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Lamotrigine augmentation for the treatment-resistant mood disorder

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ABSTRACT

Purpose: A number of depressed patients do not respond adequately to standard antidepressant treatments, and some of them subsequently suffer from treatment-resistant mood disorder (TRMD). Lamotrigine (LTG) is the only mood stabilizer that is effective for preventing depressive episodes of bipolar disorders. This study aimed to evaluate the efficacy of LTG augmentation in Japanese patients with TRMD.
Methods: The subjects were 30 patients with refractory depression who had already shown insufficient response to multiple pharmacotherapy including antidepressants, mood stabilizers and atypical antipsychotics. The diagnoses were major depressive disorder (n=16), bipolar disorder (n=10) and dysthymic disorder (n=4). All patients gave written informed consent to receive LTG as an off-label indication in Japan after explanation for possible risks of unwanted skin reactions. The daily dose of LTG was titrated by the clinician's decision (88.0±61.9 mg/day). Treatment response was assessed by Montgomery-Åsberg Depression Rating Scale (MADRS) and Global Assessments of Functioning (GAF) before and after the 8-week LTG augmentation.
Results: Significant improvements were observed in the scores of MADRS (25.3±10.1 → 14.7±10.5) and GAF (49.2±12.3 → 64.1±11.7) after the 8-week LTG augmentation (p=0.0010). Greater number of the past mood episodes and shorter duration of the present depressive episode are associated with better response to LTG. Mild adverse skin reactions developed in 10 patients although 8 out of them were treatment responders.
Discussion: LTG augmentation may be effective for the treatment of TRMD, especially with shorter duration of unremitted depression and more recurrent episodes. However, attention should be paid to the development of adverse skin reactions in LTG responders.

Keywords: lamotrigine augmentation, treatment-resistant mood disorder, clinical response, adverse skin reactions

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INTRODUCTION

A number of depressed patients do not respond adequately to standard antidepressant treatments, and some of them subsequently suffer from treatment-resistant mood disorder (TRMD) [1]. In

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fact, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) program with a comprehensive algorithm mainly using several classes of antidepressants demonstrated that the remission rates in depressed patients dramatically decreased after the failure of two treatment steps, and that unremitted patients were likely to have higher recurrent episodes during one-year follow-up [2]. Although the remission-oriented strategy is requisite as soon as possible after introducing the treatments of depression [3], there is no worldwide consensus among psychiatrists with regard to systematic intervention for refractory depression. As a classical augmentation therapy, lithium and thyroid hormone have been well studied, providing some evidences [4]. In reality, however, these agents are not commonly used due to their modest efficiency as well as their narrow therapeutic dose ranges and potential risks for latent unwanted effects during long-term use.

Lamotrigine (LTG) is the only mood stabilizer that is effective for preventing depressive episodes of bipolar disorders [5]. Although the US Food and Drug Administration (FDA) approved clinical indication of LTG for relapse prevention in bipolar disorders, its acute efficacy for bipolar or non-bipolar depression has not been well established. As for bipolar depression, however, it has been recently demonstrated that additional LTG treatment is apparently effective in a double-blind, placebo-controlled trial [6]. Also, LTG augmentation is suggested to have greater advantages in treating more severely depressed patients with bipolar disorders [5] and have benefit for pediatric bipolar disorders [7]. The efficacy of LTG is regarded to be comparable to that of lithium for the treatment of bipolar Ⅱ disorder [8]. On the other hand, the efficacy of LTG as monotherapy in the acute treatment of bipolar disorder is still controversial [8, 9].

A few studies have examined whether LTG augmentation therapy is also applicable to unipolar TRMD. Some studies reported that LTG accelerated the onset of antidepressant with sufficient tolerability in patients with major depressive disorder [1, 10], while another failed to find that LTG was an efficient augmentation for non-bipolar patients [11]. Although diagnostic aspects of mood disorders, e.g., acuteness/chronicity or unipolarity/bipolarity, may affect the overall efficacy LTG augmentation to some extent, no reliable evidence has yet been obtained regarding LTG use for TRMD. It appears more important to specify profiles of TRMD patients who may benefit from LTG augmentation therapy.

Thus, this study aimed to find significant factors affecting clinical response to LTG as well as an evaluation of the efficacy of LTG augmentation in Japanese patients with refractory depression in clinical settings.

SUBJECTS AND METHODS

Subjects

Thirty Japanese patients (17 males, 13 females) with TRMD were enrolled in this study, consisting of 20 outpatients and 10 inpatients. All of them had previously failed to respond to at least 3 antidepressants or mood stabilizing agents despite enough therapeutic doses and durations. The average (±SD) number of the past ineffective psychotropic medication was 5.6±2.3. The mean (range) age was 35.5 (15-58) years. The average (range) number of previous mood episodes was 4.1 (1-10), and that of duration of the present depressive episode was 14.4 (1-40) months. The age of onset and duration of the disease were 28.1±12.5 years and 7.9±7.1 years, respectively.

Prescribed drugs (number of cases) just before introduction of LTG were the following: paroxetine (13), milnacipran (5), mianserin (5), setiptiline (5), sertraline (3), fluvoxamine (3), clomipramine (3), and amoxapine (3) for antidepressants; lithium carbonate (15), sodium valproate (15), gabapentin (5), and carbamazepine (1) for mood stabilizers; aripiprazole (9), quetiapine (6), risperidone (3), and olanzapine (3) for atypical antipsychotics. The average (±SD) number of above-mentioned psychotropic medication was 3.3 (±1.5).

All patients gave written informed consent to receive LTG as an off-label indication in Japan after explanation for possible risks of adverse skin reactions. The study protocol was approved by the Ethics Committee of University of the Ryukyus.

