OPEN

Impact of Selected Initial Titration Schedules on Safety and Long-Term Effectiveness of Lamotrigine for the Treatment of Mood Disorders

Tomoyuki Nakamura, MD, PhD,[1] Masaru Tomita, MD, PhD,[2] Susumu Hirota, MD,[3] Takamasa Matsunaga, MD,[4] and Naohisa Uchimura, MD, PhD[1]

Abstract:

Purpose: Lamotrigine (LTG) is used for treatment of mood disorders, but it is associated with the risk of rash occurrence in the initial administration phase. Although slow titration reduces this risk, its effectiveness in the treatment of mood disorders has not been verified. The effects of titration method on the safety and effectiveness of LTG for the treatment of mood disorders were examined in this study.

Methods: This retrospective cohort study included 312 patients with mood disorders who underwent initiation of LTG therapy. Data regarding baseline demographics, titration schedules, concomitant medications, and time to and cause of discontinuation of LTG were collected. A multivariate analysis was used to evaluate the effects of the titration schedules. The 12-month effectiveness was also evaluated.

Results: The 12-month discontinuation rate of LTG was 16.7%. The most frequent cause of discontinuation was development of a rash (47.7%, n = 312). Fast titration (adjusted odds ratio, 8.15) significantly increased the risk of rash development, and slow titration (adjusted odds ratio, 0.29) significantly decreased this risk. The time to all-cause discontinuation was not significantly different between the slow and standard titration groups (n = 303). After 12 months of treatment, the condition of 46.7% patients were rated much or very much improved using CGI-C.

Conclusions: Although slow titration of LTG reduces the occurrence of a rash, it is not more effective than standard titration in the long term. Optimizing the initial LTG titration schedule for patients with mood disorders is challenging.

Key Words: lamotrigine, long term, mood disorders, titration, rash

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Lamotrigine (LTG) has been widely used for the treatment of partial epilepsy, bipolar disorder (BD), and other mood disorders. In Japan, LTG was approved for partial epilepsy in 2008 and for the prevention of relapses of BD in 2011.

During the initial administration phase, the appearance of a rash is the most frequent cause of LTG discontinuation.[1,2] As the rash can develop into fatal symptoms,[3,4] the initial titration schedule of LTG has been regulated.[5] The estimated incidence of a rash with the regulated standard titration schedule is 5% to 10% in patients with epilepsy[6,7] and 8% to 15% in patients with mood disorders.[2,8–10] The risk factors for rash development include a fast titration schedule,[3,5,11] concomitant use of valproate (VPA),[3,5,11] age of less than 13 years,[3,6,11] female sex, and a history of rash development due to other antiseizure drugs.[6,11,12] Whether patients with epilepsy and those with mood disorders, who receive different treatment settings, have the same risk factors remains unclear.

Several studies regarding the effects of slow titration of LTG on the risk of rash development have been conducted. An open-label, naturalistic study[2] and a retrospective, cross-sectional study[13] reported that slow titration reduced the risk of rash development compared with standard titration, suggesting that slow titration during the initiation of LTG may increase patients' tolerance of LTG. In contrast, Jang et al[14] recently reported a modified rapid titration method that resulted in good tolerability of LTG in terms of rash occurrence. The ideal initial titration schedule of LTG is still controversial. Moreover, how the selected initial titration method affects long-term effectiveness of LTG remains unclear.

This retrospective cohort study examined the impact of selected titration methods on the safety and long-term effectiveness of LTG in patients with mood disorders.

MATERIALS AND METHODS

Ethics Statement

This multicenter study was approved by the ethics committee and was conducted in accordance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. The requirement for informed consent was waived by the ethics committee based on the retrospective cohort design with anonymization of the medical records.

