Preventive Effects of Lamotrigine in Bipolar II Versus Bipolar I Disorder

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ABSTRACT

Objective: The preventive effects of mood stabilizers on recurrence/relapse in bipolar disorders have been investigated mostly in bipolar I disorder (BPI) patients, with limited reports on bipolar II disorder (BPII) patients. Here, we conducted an explorative data analysis to investigate whether the preventive effect of lamotrigine on recurrence /relapse in BPII is better than in BPI.

Methods: Data from Japanese patients with a diagnosis of BPI or BPII according to *DSM-IV-TR* were analyzed in an open-label, noninterventional, naturalistic, prospective postmarketing surveillance study of lamotrigine. This study was carried out from October 2011 to November 2014, and each patient was observed for 1 year. The time to recurrence/relapse of mood episodes after commencement of lamotrigine treatment was evaluated as a primary endpoint. Kaplan-Meier curves were generated to compare the time to recurrence/relapse of mood episodes in BPI with in BPII using a log-rank test.

Results: Lamotrigine was associated with a significantly longer time to recurrence/relapse of mood episodes in BPII than in BPI (log-rank test, $P = .0103$). Lamotrigine also prolonged time to recurrence/relapse of mania-related episodes, including hypomanic episodes, more in BPII than in BPI ($P = .0110$).

Conclusions: Although the preventive effect of lamotrigine on recurrence/relapse of mood episodes in BPI has been established in a variety of clinical studies, the present study suggests that lamotrigine may be more suitable for maintenance treatment in BPII than in BPI.

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Bipolar disorder is a chronic mental disorder with repetitions of manic/hypomanic episodes and depressive episodes. It is subclassified into bipolar I disorder (BPI), presenting with manic episodes, and bipolar II disorder (BPII), presenting with major depressive episodes as well as hypomanic episodes. BPI is characterized by severe pathology including psychotic symptoms, occasionally requiring hospitalization. BPII also has severe pathological characteristics in different aspects: a shorter asymptomatic period,[1,2] more frequent recurrences of mood episodes (hypomanic/depressive phases),[3,4] and more comorbidities such as anxiety disorder and personality disorder.[4] The risk of suicide is higher in bipolar disorder patients than in patients with other mental disorders,[5] and BPII patients tend to be at increased risk of suicide-associated events as compared with BPI patients. This elevated risk might be related to the longer period of the depressive and mixed phases in BPII patients, during which suicidal risk increases, than in BPI patients.[6] In addition, bipolar disorder patients are at higher risk of recurrence/relapse of mood episodes, and the 5-year recurrence rate has been reported to be 81%–91%.[7] On the basis of these findings, in order to reduce the burden on patients and families, bipolar disorder treatment focuses mainly on preventing the recurrence/relapse of mood episodes using mood stabilizers.

Most studies to date have investigated the preventive effects of mood stabilizers on recurrence/relapse of mood episodes in BPI patients, with limited reports in BPII patients. However, lamotrigine, a mood stabilizer, is recommended for use in BPII patients in the guidelines of the British Association for Psychopharmacology[8] and the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders.[9] The preventive effect of lamotrigine on recurrence/relapse of mood episodes in BPI has been investigated in a placebo-controlled, double-blind study, in which lamotrigine had superior clinical characteristics for the prevention of recurrence/relapse in depressive episodes compared with mania-related (manic, hypomanic, or mixed) episodes.[10–12] BPII patients, who have longer depressive phases and more frequent recurrence of them, might experience greater advantages of maintenance treatment with lamotrigine than BPI patients, who have more severe pathology in their manic phases. When the preventive effect of lamotrigine on recurrence/relapse of mood episodes in rapid-cycling bipolar disorder patients was investigated in a placebo-controlled, double-blind, comparative study, a significant difference in the prevention of recurrence/relapse of mood episodes was demonstrated between lamotrigine and placebo in the BPII patients, but not in the BPI patients.[13] This result suggests that lamotrigine might have a superior preventive effect on recurrence/relapse of mood episodes in BPII patients to that in BPI patients.

This analysis was conducted to investigate a hypothesis that the preventive effect of lamotrigine on recurrence/relapse in BPII is better than in BPI.

