

Comparison of Psychiatric Disorders Between Levetiracetam Combined With Lacosamide and Perampanel

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Research Article

Keywords: antiepileptic drug, epilepsy, lacosamide, levetiracetam, perampanel, psychiatric disorder

Posted Date: January 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-161799/v1>

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Abstract

Background The number of patients with epilepsy receiving perampanel or lacosamide as an add-on treatment following levetiracetam treatment has increased. Although levetiracetam causes psychiatric disorders, it is unclear whether they occur with the combined use of these antiepileptic drugs.

Objective To determine the frequency of psychiatric disorders in patients using lacosamide or perampanel as an add-on therapy to levetiracetam. *Setting* A single-center retrospective cohort study.

Methods Patients who received levetiracetam, lacosamide, and perampanel between April 1, 2014 and April 30, 2019 in Hachioji Medical Center were selected. They were classified into the levetiracetam+lacosamide or levetiracetam+perampanel group. Medical records from the start of combination therapy contained patient background and the incidence of psychiatric disorders. *Main outcome measure* Onset of psychiatric disorders.

Results Forty-four patients used levetiracetam+lacosamide and 50 used levetiracetam+perampanel. The incidence of psychiatric disorders was significantly lower ($p = 0.000047$) with levetiracetam+lacosamide (6.8%) than with levetiracetam+perampanel (46%). The time to the onset of psychiatric disorders was within 1 month of dose initiation or increase in one case (33.3%) with levetiracetam+lacosamide and 16 cases (76.2%) with levetiracetam+perampanel. The median time to onset was 56 and 6.5 days with levetiracetam+lacosamide and levetiracetam+perampanel, respectively. There was no significant difference in antiepileptic drug dosages owing to the presence or absence of psychiatric disorders.

Conclusion As the frequency of psychiatric disorders was higher with levetiracetam+perampanel therapy, levetiracetam+lacosamide may be preferable. These disorders tended to develop within 1 month of therapy and were not dose-dependent. Antiepileptic drugs should be cautiously prescribed to avoid psychiatric disorders.

Impacts On Practice

- Effects of combination therapies of lacosamide or perampanel with levetiracetam are described.
- Incidence of psychiatric disorders is lower with levetiracetam + lacosamide than with levetiracetam + perampanel.
- Levetiracetam + lacosamide is expected to be a preferable combination therapy over levetiracetam + perampanel in terms of psychiatric aspects.

Introduction

The quality of life of patients with epilepsy is affected more by adverse reactions associated with treatment than by the frequency of seizures [1]. Therefore, comprehensive care is an important aspect of epilepsy care [1]. Adverse reactions add to the complexity when treating epilepsy with adequate doses of antiepileptic drugs (AEDs) [2], leading to poor adherence and treatment interruption [3, 4].

Among the newer AEDs, levetiracetam (LEV) prescription has considerably increased [5]. LEV has a rapid onset of action and reaches a steady-state concentration in 2 days [7, 8]. Although drug interactions have been associated with conventional AEDs, LEV does not interact with other drugs [7]. It is available in oral dosage and injection forms, facilitating administration via various routes. It is recommended as one of the first-line AEDs for focal and generalized epilepsy in the Japanese Epilepsy Treatment Guidelines (Japanese Society of Neurology, 2018). In addition to LEV, perampanel (PER) and lacosamide (LCM) were approved in Japan in 2016, and they are being increasingly prescribed. PER and LCM have been recommended in the aforementioned guidelines as second-line AEDs for focal epilepsy (Japanese Society of Neurology, 2018). However, among adverse effects of LEV, psychiatric disorders have been reported in several cases. In a study on psychiatric and behavioral disorders in 4,085 new patients receiving AEDs, LEV was associated with the highest frequency (22.1%) of psychiatric and behavioral disorders, and the average incidence of AED-induced psychiatric disorders in patients receiving AED monotherapy was 7.2% [9]. Moreover, in a case–control study on the relationship between the use of each AED and psychiatric disorders, a substantially higher rate of LEV use was reported in the group with psychiatric disorders [10]. The Japanese Epilepsy Treatment Guidelines also state that the use of LEV should be avoided in patients with depression, anxiety, or psychotic disorders [8].