Patients and Study Procedures

This retrospective, multicenter, cohort study included patients who underwent LTG initiation at one of the following centers between July 2011 and July 2016: Kurume University Hospital, Sanare Clinic at the Mountain, Hayatsue Hospital, or Hirota Clinic. The patients were included if they met the diagnostic criteria for mood disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (codes from 296.00 Bipolar I Disorder to 296.90 Mood Disorder not otherwise specified (NOS) and 300.4 Dysthymic Disorder, 301.13 Cyclothymic Disorder, 311 Depressive Disorder NOS). A total of 317 patients were enrolled in the study, but 2 were excluded (because of

From the [1]Department of Neuropsychiatry, Kurume University School of Medicine, Kurume City; [2]Elm-tree Mental Clinic, Ogori City; [3]Hirota Clinic, Kurume City; and [4]Hayatsue Hospital, Saga City, Japan.

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Address correspondence to: Tomoyuki Nakamura, MD, PhD, Department of Neuropsychiatry, Kurume University School of Medicine, 67 Asahimachi, Kurume City, Fukuoka, Japan (e-mail: nakamura_tomoyuki@med.kurume-u.ac.jp).

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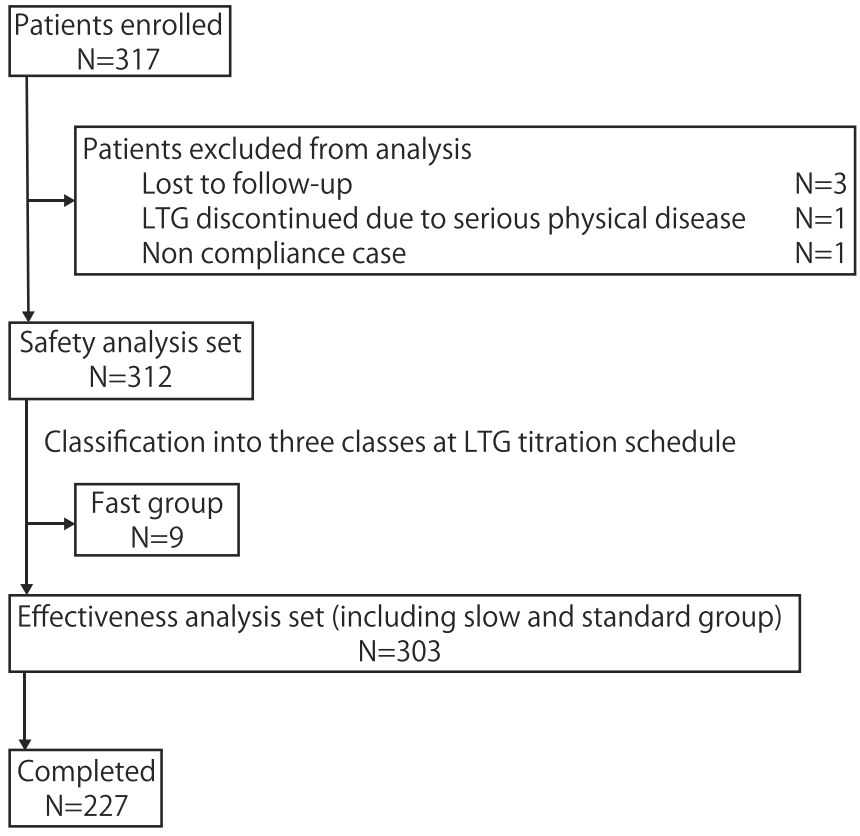

FIGURE 1. Patient flowchart. Flow chart illustrating the patient selection procedure.

a serious physical disease [n = 1] and noncompliance [n = 1]) and 3 were lost to follow-up (Fig. 1).

Data regarding the patients' baseline demographics, diagnoses, concomitant medications, and LTG titration schedules were retrospectively collected from the medical records 12 months after the initiation of LTG. Major adverse drug reactions (ADRs) associated with LTG discontinuation and the time to their occurrence were evaluated in the safety assessment. The primary end point of the study was the time to all-cause discontinuation reflecting the effectiveness of LTG. In addition, physicians assessed the change in the duration, cycle, and severity of mood episodes or in quality of life using the Clinical Global Impression of Change (CGI-C) to evaluate the efficacy of treatment in patients who continued LTG successfully for 12 months.