Clinical Points

- Previous clinical studies have demonstrated that lamotrigine appeared to be more prophylactic for depressive episodes than for manic episodes in bipolar I disorder. Unexpectedly, the present study suggests that lamotrigine may be more effective in the prevention of recurrence/relapse of mania-related episodes, including hypomanic episodes, in bipolar II than in bipolar I disorder.

- The result of the present study supports clinical practice for psychiatrists due to lack of sufficient data stratified by bipolar I vs bipolar II diagnosis.

METHODS

Study Design and Participants

This study was carried out in Japanese inpatients as well as outpatients diagnosed with bipolar disorder according to *DSM-IV-TR*, who were prescribed lamotrigine for the first time in daily clinical practice to prevent recurrence/relapse of mood episodes. During the 2-year period from October 2011 to October 2013, investigators registered patients prospectively to a register center within 14 days of starting lamotrigine treatment using a central registration method. The observation period for each patient was 1 year. In addition, there is a strict titration schedule of lamotrigine, but no limitation on concomitant drugs. Investigators were requested to prescribe lamotrigine in accordance with the Japanese package insert. When lamotrigine was used as monotherapy, patients began a 6-week escalation of lamotrigine to a target dose of 200 mg/d (weeks 1–2, 25 mg/d; weeks 3–4, 50 mg/d; week 5, 100 mg/d; week 6, 200 mg/d). When used as adjunctive therapy with valproate, the lamotrigine starting and target doses were halved (weeks 1–2, 25 mg/every other day; weeks 3–4, 25 mg/d; week 5, 50 mg/d; week 6, 100 mg/d). When used as adjunctive therapy with carbamazepine, the lamotrigine starting and target doses were doubled (weeks 1–2, 50 mg/d; weeks 3–4, 100 mg/d; week 5, 200 mg/d; week 6, 300 mg/d).

Before implementation of the study, a written contract was finalized with the head of each medical institution (eg, hospital directors) at which lamotrigine had been adopted and delivered and cooperation with this study had been obtained. Institutional review boards provided approval as needed in accordance with the regulations at the medical institutions that had been requested to conduct the study. This was an observational, interventional postmarketing surveillance study, and patient consent was obtained in accordance with the regulations at each medical institution.

Procedures

The data of patients who had been diagnosed as suffering from BPI or BPII at the time of starting lamotrigine treatment in routine clinical practice, with records including all variables of interest (diagnosis, gender, age, disease duration, incidences of mood episode within the past year, type of mood episode at the start of lamotrigine treatment, severity of mood episode at the start of lamotrigine treatment, and presence/absence of concomitant treatment with other mood stabilizers, antipsychotics, or antidepressants), were analyzed for the time to recurrence/relapse of mood episodes. These were compared between the 2 patient groups.

Criteria for Efficacy and Safety Evaluation

In this postmarketing surveillance study, patients were asked at every visit about the recurrence or relapse of mood episodes after starting lamotrigine treatment. If mood episodes had recurred, the patient was asked about the type of mood episode, time of onset, and whether and when the episode had remitted. Mood episodes were diagnosed as "manic," "hypomanic," "mixed," or "major depressive" based on the *DSM-IV-TR*. Manic, hypomanic, or mixed episodes are referred to as *mania-related episodes* in this article.

All adverse events (AEs) reported after starting lamotrigine treatment were investigated for the name of the event, date of onset, outcome, seriousness, and causal relationship with lamotrigine. AEs causally related to lamotrigine were treated as adverse drug reactions (ADRs).

The time to recurrence/relapse of mood episodes was calculated as the time to onset of the first mood episode after starting lamotrigine treatment. The time to recurrence/relapse of major depressive episodes was defined as the time to onset of the first major depressive episode, and the time to recurrence/relapse of mania-related episodes was defined as the time to onset of manic, hypomanic, or mixed episodes. For patients who had a mood episode at the start of lamotrigine treatment, the duration from the time of remission of the episode to the onset of a subsequent mood episode was estimated as the time to recurrence/relapse, and for those who had not, the duration from the time of starting lamotrigine to the onset of a subsequent mood episode was used. Remission was defined as no mood episode when the patient visited a medical institution.

