM administration, 21 (52.5%) patients were classified into the improved group for psychiatric changes (Table 2), 14 (35%) into the unchanged group (Table 3), and 5 (12.5%) into the worsened group (Table 4).

Of the 21 patients in the improved group for psychiatric changes, 11 (52.4%), 10 (47.6%), and 0 (0%) patients had improved,

Table 3
List of patients whose psychiatric symptoms did not change after initiation of lacosamide.

No	Age	Sex	Epilepsy syndrome	Etiology	Types of psychiatric comorbidities	LCM dose (mg/day)	Seizure prognosis	Concomitant ASMs	ASMs terminated after LCM initiation	ASMs added after LCM initiation	Psychiatric medication	Changes in psychiatric medication after LCM initiation
22	67	F	Focal epilepsy	Unknown	Psychosis	400	Improved	GBP	PHT		haloperidol	
23	63	M	Mesial temporal epilepsy	Unknown	Psychosis	400	Improved	PHT, LEV, PER		PER		
24	70	F	Mesial temporal epilepsy	Amygdala enlargement	Amnesia	300	Improved	None			paroxetine	discontinue paroxetine
25	27	M	Focal epilepsy	Unknown	Irritability	200	Improved	CBZ		Added CBZ for mood stabilization		add risperidone
26	55	F	Focal epilepsy	Periventricular nodular heterotopia	Personality disorder	400	Improved	LEV,TPM	CBZ, PHT			
27	66	M	Mesial temporal epilepsy	Hippocampal sclerosis	Psychosis	400	Unchanged	PER	PHT	PER	haloperidol, risperidone	discontinue risperidone
28	46	M	Focal epilepsy	Unknown	Psychosis	200	Unchanged	PHT,VPA,PER, DZP			haloperidol, pimozide	
29	48	M	Focal epilepsy	Brain contusion	Irritability	400	Unchanged	VPA,LEV,PER	CBZ		risperidone	
30	48	M	Mesial temporal epilepsy	Brain contusion	Irritability	400	Unchanged	CLB, LEV, LTG, PER	LTG			
31	27	M	Focal epilepsy	Unknown	Irritability	400	Unchanged	None	CBZ		risperidone	
32	62	F	Focal epilepsy	Porencephaly	Psychosis	400	Unchanged	PB	PHT		risperidone	
33	79	F	Focal epilepsy	Unknown	depression	200	Unchanged	PER	PHT		paroxetine	
34	42	M	Focal epilepsy	Brain contusion	Irritability	400	Worsened	CLB, PRM, LEV, PER	PHT	PER	risperidone	
35	66	F	Focal epilepsy	Unknown	Psychosis	300	Worsened	CBZ, PHT, PRM, LTG, LEV	PHT			

ASM: antiseizure medicine; CBZ: carbamazepine; CLB: clobazam; DZP: diazepam; GBP: gabapentin; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; PB: phenobarbital; PER: perampanel; PHT: phenytoin; PRM: primidone; TPM: topiramate; VPA: sodium valproate.

Table 4
List of patients whose psychiatric symptoms worsened after initiation of lacosamide.

No	Age	Sex	Epilepsy syndrome	Etiology	Types of psychiatric comorbidities	LCM dose (mg/day)	Seizure prognosis	Concomitant ASMs	ASMs terminated after LCM initiation	ASMs added after LCM initiation	Psychiatric medication	Changes in psychiatric medication after LCM initiation
36	80	F	Mesial temporal epilepsy	Hippocampal sclerosis	Psychosis	200	Improved	LEV	PHT			add risperidone
37	35	F	Focal epilepsy	Focal cortical dysplasia	Psychosis	400	Improved	LEV, PER	PB,PHT	PER		add risperidone
38	29	M	Focal epilepsy	Brain contusion	Psychosis	400	Improved	CBZ, LTG, LEV, PER			paliperidone	
39	22	M	Frontal epilepsy	Unknown	Irritability	400	Unchanged	PER	CBZ			
40	54	M	Occipital epilepsy	Focal cortical dysplasia	Psychosis	400	Worsened	PHT, PRM, LEV	ZNS		blonanserin	add olanzapine

ASM: antiseizure medicine; CBZ: carbamazepine; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; PB: phenobarbital; PER: perampanel; PHT: phenytoin; PRM: primidone; ZNS: zonisamide.

unchanged, and worsened seizure outcomes, respectively. Of the 14 patients in the unchanged group for psychiatric changes, five (35.7%), seven (50%), and two (14.3%) patients had improved, unchanged, and worsened seizure outcomes, respectively. Of the five patients in the worsened group for psychiatric changes, three patients were in the improved group for seizure outcomes, and the other two were in the unchanged and worsened groups, respectively. The chi-squared test did not reveal a significant association between psychiatric and seizure prognoses ($p = 0.29$).

In the improved group for psychiatric changes, 11 of the 21 patients received psychiatric medication prior to LCM. The psychiatric medications were discontinued or reduced in dose in five of these 11 patients, whereas only one patient received an additional psychiatric drug after LCM administration. In the remaining five patients, psychiatric medication did not change during the observation period.

In the worsened group for psychiatric changes, three patients received additional antipsychotics after LCM administration. However, none of the patients in this group had serious behavioral problems, such as suicide attempts, after LCM administration.

Regarding concomitant ASMs, four out of five patients (80%) in the psychiatrically worsened group received LEV, whereas seven out of 21 patients (33.3%) in the psychiatric improvement group and six out of 14 patients (42.9%) in the unchanged group received LEV.