Our hospital has an acute care facility, and we treat several cases of status epilepticus in the emergency room. Patients are commonly administered LEV initially for seizure prophylaxis, and LCM or PER is added in cases of uncontrolled disease. PER has been found to be associated with the development of psychiatric disorders [11]. Psychiatric disorders occurred more frequently in the 8 (17.2%) and 12 (22.4%) mg PER groups versus the placebo group (12.4%) [12]. LCM may be well tolerated in patients with comorbid psychiatric disorders [13]. Treatment of 40 epilepsy patients with comorbid psychiatric disorders due to LCM resulted in an improvement in 21 patients (52.5%), stable status in 14 (35%), and worsening in 5 (12.5%) patients [14]. One study reported the frequency of psychiatric disorders with the combination therapy of LEV and PER [15]. However, the incidence of psychiatric disorders associated with the combination therapy of LEV and LCM is unknown.

Aim of the study

We determined the frequency of psychiatric disorders in patients who were prescribed LCM or PER in combination with LEV. We also determined the characteristics of AED-induced psychiatric disorders in detail by investigating the time to onset, dose reduction or discontinuation following psychiatric disorders, and the clinical course following disorder onset.

Ethics approval

This study was approved by the Showa University ethics committee (number: 3097). Information regarding retrospective research was made available on our website to ensure that the research subjects had the opportunity to refuse their data being used in this study.

Methods

Patients

This study was conducted in the Tokyo Medical University Hachioji Medical Center, Japan. Patients who received LCM or PER in combination with LEV for epilepsy between April 1, 2016 and April 30, 2019 were included in the study. The following patients were excluded: those who received the above drugs for a diagnosis other than epilepsy; those who had already developed psychiatric symptoms following AED use before initiating the combination therapy; those with a history of psychiatric disorders caused by AEDs; those in whom AEDs increased with a titration scheme that did not follow the approved dosage; those who were not followed up after the initiation of AEDs during the study period; and patients whose data were not available for analysis.

Study design

This was a retrospective cohort study. One investigator examined the medical records of the patients for medication history. The duration covered was from the start of the combination therapy with the two AEDs to the last follow-up. Data, including those for the presence and absence of psychiatric disorders, were statistically analyzed for differences between the following groups: LEV and LCM combination therapy (LEV+LCM) and LEV and PER combination therapy (LEV+PER) groups. AEDs were prescribed by neurosurgeons, neurologists, and emergency physicians; the patients were examined for the development of psychiatric symptoms at check-up, as psychiatric symptoms are a well-known adverse effect of LEV. Data were collected by a single investigator to minimize inter-observer variability caused by multiple individuals collecting and recording data.

Evaluation criteria and data collection

The primary endpoint of the study was the onset of psychiatric disorders. The presence or absence of psychiatric disorders was determined by the investigator based on the information assessed and recorded by the neurosurgery, neurology, and emergency physicians in routine practice. Psychiatric disorders were categorized into System Organ Class in MedDRA/J ver. 5, with each adverse effect assigned to one of its preferred terms (e.g., depression, psychotic symptoms, anxiety, affect lability, suicide attempt, suicidal ideation, nervousness, aggression, restlessness, hyperkinesia, and mood alteration). Data on time to psychiatric disorder onset, coping (reduction and discontinuation) following psychiatric disorder onset, and the subsequent changes in coping were collected. Data on patient background; age; sex; number of AEDs taken at the start of the target duration; epilepsy classification; each AED dosage; concomitant use of ZNS and TPM, which is supposed to induce psychiatric disorders; and concomitant use of carbamazepine (CBZ), lamotrigine (LTG), and sodium valproate (VPA), which are beneficial for psychiatric disorders, were also collected.

Statistical analysis

The sample size (116) was determined using the average incidence of psychiatric disorders, a 3-fold odds ratio for the development of AED-induced psychiatric disorders, a power of 80%, and a significant difference of 5%. Comparisons between groups were performed using Pearson's chi-square test and Fisher's exact test for categorical data and Mann–Whitney *U* test for quantitative data. To eliminate confounding factors from patient background data, a multivariate logistic regression analysis was performed. The significance level was set at 5%. The statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY, USA).