Outcomes

Time to recurrence/relapse of mood episodes in patients with a diagnosis of BPI or BPII was evaluated as the primary endpoint and was calculated separately for BPI and BPII patients.

Statistical Analysis

Kaplan-Meier analysis was used to estimate the time to recurrence/relapse of mood episodes, and the difference in recurrence/relapse rate between BPI and BPII was evaluated using the log-rank test ($\alpha = .05$ 2-tailed). In addition, quartile points were estimated with its 95% CI for the time to recurrence/relapse of mood episodes.

Variable selection (stepwise method, entering = 0.05, removing = 0.05), with a dependent variable of time to recurrence/relapse and gender (female/male), age ($\geq 65/< 65$ years), diagnosis (BPII/BPI), type of mood episode at the start of lamotrigine treatment (mania, hypomania, mixed, unspecified, euthymia/major depression), concomitant use of mood stabilizers (yes/no), concomitant use of antipsychotics

Table 1. Patient Characteristics (Patients Included in Analysis of Time to Recurrence/Relapse of Mood Episodes)

Characteristic	Bipolar I (n = 191)	Bipolar II (n = 399)	χ² Test
Gender			
Male	87 (45.5)	180 (45.1)	P = .9205
Female	104 (54.5)	219 (54.9)	
Age, y			
<65	165 (86.4)	361 (90.5)	P = .1351
≥65	26 (13.6)	38 (9.5)	
Min–max	13–80	18–83	
Mean ± SD	47.71 ± 14.22	44.02 ± 13.79	
Median	48	43	
Disease duration, y[b]			
Min–max	0–47	0–47	
Mean ± SD	14.71 ± 10.46	10.13 ± 8.73	
Median	13	8	
Incidences of mood episode within the past year			
0	7 (3.7)	9 (2.3)	P = .3613
1	68 (35.6)	152 (38.1)	
2	46 (24.1)	92 (23.1)	
3	22 (11.5)	38 (9.5)	
≥4	11 (5.8)	11 (2.8)	
Unknown	37 (19.4)	97 (24.3)	
Min–max	0–14	0–7	
Mean ± SD	1.97 ± 1.85	1.67 ± 0.98	
Median	2	1	
Type of mood episode at the start of lamotrigine treatment			
Mania	21 (11.0)	…	P < .0001
Hypomania	16 (8.4)	45 (11.3)	
Mixed	15 (7.9)	…	
Major depression	102 (53.4)	314 (78.7)	
Unspecified	8 (4.2)	5 (1.3)	
Euthymia	29 (15.2)	35 (8.8)	
Severity of mood episode at the start of lamotrigine treatment			
Normal/cannot rule out the presence of disease/mild	89 (46.6)	142 (35.6)	P = .0270
Moderate	79 (41.4)	209 (52.4)	
Severe/very severe/extremely severe	22 (11.5)	47 (11.8)	
Unknown	1 (0.5)	1 (0.3)	
Concomitant medications			
Mood stabilizers	122 (63.9)	171 (42.9)	P < .0001
Lithium	91 (47.6)	105 (26.3)	P < .0001
Valproate sodium	48 (25.1)	66 (16.5)	P < .0001
Typical antipsychotics	26 (13.6)	42 (10.5)	P = .2720
Atypical antipsychotics	98 (51.3)	126 (31.6)	P < .0001
Antidepressants	55 (28.8)	195 (48.9)	P < .0001

[a]Values expressed as n (%) unless otherwise noted.
[b]Bipolar I, n = 153; bipolar II, n = 290.

(typical [yes/no], atypical [yes/no]), and concomitant use of antidepressants (yes/no) as explanatory variables, was performed for the time to recurrence/relapse with lamotrigine using a Cox proportional hazards regression model with patient characteristics as candidate variables to explore the factors that might affect recurrence/relapse of mood episodes.

The numbers of patients with ADRs were summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term. Skin disorders were regarded as "skin and subcutaneous tissue disorders" in the MedDRA SOC and classified using MedDRA/J version 18.1.

Statistical Analysis System version 9.3 (SAS Institute Japan Ltd, Tokyo, Japan) was used for the statistical analysis.