The LTG titration schedule was classified according to the prescription during the first 8 weeks of LTG administration as standard (based on the locally approved titration schedule that distinguishes three schedules: LTG monotherapy or with concomitant medication that includes types of glucuronic acid conjugation inhibitors/promotors), fast (exceeds the standard schedule in terms of interval or dosing), and slow (doses at 4 weeks were fewer than those in the standard schedule and the increased interval and dose never exceeded those of the standard schedule). Examples of the titration schedules are shown in Supplemental Digital Content 1, http://links.lww.com/JCP/A808.

The sample size was calculated using PROC POWER of SAS 9.2 software (SAS Institute, Cary, NC) assuming that a 15% difference in the discontinuation rate after 12 months could be detected with 80% statistical power and a bilateral α level of 0.05%. The required sample size was determined to be 131 patients per group.

Statistical Analysis

All statistical analyses were conducted using JMP Pro 15 software. Based on the Shapiro-Wilks test, continuous variables are presented as median and range; differences across groups were compared using the Mann-Whitney *U* test or Kruskal-Wallis test. Categorical variables are presented as the number and percentage of patients; differences across groups were analyzed using the χ^2 test or Fisher exact test. Risk factors for ADRs were calculated using adjusted odds ratios (ORs) via a multivariate logistic regression analysis. Among the baseline characteristics and selected titration schedules, factors that showed a significant difference or a tendency to show a difference in the univariate analysis (sex, concomitant VPA and titration schedules) were used as independent variables in the multivariate logistic regression analysis. Among the baseline characteristics, the effect of a factor (concomitant carbamazepine, Table 1) that showed a significant difference in the 3 titration groups was adjusted as a confounder in the multivariate logistic regression analysis. The times to all-cause discontinuation in the standard and slow titration groups were compared using multivariate Cox proportional hazards models with sex, diagnosis, and concomitant medications as covariates. Statistical significance was set at $P < 0.05$.

RESULTS

Safety Analysis

Lamotrigine was administered to patients with BD-I (n = 32, 10.3%), BD-II (n = 126, 40.4%), BD-NOS (n = 77, 24.7%), and depressive disorder NOS (n = 77, 34.7%; Table 1). As shown in Figure 1, the data of 312 patients were included in the safety analysis.

TABLE 1. Patient Characteristics

		Titration			
	Total (N = 312)	Fast (n = 9 [2.9])	Standard (n = 150 [48.1])	Slow (n = 153 [49])	*P*
Age, y	39 (14–85)	33 (17–65)	41 (14–82)	39 (15–85)	0.50*
Sex					0.27†
Female	224 (71.8)	5 (55.6)	104 (69.3)	115 (75.2)	
Male	88 (28.2)	4 (44.4)	46 (30.7)	38 (24.8)	
Diagnosis					0.25†
BDI	32 (10.3)	2 (22.2)	14 (9.3)	16 (10.5)	
BDII	126 (40.4)	1 (11.1)	61 (40.7)	64 (41.8)	
BD-NOS	77 (24.7)	1 (11.1)	39 (26)	37 (24.2)	
DD-NOS	77 (24.7)	5 (55.6)	36 (24)	36 (23.5)	
Concomitant medication at initiation					
None	44 (14.1)	3 (33.3)	23 (15.3)	18 (11.8)	0.13†
Lithium	72 (23.1)	1 (11.1)	32 (21.3)	39 (25.5)	0.51†
Antiseizure drugs					
Valproate	41 (13.1)	2 (22.2)	20 (13.3)	19 (12.4)	0.56†
Carbamazepine	20 (6.4)	0	3 (2)	17 (11.1)	<0.005†
Antipsychotics	148 (47.4)	4 (44.4)	65 (43.3)	79 (51.6)	0.35†
Antidepressants	147 (47.1)	1 (11.1)	73 (48.7)	73 (47.7)	0.09†

*Kruskal-Wallis test.

†Fisher exact test. Data are presented as number (percentage) or median (range).

‡Indicates $P < 0.05$.