4. Discussion

In the present study, 42% of patients with epilepsy with psychiatric comorbidities experienced a $\geq 50\%$ reduction in seizure frequency after LCM administration. In addition, LCM had to be discontinued in only one patient owing to psychiatric symptoms within 3 months after LCM administration. After a relatively long period following LCM introduction (an average of 18 months), only 5 of the 40 patients (12.5%) experienced worsening of psychiatric comorbidities, and the remaining patients exhibited improvement or no change in psychiatric symptoms. These results indicate that LCM is a safe ASM in patients with psychiatric symptoms. Patients with epilepsy and psychiatric comorbidities have been reported to be at an increased risk of psychiatric adverse events due to ASMs [1]. However, previous studies have reported that LCM has fewer and less severe psychiatric and behavioral side effects than other ASMs [6,11]. The present results also suggest that LCM has relatively few psychiatric adverse effects and high retention rates over relatively long periods, even in patients with psychiatric symptoms.

We found no significant association between the prognosis of psychiatric comorbidities and epileptic seizures after LCM administration. Approximately half of the patients who had an improvement in psychiatric comorbidities also experienced an improvement in seizure outcomes following administration of LCM and other ASMs. Additionally, only 1 of the 21 patients with improved psychiatric symptoms after LCM administration required additional psychotropic medication. In patients who had improvements in both seizures and psychiatric comorbidities, the psychiatric comorbidities were peri-ictal psychiatric symptoms, which appear with seizure occurrence [3] and have been reported to improve when epileptic seizures are suppressed [10].

In the present study, the proportion of patients who received LEV as concomitant ASMs was relatively high among patients whose psychiatric symptoms worsened after LCM administration. In addition, the only patient for whom LCM was discontinued due to a worsening of psychiatric symptoms, also received LEV. LEV is an ASM with evidence for psychiatric side effects, such as irritability and aggression [11]. However, to our knowledge, there have been no previous reports that suggested that the combination of LCM and LEV is more likely to cause psychiatric side effects. Although it is difficult to draw definitive conclusions from our results, the combination of LCM and LEV to treat patients with epilepsy with psychiatric symptoms we speculate may increase the risk of exacerbation of psychiatric symptoms. Larger-scale studies are required to investigate this possibility further.

The present study has a number of limitations, including its retrospective approach. This was a case-series study, which limits the objectivity of the results and their interpretation. Various factors not considered in this discussion, such as types of psychiatric symptoms and concomitant ASMs, could also be involved in the prognosis of psychiatric symptoms. Additionally, the evaluation of psychiatric symptoms was not based on systematic evaluations, such as structured interviews or quantitative evaluations using rating scales. Consequently, the assessments of the presence and severity of psychiatric and behavioral symptoms were subjective. Further intervention studies that adopt systematic evaluations are needed to verify this preliminary report on the utility of LCM in these patients.

5. Conclusion

LCM polytherapy did not lead to the worsening of outcomes of psychiatric symptoms in most patients with epilepsy with psychiatric comorbidities. In addition, the retention rate of LCM in these patients was relatively high. Our result suggest in some patients,

LCM is not detrimental when used in patients with psychiatric comorbidities and focal epilepsies.

Ethical statement

This manuscript has not been published and is not under consideration for publication elsewhere. Both authors have read the manuscript and have approved this submission. The study design was approved by Nishiniigata Chuo Hospital Ethics Committee. This study was performed in compliance with the Declaration of Helsinki.

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Author contributions

Dr. Hasegawa conceived the idea, collected and analyzed the data, and wrote the manuscript. Dr. Fukuda helped to write the manuscript. Both authors discussed the results and contributed to the final manuscript.

References

- [1] Kanner AM. Psychiatric comorbidities in epilepsy: Should they be considered in the classification of epileptic disorders?. *Epilepsy Behav* 2016;64:306–8.
- [2] Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* 2004;62:258–61.
- [3] Mula M, Monaco F. Ictal and peri-ictal psychopathology. *Behav Neurol* 2011;24:21–5.
- [4] de Toffol B, Trimble M, Hesdorffer DC, Taylor L, Sachdev P, Clancy M, et al. Pharmacotherapy in patients with epilepsy and psychosis. *Epilepsy Behav* 2018;88:54–60.
- [5] Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet* 2013;382:1646–54.
- [6] Moavero R, Santarone ME, Galasso C, Curatolo P. Cognitive and behavioral effects of new antiepileptic drugs in pediatric epilepsy. *Brain Dev* 2017;39:464–9.
- [7] Errington AC, Stohr T, Heers C, Lees G. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. *Mol Pharmacol* 2008;73:157–69.
- [8] McGinty RN, Costello DJ. Long-term lacosamide retention-Real-world experience at a tertiary epilepsy center in Ireland. *Epilepsy Behav* 2017;68:141–5.
- [9] Schmitz B, Dimova S, Zhang Y, Chellun D, De Backer M, Gasalla T. Tolerability and efficacy of lacosamide and controlled-release carbamazepine monotherapy in patients with newly diagnosed epilepsy and concomitant psychiatric conditions: Post hoc analysis of a prospective, randomized, double-blind trial. *Epilepsy Res* 2020;159:106220.
- [10] Hingray C, McGonigal A, Kotwas I, Micoulaud-Franchi JA. The relationship between epilepsy and anxiety disorders. *Curr Psychiatry Rep* 2019;21:40.
- [11] Hansen CC, Ljung H, Brodtkorb E, Reimers A. Mechanisms underlying aggressive behavior induced by antiepileptic drugs: focus on topiramate, levetiracetam, and perampanel. *Behav Neurol* 2018;2018:2064027.