RESULTS

Of the 966 patients included in the efficacy analysis set, 254 were patients with BPI, 643 were patients with BPII, 28 were patients with cyclothymic disorder, 39 were patients with bipolar disorder not otherwise specified, and 2 were patients with other diagnoses. Of these, 191 BPI and 399 BPII patients were included as analysis sets because data were available for all patient characteristics investigated.

The BPI and BPII groups differed in the type of mood episodes and their severity at the time of starting lamotrigine treatment (Table 1). Significantly more BPII than BPI patients had major depressive episodes (78.7% vs 53.4%) and mood episodes of moderate severity (52.4% vs 41.4%) (Table 1). Furthermore, there were differences in the
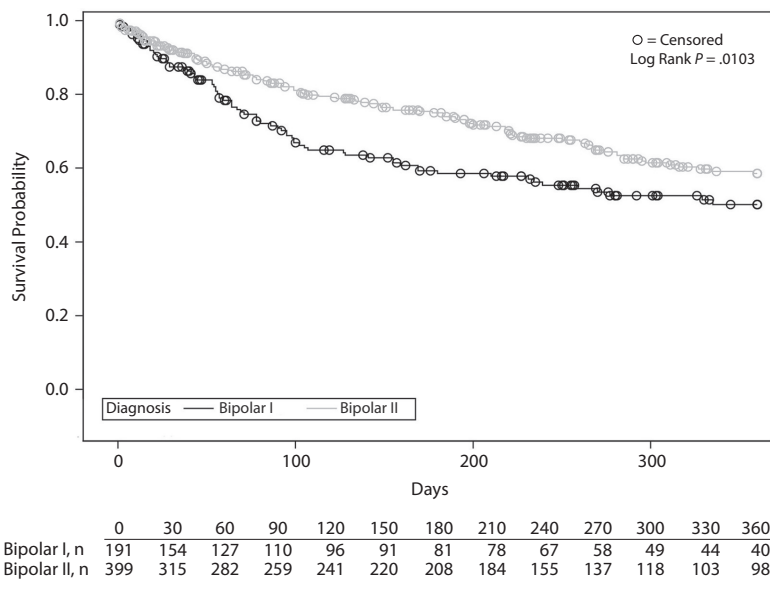
percentages of concomitant use of mood stabilizers (lithium and valproate sodium), atypical antipsychotics, and antidepressants (Table 1). Significantly more BPI than BPII patients concomitantly used lithium (47.6% vs 26.3%), valproate sodium (25.1% vs 16.5%), and atypical antipsychotics (51.3% vs 31.6%) (Table 1). Conversely, the percentage of patients with concomitant antidepressant use was significantly higher in BPII patients (28.8% vs 48.9%) (Table 1). In addition, no differences in the mean daily dose of lamotrigine were observed between BPI (median value: 106.8 mg/d) and BPII (median value: 136.2 mg/d) patients (Supplementary eTable 1). The percentages of patients using lamotrigine with rapid titration and/or high starting dose were 44.5% in BPI (85/191 patients) and 34.3% in BPII (137/399 patients).

Kaplan-Meier estimates of the time to recurrence/relapse of mood episodes for bipolar diagnosis revealed that lamotrigine prolonged the time to recurrence/relapse of mood episodes in BPII patients compared with BPI patients ($P = .0103$) (Figure 1). Likewise, estimates of the time to recurrence/relapse of major depressive episodes or mania-related episodes stratified by bipolar diagnosis demonstrated that lamotrigine significantly prolonged the time to recurrence/relapse of mania-related episodes in BPII patients compared with BPI patients ($P = .0110$). However, there was no difference between the bipolar patient groups in the time to major depressive episodes ($P = .2468$) (Figures 2 and 3).