Results

Patient background

One hundred and eighteen patients who were treated with LEV, LCM, and PER during the study period were identified from the hospital medical records. Of these, 24 patients who met the exclusion criteria were excluded from the analysis; thus, 94 patients remained in the study. Forty-four patients treated with LEV + LCM and 50 treated with LEV + PER were enrolled, and patient information was collected from the start of the combination therapy to the observable period. The average age of the patients was 54.6 years; 52.3% of the patients were men. The intergroup differences in age, sex, epilepsy classification, psychiatric disorder history, follow-up period, and LEV dose were not significant. The number of concomitant AEDs was higher in the LEV + PER group than in the LEV + LCM group. Furthermore, the concomitant use of CBZ and VPA was significantly higher in the LEV + PER group than in the LEV + LCM group (20% vs. 0%; $p = 0.0014$, and 20% vs. 4.5%; $p = 0.003$) (Table 1).

All patients receiving PER were started on 2 mg once daily dose, which was increased to a maximum of 2 mg per week, with a maximum dose of 12 mg per day. All patients receiving LCM were started on 50 mg twice daily dose, which was increased to a maximum dose of 100 mg per week, with a maximum dose of 400 mg per day. LEV was started at 250 to 1000 mg per day, with a maximum daily dose of 3000 mg.

Table 1
Background of the patients

		LEV+ LCM n = 44	LEV+ PER n = 50	p value
Age (years) ^{a)}		57.3 ± 21.4	51.8 ± 19.3	0.20
Sex (%)	Male	54.5	50	0.66
	Female	45.5	50	
Epilepsy classification (%)	Generalized	0	6	0.25
	Focal	90.9	88	0.75
	Unknown	9.1	6	0.70
History of psychiatric disorders (%)		6.8	10	0.58
Follow-up period (months) ^{b)}		6.0	9.0	0.81
Number of concomitant AEDs (%) (Excluded LEV, LCM, and PER)	0	86.4	48	< 0.001
	1	4.5	22	0.0171
	2	6.8	12	0.495
	3 or more	2.3	18	0.0133
Concomitant AEDs supposed to induce psychiatric disorders (%)	ZNS	2.3	6.0	0.62
	TPM	4.5	6.0	1.00
Concomitant AEDs beneficial for psychiatric disorders (%)	CBZ	0	20	0.0014
	LTG	6.8	16	0.21
	VPA	4.5	20	0.003
LEV dose (mg/day) ^{a)}		1,858 ± 698	1,900 ± 639	0.76
(a Mean ± standard deviation, (b Median				
AED, antiepileptic drug; LEV, levetiracetam; LCM, lacosamide; PER, perampanel; ZNS, zonisamide; TPM, topiramate; CBZ, carbamazepine; LTG, lamotrigine; VPA, sodium valproate				

Onset of AED-induced psychiatric disorders

The incidence of AED-induced psychiatric disorders was significantly higher in the LEV + PER group (46%) than in the LEV + LCM group (6.8%) ($p = 0.000047$; Fig. 1). AED-induced psychiatric disorders included depression (1 and 4 cases), affect lability (1 and 9 cases), aggression (1 and 5 cases), and anxiety (1 and 6 cases) in the LEV + LCM and LEV + PER groups, respectively. The incidence of affect lability was significantly higher in the LEV + PER group than in the LEV + LCM group ($p = 0.018$). Only one patient had both depression and irritability (Table 2). The time from the start of combination therapy to the onset of AED-induced psychiatric disorders was less than 1 month in one case and more than 1 month in two cases in the LEV + LCM group, and it was less than 1 month in 16 cases and more than 1 month in six cases in the LEV + PER group. The median time to onset was 56 and 7 days in the LEV + LCM and LEV + PER groups, respectively. There was no significant difference in AED dosage according to the presence or absence of psychiatric disorders (Table 3).

Table 2
Details of AED-induced psychiatric disorders

Psychiatric disorders	LEV + LCM n = 3	LEV + PER n = 23	<i>p</i> value
Depression	1	5	0.209
Affect lability	1	9	0.018
Aggression	1	4	0.489
Anxiety	0	6	1.000
LEV, levetiracetam; LCM, lacosamide; PER, perampanel			

Table 3
Comparison of AED doses with respect to the presence or absence of psychiatric disorders ^(a)

		Dose associated with the absence of psychiatric disorders (mg/day)	Dose associated with the presence of psychiatric disorders (mg/day)	<i>p</i> value
LEV + LCM	LEV LCM	1,872 ± 710 163 ± 58	1,667 ± 577 200 ± 0	0.69 0.32
LEV + PER	LEV PER	1,839 ± 653 4.18 ± 2.5	1,977 ± 626 4.91 ± 2.94	0.38 0.38
^(a) Mean ± standard deviation				
LEV, levetiracetam; LCM, lacosamide; PER, perampanel				

Multivariate logistic regression analysis

A multivariate analysis was performed to determine the effects of confounding factors that were significant in the LEV + PER group. The presence of psychiatric disorders was set as the dependent variable. The LEV + PER group was an independent determinant of psychiatric disorder development (odds ratio: 10.275, 95% CI: 2.613–40.398, *p* value: 0.001). No significant factors affecting psychiatric disorders were detected, except in the LEV + PER group (Table 4).

