The effect of lacosamide on psychiatric comorbidities in patients with epilepsy

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A R T I C L E   I N F O

Article history:
Received 20 August 2020
Revised 2 November 2020
Accepted 5 November 2020
Available online 19 November 2020

Keywords:
Lacosamide
Psychiatric comorbidities
Peri-ictal psychiatric symptoms
Psychiatric side effects

A B S T R A C T

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 Nishinigiita 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
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 Nishinigata 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 Nishinigata 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 ≥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 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.

| Measure                                     | N   | Result                          |
|---------------------------------------------|-----|--------------------------------|
| N                                           | 45  |
| Sex (male/female)                           | 25/20|
| Age, mean ± SD (range)                      | 46.2 ± 17.2 years (22–80 years) |
| Age at epilepsy onset, mean ± SD (range)    | 20.4 ± 19.7 years (0–67 years)  |
| Duration of epilepsy, mean ± SD (range)     | 25.8 ± 17.6 years (1–54)       |
| Seizure frequency at initiation of LCM (per month) | 20.2 ± 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 ± SD (range)  | 328 ± 92.5 mg/day (200–400 mg/day) |
| Follow-up period after initiation of LCM, mean ± SD (range) | 542 ± 301 days (28–1084 days) |
| ASMs                                        |     |
| No. of concomitant ASMs at initiation of LCM, mean ± SD (range) | 1.89 ± 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 (%) | 19 (42.2%) |
| 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.
| 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 |                      |                               |                      |                                            |
| 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, LEV, CZP, TPM, LTG, PER |                               |                      | levomepromazine, risperidone, discontinue risperidone |
| 6  | 34  | F   | Focal epilepsy    | Unknown  | Psychosis                         | 400              | Improved         | 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, discontinue haloperidol                           |
| 15 | 24  | M   | Frontal epilepsy  | Unknown  | Irritability                       | 300              | Unchanged        | None            | LEV                           |                               |                      | haloperidol                                               |
| 16 | 39  | M   | Focal epilepsy    | Lissencephaly | Irritability | 200 | Unchanged | PB, VPA, LEV |                            |                               |                      | risperidone, discontinue haloperidol                           |
| 17 | 26  | F   | Temporal epilepsy | Unknown  | Irritability                       | 400              | Unchanged        | VPA, LEV | LEV                      |                               |                      |                                                                    |
| 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                           |                               |                      |                                                                    |
| 21 | 28  | F   | Focal epilepsy    | Autoimmunity | Irritability | 400 | Unchanged | PB, VPA, LEV |                            |                               |                      |                                                                    |

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, 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.

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Of the 21 patients in the improved group for psychiatric changes, 11 (52.4%), 10 (47.6%), and 0 (0%) patients had improved,
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 Nishinigata Chuo Hospital Ethics Committee. This study was performed in compliance with the Declaration of Helsinki.

**Acknowledgments**

The authors would like to thank the patients, their caregivers, and the staff at our epilepsy center who facilitated this study as investigators. We also thank Nia Cason, PhD, and Sarina Iwabuchi, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

**Funding**

The authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors for this study.

**Declaration of interest**

Dr. Hasegawa has received honoraria from DAIICHI SANKYO Co Ltd., UCB Japan Co. Ltd. and Eisai Co. Ltd., and research support from Eisai Co. Ltd. Dr. Fukuda is a Principal Investigator of clinical trials sponsored by UCB Japan Co. Ltd., and received research support from Eisai Co., Ltd., and an honoraria lecture fee from DAIICHI SANKYO Co Ltd.

**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.

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