The estimated times to recurrence/relapse of mood episodes by bipolar diagnosis (25th percentile) were 71 days and 183 days for BPI and BPII, respectively. The times to recurrence/relapse of major depressive episodes (25th percentile) were 234 days and 295 days for BPI and BPII, respectively. The times to recurrence/relapse of mania-related episodes (25th percentile) were 105 days for BPI and unable to be calculated for BPII (Table 2). In order to reveal the factors that might affect the time to recurrence/relapse of mood episodes, variable selection was performed using Cox proportional hazards regression model, and only diagnosis (BPI or BPII) was selected as an influential factor (hazard ratio in BPI = 1.4506 for BPII; 95% CI, 1.0893–1.9316; $P = .0109$).
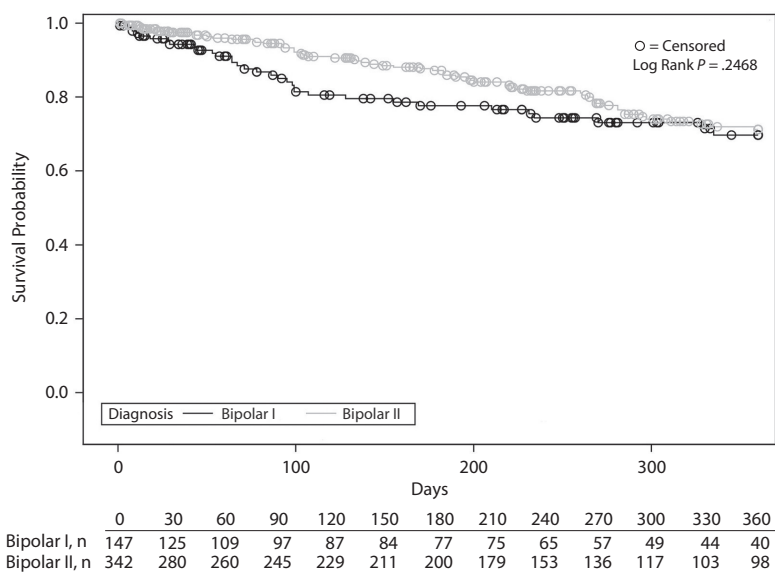
As shown in Supplementary eTable 2, the incidence rates for ADRs by bipolar

Figure 1. Kaplan-Meier Survival Curves for Time to Recurrence/Relapse of Mood Episode[a]

	0	30	60	90	120	150	180	210	240	270	300	330	360
Bipolar I, n	191	154	127	110	96	91	81	78	67	58	49	44	40
Bipolar II, n	399	315	282	259	241	220	208	184	155	137	118	103	98

[a]Lamotrigine significantly prolonged the time to recurrence/relapse of mood episodes in bipolar II patients than in bipolar I patients ($P = .0103$).

Figure 2. Kaplan-Meier Survival Curves for Time to Recurrence/Relapse of Depressive Episode[a]
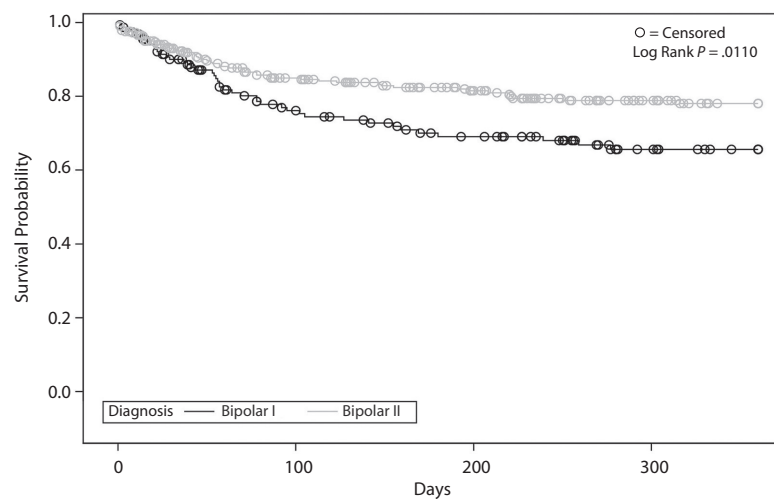

	0	30	60	90	120	150	180	210	240	270	300	330	360
Bipolar I, n	147	125	109	97	87	84	77	75	65	57	49	44	40
Bipolar II, n	342	280	260	245	229	211	200	179	153	136	117	103	98

[a]There was no difference between bipolar I and bipolar II patients in the time to major depressive episode.