Table 4
Multivariate analysis of selected factors

	OR	95% CI	<i>p</i> value
LEV + PER	10.275	2.613–40.398	0.001
No concomitant use of AEDs (Excluded LEV, LCM, and PER)	1.235	0.307–4.971	0.766
Concomitant CBZ	1.480	0.302–7.244	0.629
Concomitant VPA	1.357	0.283–6.515	0.703
LEV, levetiracetam; PER, perampanel; AED, antiepileptic drug; CBZ, carbamazepine; VPA, sodium valproate			

Clinical course following the onset of psychiatric disorders

Following the onset of psychiatric disorders, AED was continued, reduced, or discontinued. In the LEV + LCM group, there was one case each for LEV reduction or discontinuation, LCM reduction or discontinuation, and both drug continuation. All patients who developed psychiatric disorders in the LEV + LCM group showed an improvement during the follow-up period. In the LEV + PER group, there were 6 cases of LEV reduction or discontinuation, 7 cases of PER reduction or discontinuation, 4 cases of both reduction and discontinuation, and 5 cases of continuation. Of the patients who developed psychiatric disorders in the LEV + PER group, 13 patients (81.3%) improved, 3 did not show an improvement or worsening during the follow-up period, and 6 were not assessed after the onset of psychiatric disorders during the study (Fig. 2).

Discussion

We conducted a retrospective study of psychiatric disorders in patients treated with LEV + LCM and LEV + PER and compared the onset of psychiatric disorders between them. The onset of AED-induced psychiatric disorders was significantly higher in the LEV + PER group than in the LEV + LCM group. AED-induced psychiatric disorders were depression, affect lability, aggression, and anxiety. The incidence of affect lability was significantly higher in the LEV + PER group than in the LEV + LCM group. The multivariate analysis was performed to eliminate confounding factors between the groups; significant factors affecting psychiatric disorders that were significantly more common in the LEV + PER group were not detected. The time from the start of combination therapy to the onset of AED-induced psychiatric

disorders tended to be less than 1 month in both the groups. There was no significant difference in AED dosage with respect to the presence or absence of psychiatric disorders. Most cases of psychiatric disorders improved with the reduction and discontinuation of LEV, LCM, and PER.

Several studies on LEV-induced psychiatric disorders have been reported. Chen *et al.* conducted a retrospective study (n = 4,085) and found that 22.1% of patients receiving LEV develop psychiatric disorders [9], whereas another single-center study reported psychiatric disorders in 53 (10.1%) of 517 patients [16]. In the present study, 6.8% of patients receiving LEV + LCM developed psychiatric disorders. This frequency was lower than that reported in previous studies on LEV-induced psychiatric disorders.

The risk factors for overall AED adverse effects include depression, female sex, etiology of symptoms, younger age at seizure onset, two or more seizures, and a history of febrile attacks as reported by Perucca *et al.* [17], as well as polytherapy with three or more AEDs, female sex, older age, and poor seizure control as reported by Martins *et al.* [18]. The risk factors for LEV-induced psychiatric disorders include female sex, a history of depression, anxiety, and recreational drug use [19]. On the contrary, there are two case reports on LCM-induced psychotic disorders [24, 25]; however, a retrospective study has shown a low frequency (5.1%) of psychotic disorders with LCM use [9]. The incidence of psychiatric disorders induced by PER was significantly higher than that induced by placebo in several randomized control trials [22]-28]. It has also been reported that 16.7% of patients for whom PER is added to an existing treatment discontinue the medication owing to psychiatric disorders [24]. Other AEDs such as ZNS [14, 29] and TPM [10],29] have also been found to be associated with psychiatric disorders.