Lamotrigine was discontinued because of ADRs in 52 patients (16.7%; Table 2). The most frequent major ADR was a rash (n = 38, 12.2%; Table 2), and the median was 21 days (range, 2–307 days). The LTG titration schedule ($P < 0.0001$) and concomitant use of VPA ($P = 0.002$) were significantly associated with the occurrence of a rash (Table 3). Female sex (adjusted OR, 3.06; 95% confidence interval [CI], 1.114–8.433; $P < 0.05$), a fast titration schedule (adjusted OR, 8.15; 95% CI, 1.903–34.911; $P < 0.005$), and concomitant use of VPA (adjusted OR, 3.37; 95% CI, 1.439–7.888; $P < 0.01$) were identified as risk factors for the development of a rash. Slow titration (adjusted OR, 0.29; 95% CI, 0.126–0.687; $P < 0.005$) significantly decreased this risk (Fig. 2). No patient in this study developed a severe rash such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug-induced hypersensitivity syndrome.

Effectiveness Analysis

A total of 303 patients were included in the effectiveness analysis, but 9 patients in whom LTG was initiated using a fast titration schedule and ultimately discontinued before 12 months were excluded (Fig. 1). Patients in the fast titration group discontinued LTG because of rash occurrence (n = 5), ineffectiveness (n = 2), psychotic symptoms (n = 1), and parkinsonism (n = 1). Of the 303 patients included in the effectiveness analysis, 227 (75%) received LTG for 12 months and 76 (25%) discontinued

TABLE 2. Major ADRs and Time to LTG Discontinuation

			Titration					
	Total (N = 52/312 [16.7%])		Fast (n = 7/9 [77.8%])		Standard (n = 31/150 [20.7%])		Slow (n = 14/153 [9.2%])	
	n (%)	Days	n (%)	Days	n (%)	Days	n (%)	Days
Rash	38 (12.2)	21 (2–307)	5 (1.6)	10 (3–118)	24 (7.7)	30 (14–307)	9 (2.9)	21 (2–165)
Psychiatric symptoms	3 (0.9)	28 (3–126)	1 (0.3)	3			2 (0.6)	77 (28–123)
Headache	2 (0.6)	22 (3–41)			2 (0.6)	22 (3–41)		
Nausea	2 (0.6)	9.5 (5–14)			1 (0.3)	5	1 (0.3)	14
Irritability	2 (0.6)	43 (30–56)			2 (0.6)	43 (30–56)		
Edema	1 (0.3)	13			1 (0.3)	13		
Sedation	1 (0.3)	69					1 (0.3)	69
Parkinsonism	1 (0.3)	128	1 (0.3)	128				
Obsessive symptoms	1 (0.3)	13			1 (0.3)	13		
Hypomanic switch	1 (0.3)	67					1 (0.3)	67

The number of day data is presented as median (range).

TABLE 3. Risk Factors for Development of a Rash

	Nonrash Group (n = 274 [87.8%])	Rash Group (n = 38 [12.2%])	Test of Significance
Age, y	39 (14–85)	40.5 (17–69)	$z = 0.15$; $P = 0.87$*
Sex			$\chi^2 = 3.3$; $df = 310$; $P = 0.06$
Female	192 (70.1)	32 (84.2)	
Male	82 (29.9)	6 (15.5)	
Diagnosis			$\chi^2 = 4.0$; $df = 3$; $P = 0.74$
BDI	28 (10.2)	4 (10.5)	
BDII	108 (39.4)	18 (47.4)	
BD-NOS	70 (25.5)	7 (18.4)	
DD-NOS	68 (24.8)	9 (23.7)	
LTG titration schedule			<0.0001†‡
Fast	4 (1.5)	5 (13.2)	
Standard	126 (45.9)	24 (63.2)	
Slow	144 (52.6)	9 (23.7)	
Concomitant medication at initiation			
None	38 (13.8)	6 (15.8)	$\chi^2 = 0.1$; $df = 1$; $P = 0.74$
Lithium	63 (22.9)	9 (23.7)	$\chi^2 = 0.008$; $df = 1$; $P = 0.92$
Antiseizure drugs			
Valproate	30 (10.9)	11 (28.9)	$\chi^2 = 9.5$; $df = 1$; $P = 0.002$†
Carbamazepine	18 (6.5)	2 (5.3)	$\chi^2 = 0.09$; $df = 1$; $P = 0.76$
Antipsychotics	132 (48.2)	16 (42.1)	$\chi^2 = 0.49$; $df = 1$; $P = 0.48$
Antidepressants	128 (46.7)	19 (50.0)	$\chi^2 = 0.14$; $df = 1$; $P = 0.70$