diagnosis were 22.0% (n = 42/191) and 21.8% (n = 87/399) in BPI and BPII patients, respectively, with no significant difference in safety. For both BPI and BPII, rash was the most frequently reported ADR (Supplementary eTable 2). The incidence rates of skin disorders were 11.5% (n = 22/191) in BPI and 11.5% (n = 46/399) in BPII, and the incidence rates for serious skin disorders were 0.5% (n = 1/191) and 1.5% (n = 6/399), respectively. The serious skin disorders included rash (n = 1) in BPI patients, and rash (n = 2),

Figure 3. Kaplan-Meier Survival Curves for Time to Recurrence/Relapse of Mania-Related Episode[a]

Days	0	30	60	90	120	150	180	210	240	270	300	330	360
Bipolar I, n	158	129	106	95	87	83	75	72	64	55	47	43	40
Bipolar II, n	336	260	231	212	203	188	179	162	138	126	114	101	98

O = Censored
Log Rank P = .0110

[a]Lamotrigine significantly prolonged the time to recurrence/relapse of mania-related episodes (manic, hypomanic, or mixed) in bipolar II patients than in bipolar I patients (P = .0110).

Table 2. Prolongation of Time to Recurrence/Relapse of Mood Episode (Depression, Mania, Hypomania, or Mixed)

	Diagnosis	
Item	Bipolar I	Bipolar II
Recurrence/relapse of mood episode		
n	191	399
Patients with recurrence/relapse of mood episode, n (%)	77 (40.3)	120 (30.1)
Days to recurrence/relapse of mood episode (25th percentile)	71	183
95% CI	55.0–98.0	113.0–220.0
Recurrence/relapse of depressive episode		
n	147	342
Patients with recurrence/relapse of depressive episode, n (%)	33 (22.4)	63 (18.4)
Days to recurrence/relapse of depressive episode (25th percentile)	234	295
95% CI	99.0–…	261.0–…
Recurrence/relapse of mania-related episode[a]		
n	158	336
Patients with recurrence/relapse of mania-related episode, n (%)	44 (27.8)	57 (17.0)
Days to recurrence/relapse of mania-related episode (25th percentile)	105	…
95% CI	59.0–259.0	221.0–…

[a]Any of the following: manic, hypomanic, or mixed episodes.

Stevens-Johnson syndrome (SJS), drug-induced hypersensitivity syndrome, erythema multiforme, and drug eruption (n = 1 for each) in BPII patients. All patients recovered or were recovering from the ADRs except for 1 BPI patient who was experiencing rash of which the outcome was unknown and 1 BPII patient who was experiencing SJS of which the outcome was sequela (visual impairment). Furthermore, the incidence rates of serious skin disorders in patients using lamotrigine with rapid titration and/or high starting dose were 0.0% in BPI (0/85 patients) and 1.5% in BPII (2/137 patients). No increasing trend was seen in the incidence rates of serious skin disorders, compared with those in patients using lamotrigine properly (1.0% in BPI [1/105 patients], 1.5% in BPII [4/262 patients]), dosage unknown (0.0% in BPI [0/1 patients]).

DISCUSSION

In this analysis, time to recurrence/relapse of mood episodes was significantly longer in BPII patients than in BPI patients, demonstrating that lamotrigine successfully prolongs the time to recurrence/relapse in BPII patients. Our hypothesis that the preventive effect of lamotrigine on recurrence/relapse in BPII is better than in BPI is supported. When background factors were compared, however, more BPI patients than BPII patients concomitantly used mood stabilizers and atypical antipsychotics. The percentage of patients with concomitant use of antidepressants was significantly higher in BPII patients than in BPI patients. When Cox proportional hazards regression model was performed with these factors relating to the preventive effect of lamotrigine on recurrence/relapse of mood episodes as explanatory variables, bipolar diagnosis (BPI or BPII) was identified as the only influential factor. It seems probable that BPII is significantly associated with a delayed time to recurrence/relapse compared with BPI in the clinical setting of lamotrigine treatment. Due to the nature of this naturalistic study with no control group, we cannot completely rule out the possibility that BPI patients may be at increased risk of recurrence compared with BPII patients. However, considering the more frequent recurrences of the disease phase in BPII patients than BPI patients[3,4] and comparable recurrence/relapse rates before this study in our BPI and BPII patients, the results suggest that lamotrigine has a large advantage for the preventive effect on recurrence/relapse in BPII.