The results of this study can be attributed to the pharmacological effects of AEDs. LEV specifically binds to synaptic vesicle protein 2A (SV2A) in the brain [25]. PER is a selective α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist [26]. LCM is involved in the slow inactivation of sodium channels [27]. Although the main pharmacological action of LEV involves specific binding to SV2A, it has also been reported to bind to the AMPA receptor [28]. Brivaracetam, whose effects are similar to those of LEV, exhibits a higher selective control of SV2A. It has no modifying activity on AMPA receptors and has been suggested to carry a risk of fewer psychiatric disorders than LEV [34,35]. The combination of LEV and PER does not increase the frequency of psychiatric disorders (e.g., hostility and aggression) [15]; nonetheless, it was associated with a high incidence of psychiatric disorders in the present study, and it may be related to its enhanced effects on AMPA receptors. One of the pharmacological effects of mood stabilizers and antidepressants is the reduction in intracellular sodium levels by blocking sodium influx; moreover, AEDs (e.g., CBZ and LTG) acting on sodium channels are known to have a favorable effect on psychiatric symptoms [29,36]. Although it has not been reported, it is possible that LCM also acts as a stabilizer of psychiatric symptoms, leading to results such as those obtained in the present study.

There were some limitations to this study. First, this was a retrospective study, and we did not systematically assess adverse psychiatric events. PER might have been assessed by physicians more thoroughly than LCM, as PER is known to have a greater risk of adverse psychiatric effects than LCM.

Second, in many cases, the follow-up period was less than 1 year; thus, the effects of long-term medication on psychiatric disorders could not be investigated. Third, drugs that affect psychiatric disorders other than AEDs have not been analyzed because data were collected on a wide range of definitions of psychiatric disorders, including depression and aggression, and a wide range of medications that affect these disorders. Fourth, AEDs were prescribed and evaluated for adverse effects by neurosurgeons, neurologists, and emergency physicians. Thus, there is a risk of variability in the evaluations of physicians from different specialties. Fifth, it is also possible that the patients did not make their own complaints about psychiatric disorders. Because we did not use a questionnaire for the study, a bias could have occurred. Finally, all patients were selected from a single institution, which may have led to a selection bias.

The results showed that the onset of AED-induced psychiatric disorders was significantly lower in the LEV + LCM group than in the LEV + PER group. A high prevalence of psychiatric adverse effects in the LEV + PER group suggests that PER is more likely to be associated with psychiatric problems than LCM. Further research is needed to determine whether LCM suppresses LEV-induced psychotic disorders. Similar results may also be obtained with drugs acting on sodium channels (e.g., CBZ and LTG), based on their effects. Future research is also needed to investigate psychiatric disorders using combination therapy with other AEDs.

Conclusions

To the best of our knowledge, this is the first study to directly compare psychiatric disorders caused by LEV + LCM and LEV + PER combination therapies. Psychiatric disorders were suppressed by the concomitant administration of LCM and LEV and enhanced by that of PER and LEV; therefore, LEV + LCM may be preferable to LEV + PER. As the occurrence of psychiatric disorders was more frequent within the first month of concomitant use and tended to be dose-independent, it is important that the development of psychiatric disorders is observed from the start of AED administration.

Declarations

Funding

No funding was received to assist with the preparation of this manuscript.

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was approved by the Showa University ethics committee (number: 3097).

Consent to participate

The research facilities in this paper have given their prior consent that patient data may be used for research as a characteristic of university hospital.

Consent for publication

Information regarding the retrospective research for publication was made available on our website to ensure that the research subjects had the opportunity to refuse their data being used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author, S. Matsunuma, upon reasonable request.