*Mann-Whitney *U* test.
†Indicates $P < 0.05$.
‡Fisher exact test.
df, degrees of freedom.

LTG within 12 months. Overall, the most common reason for discontinuation of LTG was the occurrence of a rash (n = 33, 10.9%), ineffectiveness (n = 17, 5.6%), ADRs other than a rash (n = 12, 3.9%), patient request (n = 12, 3.9%), and unknown (n = 2, 0.7%; Table 4). The most frequent reason for discontinuation in the slow titration group was patient request (n = 12, 7.8%).

Titration schedule, sex, diagnosis, and concomitant medications did not significantly affect the time to all-cause discontinuation (overall $P = 0.25$; degrees of freedom = 10; Supplemental Digital Content 2, http://links.lww.com/JCP/A809). In the 227 patients who received LTG continuously for 12 months, 12 (5.3%) were rated very much improved with CGI-C, 94 (41.4%) patients were rated much improved, and 99 (43.6%) were rated minimally improved. Twenty-two patients (9.7%) were rated unevaluable because of the frequent change of concomitant medications. Lamotrigine was more efficacious in patients with BD than in those with depressive disorder NOS. In these patients, LTG was equally efficacious between the standard group and slow

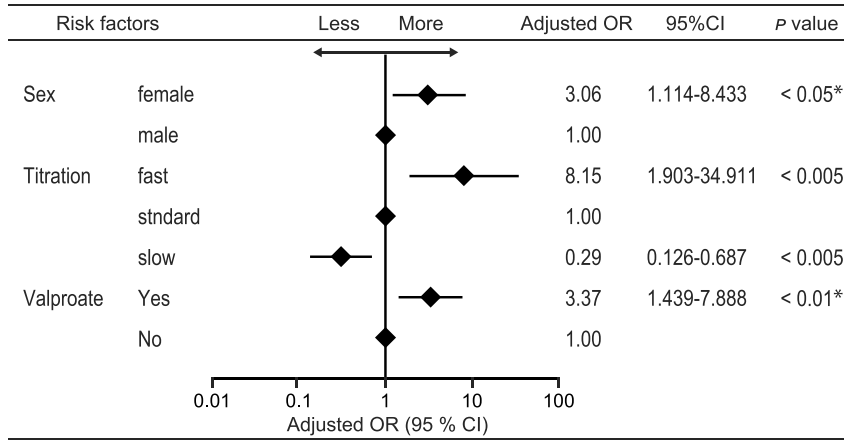

FIGURE 2. Forest plot of risk factors associated with the occurrence of a rash. Slow titration significantly reduces the risk of developing a LTG-induced rash, and fast titration significantly increases this risk compared with the standard titration in patients with mood disorders. Furthermore, female sex and the concomitant use of sodium VPA significantly increase the risk.

TABLE 4. Duration of LTG Use and Causes of Discontinuation

		Titration		
	Total (N = 76/303)	Standard (n = 42/150)	Slow (n = 34/153)	Time to Discontinuation, d
	n (%)	n (%)	n (%)	Median (Range)
Adverse effects	45 (14.8)	29 (19.3)	16 (10.4)	28 (2–307)
Rash	33 (10.9)	24 (16.0)	9 (5.8)	27 (2–307)
Others	12 (3.9)	5 (3.3)	7 (4.5)	29 (3–126)
Ineffectiveness	17 (5.6)	13 (8.7)	4 (2.6)	62 (14–300)
Patient request	12 (3.9)	0	12 (7.8)	44 (7–308)
Unknown	2 (0.7)	0	2 (1.3)	72.5 (65–80)

group (Supplemental Digital Content 3, http://links.lww.com/JCP/A810).