In the analysis of the time to recurrence/relapse by type of mood episodes, BPII patients had a longer time to recurrence/relapse of mania-related episodes compared with BPI patients. Previous studies investigating the preventive effect of lamotrigine on recurrence/relapse during the manic phase have targeted only BPI patients and evaluated the onset of a manic, hypomanic, or mixed mood episode as a recurrence/relapse event. As far as we know, there has been no published study investigating the preventive effect of lamotrigine on recurrence/relapse of hypomanic episodes in BPII patients. The time to recurrence/relapse of mania-related episodes was used as a recurrence/relapse

event in our study because of the naturalistic study design. Further studies would be required to strengthen our findings.

This study also demonstrates that the preventive effect of lamotrigine on recurrence/relapse of major depressive episodes in BPII patients is similar to that in BPI patients, which has been confirmed in a placebo-controlled, double-blind study.[10,11] In addition, lamotrigine had superiority in the depressive phase compared with the manic phase in BPI patients.[12] Therefore, although there was no control group in the present study due to a naturalistic study design, lamotrigine may have a preventive effect on recurrence/relapse of major depressive episodes both in BPI and in BPII. Also, the present findings suggest that lamotrigine may be suitable for preventing the recurrence/relapse of not only depressive but also hypomanic episodes in BPII patients.

We also found no great difference between BPI and BPII patients in lamotrigine safety profiles. Both BPI and BPII showed 11.5% as the incidence rate of skin disorders, which was the similar level as the results in clinical trials.[10,11] Overall, our findings suggest that lamotrigine may be suitable for

maintenance treatment not only in BPI but also in BPII. Of course, lamotrigine is known to cause severe skin rashes. The risk of skin rashes becomes high when prescribed beyond the definition in the dosage and administration.[14] Hence, although no difference was detected in the incidence rates of serious skin disorders between patients with the correct dosage and administration and patients with rapid titration and/or high starting dose in this study, it is required to follow the dosage and administration in the package insert when using lamotrigine.

This postmarketing surveillance study has some limitations. As it is a naturalistic observation and not a randomized controlled trial, the lack of control groups and blinding made it difficult to eliminate the possible influence of placebo effect. Moreover, patients were not registered consecutively, which could lead to the risk of sample selection bias. However, we believe that these findings could be directly applicable to real-life clinical settings in Japan.

In conclusion, the study suggests that lamotrigine may be more suitable for maintenance treatment in BPII than in BPI.

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Supplementary material follows this article.

<u>Supplementary Material</u>

Article Title: Preventive Effects of Lamotrigine in Bipolar II Versus Bipolar I Disorder

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<u>List of Supplementary Material for the article</u>

<u>Disclaimer</u>
This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1: Mean daily dose of lamotrigine, and concomitant drug for Bipolar Disorder

Patient background factor/category		Bipolar I (n=191)		Bipolar II (n=399)	
Mean daily dose (mg/d) (maintenance dose)	≤50	31	(16.2)	51	(12.8)
	>50 to ≤100	48	(25.1)	84	(21.1)
	>100 to ≤150	15	(7.9)	49	(12.3)
	>150 to ≤200	46	(24.1)	109	(27.3)
	>200 to ≤250	8	(4.2)	18	(4.5)
	>250 to ≤300	9	(4.7)	12	(3.0)
	>300 to ≤350	1	(0.5)	3	(0.8)
	>350 to ≤400	4	(2.1)	8	(2.0)
	Unknown	29	(15.2)	65	(16.3)
	Min–max	25.0-400.0		21.0-400.0	
	Mean±SD	137.6±82.1		142.7±78.2	
	Median	106.8		136.2	
	Mode	100.0		200.0	
Concomitant medications					
Mood stabilizers		122	(63.9)	171	(42.9)
Lithium		91	(47.6)	105	(26.3)
Valproate sodium		48	(25.1)	66	(16.5)
Carbamazepine		8	(4.2)	12	(3.0)
Typical antipsychotics		26	(13.6)	42	(10.5)
Sulpiride		3	(1.6)	22	(5.5)
Levomepromazine maleate		9	(4.7)	14	(3.5)
Atypical antipsychotics		98	(51.3)	126	(31.6)
Olanzapine		37	(19.4)	41	(10.3)
Aripiprazole		33	(17.3)	50	(12.5)
Quetiapine		29	(15.2)	38	(9.5)
Risperidone		13	(6.8)	4	(1.0)
Antidepressants		55	(28.8)	195	(48.9)
Duloxetine hydrochloride		2	(1.0)	53	(13.3)
Mirtazapine		8	(4.2)	48	(12.0)
Paroxetine hydrochloride hydrate		11	(5.8)	44	(11.0)
Fluvoxamine maleate		8	(4.2)	28	(7.0)
Sertraline hydrochloride		5	(2.6)	28	(7.0)
Milnacipran hydrochloride		7	(3.7)	11	(2.8)
Escitalopram oxalate		3	(1.6)	7	(1.8)
Amoxapine		6	(3.1)	6	(1.5)