Code availability

Not applicable

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Figures

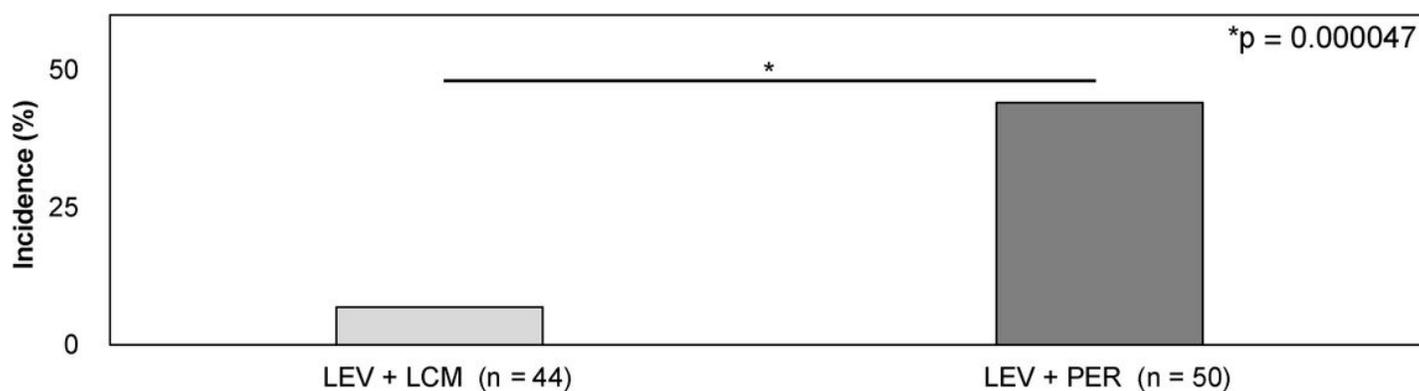


Figure 1

Incidence of AED-induced psychiatric disorders

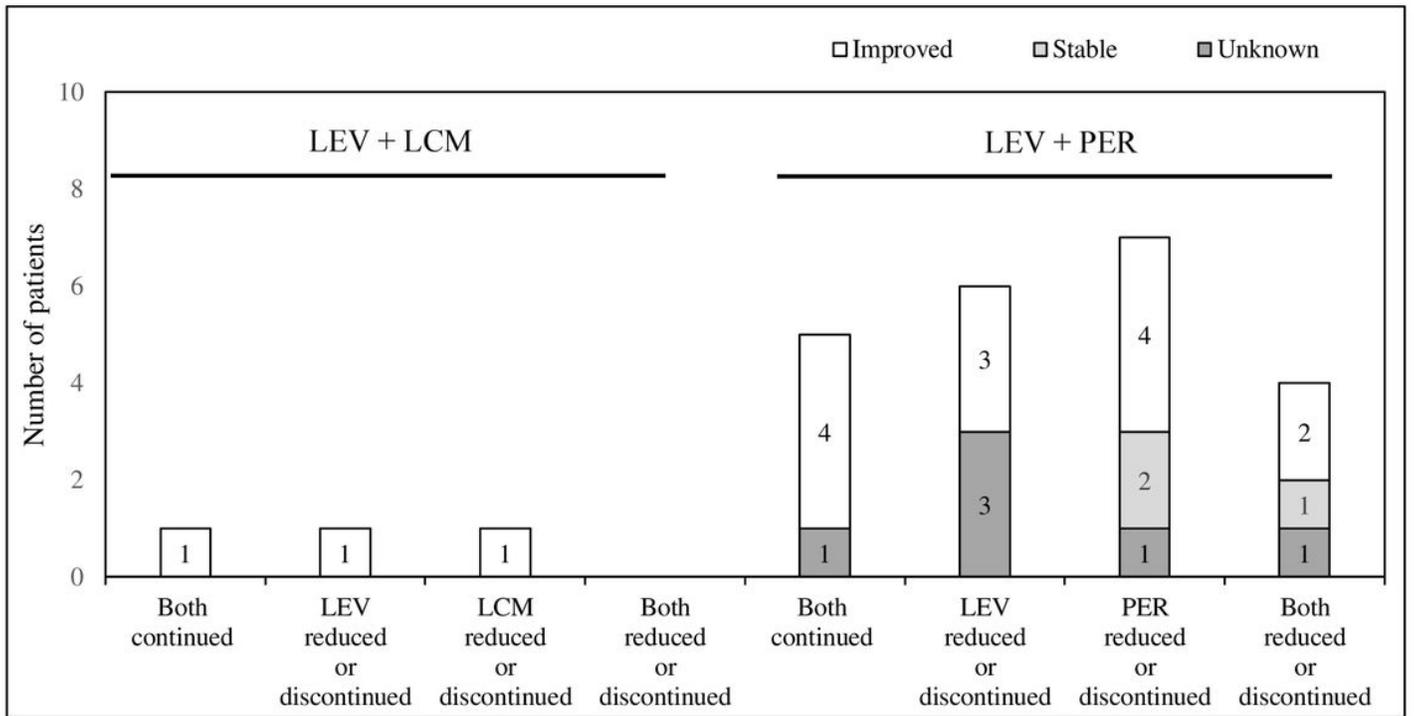


Figure 2

Clinical course following the onset of psychiatric disorders