DISCUSSION

This study reports the effects of the initial titration schedule of LTG on its safety and long-term effectiveness for the treatment of mood disorders at the 12-month follow-up. Fast titration significantly increased the risk of rash occurrence and slow titration significantly decreased this risk, compared with the standard titration schedule. Although the slow titration schedule improved the safety of LTG, it did not improve the time to all-cause discontinuation, compared with the standard titration schedule. These results suggest that optimization of the initial titration schedule for LTG in patients with mood disorders is challenging.

Safety and Titration Methods

Lamotrigine discontinuation was associated with ADRs in 16.7% of patients in this study, and a rash was the most common ADR, which is consistent with previous reports.[6,7] The occurrence of fewer ADRs other than a rash among overall patients suggests good tolerability of LTG. Previous studies have reported the effects of the initial titration schedule on the risk of rash development.[2,13] Joe et al[2] reported a significant decrease in the incidence of LTG-induced rash development during initiation with slow titration schedules and lower initial doses of LTG (12.5 mg if no concomitant antiseizure drugs were used) or increased intervals (biweekly). Fujii et al[13] reported that titration schedules with extended intervals and standard dosing also significantly decreased the development of LTG-induced rashes. As shown in these studies, the method for slow titration of LTG has not yet been standardized. In this study, the slow titration schedule was defined as a decreased total dose of LTG during the first 8 weeks of administration compared with that used in the standard titration schedule, achieved via modified doses or dose intervals. The fast titration schedule was defined as a dose interval of less than biweekly or a higher dosage than that included in the standard titration schedule. In the real-world setting, the titration schedules are determined based on various factors. Fast titration has been followed on an involuntary basis. In some cases, slow titration was selected as the physician's treatment strategy aimed at further reducing rash, but in many cases, slow titration was selected according to patient's present visiting interval. Slow titration schedules were used in 48.1% of the patients in this study, and fast titration schedules were used in 2.9% of the patients in this study. Although the small sample size in the fast titration group might have affected accurate estimation, fast titration significantly increased the risk of rash development and slow titration significantly decreased this risk, suggesting that slow titration during the initiation of LTG reduces the risk of rash development in patients with mood disorders. Previous studies have reported that very slow titration schedules prevented the recurrence of rashes during rechallenge after the first occurrence of a LTG-induced rash[15] and that low plasma LTG concentration 2 weeks after initiation was associated with a low risk of rash.[16]

The results of this study are consistent with those of previous studies regarding the risk of LTG-induced rash development in patients with epilepsy. Concomitant use of VPA[3,5,11] and female sex[5,17] have been reported to increase the risk of developing LTG-induced rashes. Concomitant use of VPA, a glucuronic acid conjugation-inhibiting drug, has been reported to increase the serum concentration of LTG, suggesting that the starting and maximum doses should be reduced to half of those used in LTG monotherapy. The results of this study suggest that using this adjusted titration method is insufficient to eliminate the risk of concomitant VPA for common LTG-induced rashes. To improve tolerability of LTG among patients on concomitant VPA, physicians may choose to discontinue VPA before LTG initiation or slow titration of LTG. The increased risk of developing LTG-induced rashes in female patients with epilepsy may be due to an altered immune response due to sex hormones.[17] Female patients may need to be monitored more carefully during LTG initiation and choosing slow titration may improve tolerability among these patients. In this study, the concomitant use of lithium or atypical antipsychotics commonly used in patients with mood disorders did not affect the risk of rash development.

No patient who experienced rash in this study developed a serious rash. This could be more than chance. All 38 patients who experienced rash stopped taking LTG immediately after the occurrence of the rash according to the prior education and direction by physicians. This action might have been responsible for preventing serious rash. Education regarding safety issues of LTG before initiation would be essential toward the safe use of LTG.