[a]Values expressed as n (%) unless otherwise noted.

Supplementary eTable 2: Frequency of ADRs (≥3% by SOC) (Safety Analysis Set)

	Bipolar I (n=191)		Bipolar II (n=399)	
No. of patients with ADRs	42		87	
No. of ADRs	54		132	
Incidence rate of ADRs (%)	22·0		21·8	
Type of ADRs	No. of patients with ADRs			
Psychiatric disorders	10	(5·2)	13	(3·3)
Aggression	1	(0·5)	0	(0·0)
Anger	1	(0·5)	3	(0·8)
Anxiety	1	(0·5)	1	(0·3)
Depression	0	(0·0)	1	(0·3)
Dissociative disorder	0	(0·0)	1	(0·3)
Hypomania	1	(0·5)	1	(0·3)
Insomnia	1	(0·5)	2	(0·5)
Intentional self-injury	0	(0·0)	1	(0·3)
Irritability	4	(2·1)	1	(0·3)
Mania	0	(0·0)	2	(0·5)
Panic attack	0	(0·0)	1	(0·3)
Suicidal ideation	2	(1·1)	1	(0·3)
Depressive symptom	0	(0·0)	1	(0·3)
Somatic hallucination	0	(0·0)	1	(0·3)
Nervous system disorders	4	(2·1)	17	(4·3)
Akathisia	1	(0·5)	0	(0·0)
Dizziness	0	(0·0)	5	(1·3)
Dizziness postural	0	(0·0)	1	(0·3)
Headache	1	(0·5)	3	(0·8)
Hypersomnia	0	(0·0)	2	(0·5)
Hypoaesthesia	0	(0·0)	1	(0·3)
Migraine	0	(0·0)	1	(0·3)
Neuralgia	0	(0·0)	1	(0·3)
Paraesthesia	0	(0·0)	1	(0·3)
Sedation	0	(0·0)	1	(0·3)
Somnolence	1	(0·5)	5	(1·3)
Tremor	1	(0·5)	2	(0.5)

[a]Values expressed as n (%) unless otherwise noted.

Skin and subcutaneous tissue disorders	22	(11·5)	46	(11·5)
Chloasma	0	(0·0)	1	(0·3)
Cold sweat	0	(0·0)	1	(0·3)
Drug eruption	2	(1·1)	3	(0·8)
Eczema	0	(0·0)	1	(0·3)
Erythema	1	(0·5)	1	(0·3)
Erythema multiforme	0	(0·0)	1	(0·3)
Pruritus	3	(1·6)	4	(1·0)
Purpura	1	(0·5)	0	(0·0)
Rash	17	(8·9)	34	(8·5)
Skin erosion	0	(0·0)	1	(0·3)
Skin exfoliation	0	(0·0)	1	(0·3)
Stevens-Johnson Syndrome	0	(0·0)	1	(0·3)
Swelling face	0	(0·0)	1	(0·3)
Drug reaction with eosinophilia and systemic symptoms	0	(0·0)	1	(0·3)

[a]Values expressed as n (%) unless otherwise noted.

(MedDRA/J version 18.1)

MedDRA=Medical Dictionary for Regulatory Activities. SOC=System Organ Class.