Effectiveness and Titration Methods

The clinical effectiveness of LTG in patients with mood disorders was evaluated using the time to all-cause discontinuation, which has been reported to reflect the efficacy and tolerability of the medication.[18] Although it was hypothesized that the titration schedule would influence the effectiveness of LTG by affecting its safety during the initiation phase, the time to all-cause discontinuation was not significantly different between the slow titration and the standard titration groups in this study. Although the risk of rash development was lower in the slow titration group than in the standard titration group, the long-term effectiveness of LTG was not significantly different between the groups. In this study, the most frequent cause of discontinuation of LTG in the slow titration group was patient request, suggesting that the occurrence of a rash did not affect the long-term use of LTG in this group. Patients

requested to discontinue LTG for several reasons including the tablet flavor and financial considerations. Because of the slow manifestation of the effects of LTG when a slow titration schedule is used, patients may subjectively experience less benefits of the medication during the initiation period. A subanalysis that excluded the 12 patients who requested discontinuation of LTG revealed that slow titration significantly increased the time to discontinuation ($P < 0.05$) and the concomitant use of VPA significantly decreased the time to discontinuation ($P < 0.05$) compared with standard titration and monotherapy (Supplemental Digital Content 4, http://links.lww.com/JCP/A811). These results suggest that the safety of LTG during the initiation phase is related to the long-term effectiveness of LTG. Because of the slow manifestation of the effects of LTG when a slow titration schedule is used, patients may subjectively experience less benefits of the medication during the initiation period. This might cause requests for discontinuation as an adherence issue in the slow titration group.

The evaluation of the long-term efficacy of mood-stabilizing agents is challenging because of the complicated disease course of mood disorders that includes several mood episodes and fluctuations. Treatment efficacy evaluated comprehensively using CGI-C in patients who used the medication for at least 12 months was similar to previously reported results.[19] Lamotrigine seemed to more efficacious in patients with BD than in those depressive disorder NOS, regardless of the selected titration methods, reflecting treatment responsiveness of the disease. As long-term LTG use results in acceptable outcomes for patients with mood disorders, avoiding early discontinuation is essential. Physicians should strive to optimize the titration schedule by using slow titration schedules for female patients and those with the concomitant use of VPA.

LIMITATIONS

This study is not without limitations. A medical record-based collection may reduce the accuracy of information. A retrospective study could result in potential selection biases. Missing demographics of entire patients with mood disorders who visited the centers make it difficult to correct possible selection biases in the demographics of the cohort. Some confounding factors, such as concomitant oral contraceptive pill, that affect the serum level of LTG[20] were not adjustable. Polarity as well as frequency and severity of mood episodes was not evaluated in the cohort. Data regarding patient allergies[6,11,12] were not collected. Moreover, pharmacogenomics factors were not assessed in the present study, although an association between HLA types (HLA-B*1502, HLA-A*2402, and HLA-A*3303) and LTG-induced rash in Asian population has been reported.[21] Serum levels of LTG would be needed for the accurate examination of the efficacy of LTG.[22] In addition, the rash was not diagnosed by a dermatologist in this study, and causes other than LTG were not excluded, which may have led to overdiagnosis.[23] Furthermore, the definition of slow titration used in this study is comprehensive, and schedules with fewer initial doses that used the standard titration interval could not be distinguished from those that used prolonged intervals with the standard titration dosing.

In conclusion, although slow titration of LTG reduced the risk of rash development, the long-term effectiveness of this schedule was not significantly different from that of standard titration. An adherence issue might occur in patients treated with slow titration. The results of this study suggest that optimizing the initial titration schedule of LTG in patients with mood disorders is challenging. On the other hand, selecting a slow titration schedule for LTG could be beneficial for female patients or for patients on concomitant VPA. Further studies using a randomized prospective design with detailed examination including mood/polarity assessment would be needed to ensure optimal titration method maximizing safety and efficacy of LTG for patients with mood disorders.

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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