Diagnosis and Assessments

Before initiating LTG trial, the patients' medical records were carefully reviewed with emphasis on previous pharmacological history, total number of mood episodes in their life and duration of the present depressive episode. The prescriptions of all 30 patients had not had a major change for at least 4 weeks prior to the study. Psychiatric diagnosis was made according to DSM-Ⅳ [12]. The subjects were diagnosed as major depressive disorder (MDD: n=16), bipolar disorders (BD: n=10) and dysthymic disorder (DD: n=4). Four subjects were rapid cyclers, and 6 had

experienced episodes of mixed depression [13]. Depressive symptoms and adjustment levels were evaluated by an investigator using Montgomery-Åsberg Depression Rating Scale (MADRS) [14] and Global Assessments of Functioning (GAF) before and after the 8-week LTG augmentation. The daily dose of LTG was titrated by the clinician's decision at each 2-week interval. Coadministered psychotropic medication was fixed throughout the study period. During the LTG trial, careful attention was paid to possible risks for development of any adverse skin reactions.

Table 1. Clinical backgrounds in three groups with different diagnoses

	MDD (n=10)	BD (n=16)	DD (n= 4)
Age at study initiation (years)	37.3±14.8	34.8±13.9	30.0±18.2
Age at onset (years)	29.4±13.6	27.7±10.6	24.0±14.7
Number of previous mood episodes	3.7±2.3	4.9±3.1	4.0±4.1
Number of past ineffective medications	5.3±2.2	5.8±2.6	6.3±1.9
Duration of the present depressive episode (months)	16.0±19.0	9.3±11.1	20.5±17.3
Duration of the disease (months)	69.9±67.2	107.4±122.7	56.5±25.6
Number (percentage) of coadministered drugs			
Mood stabilizers			
Lithium carbonate	9 (90)	4 (25)	2 (50)
Sodium valproate	6 (60)	5 (31)	4 (100)
Gabapentin	0 (0)	3 (19)	2 (50)
Carbamazepine	1 (10)	0 (0)	0 (0)
Antidepressants			
Paroxetine	7 (70)	4 (25)	2 (50)
Milnacipran	1 (10)	1 (6)	3 (75)
Mianserin	2 (20)	3 (19)	0 (0)
Setiptiline	0 (0)	5 (31)	0 (0)
Sertraline	1 (10)	1 (6)	1 (25)
Fluvoxamine	1 (10)	2 (13)	0 (0)
Clomipramine	2 (20)	0 (0)	1 (25)
Amoxapine	0 (0)	2 (13)	1 (25)
Atypical antipsychotics			
Aripiprazole	5 (50)	2 (13)	2 (50)
Quetiapine	4 (40)	1 (6)	1 (25)
Risperidone	1 (10)	2 (13)	0 (0)
Olanzapine	1 (10)	2 (13)	0 (0)

MDD: Major depressive disorder, BD: Bipolar disorder, DD: Dysthymic disorder

Statistical Analysis

Data were mainly analyzed on the basis of nonparametric statistics. The Spearman rank test was used for analysis of relationship between percentage improvement in MADRS scores and number of the past mood episodes or duration of the present depressive episode. Intraindividual changes in MADRS and GAF scores before and after LTG augmentation were compared using the Wilcoxon signed-rank test. Comparison of the data among the three different diagnosed subgroups DD, MDD and BD were made by using the Kruskal-Wallis test or the one-way ANOVA followed by the Tukey test as a post-hoc analysis. Occurrence of adverse skin reactions in association with gender difference and clinical response was analyzed by Fisher's exact test. Other data between two groups were compared using the Mann-Whitney U test.

A two-tailed P value of 0.05 or less was regarded as statistically significant. SPSS 11.0.1 J for Windows (SPSS Japan Inc., Tokyo, Japan) was used for these statistical analyses

RESULTS

Clinical Outcome of LTG Augmentation

After the 8-week treatment, the maintenance dose of LTG was finally 88.0±61.9 (25-200) mg/day on average (range). No significant difference in the mean daily LTG dose was found among the 3 subgroups with nonresponders (115.6±104.3 mg/day), partial responders (67.9±40.1 mg/day) and responders (82.7±33.6 mg/day).

Fifteen out of 30 patients (50.0%) were treatment responders (50% or more symptom reduction from the baseline), while partial response was observed in 7 cases (23.3%) and nonresponse in 8 cases (26.7%) after the 8-week trial of LTG augmentation (Fig.1). Four patients (13.3%) showed a remarkable improvement, fulfilling the latest criteria for complete remission by cut-off score <5 on the MADRS for more than 2 weeks [15].

The average (±SD) MADRS score shifted from 25.3±10.1 to 14.7 ±10.5 (p=0.0010), and that for GAF from 49.2±12.3 to 64.1 ±11.7 (p=0.0010) after the 8-week LTG augmentation. The mean (±SD) percentage improvements in MADRS and GAF were 43.1±33.4 % and 34.2±39.6%, respectively.

Age, sex, admission, onset of the disease and duration of illness did not affect clinical outcome of LTG augmentation. Although there appears greater MADRS improvement in 4 rapid cyclers (69.1±14.4%) than non-rapid cyclers (39.1±33.9%) and lower improvement in 6 subjects having the past episodes of mixed depression (15.7±46.0%) than those without them (49.9±14.4%), these differences did not reach significant levels. Three out of 4 rapid cyclers and 5 out of 6 mixed depression were diagnosed as BD. Within the BD subgroup, rapid cyclers improved more (65.1±14.5%) than non-rapid cyclers (33.7±36.4%) although for the 5 subjects with mixed depression episodes the MADRS improvement was lower (26.8±41.4%) than those without mixed depression episodes (59.4±15.4%).

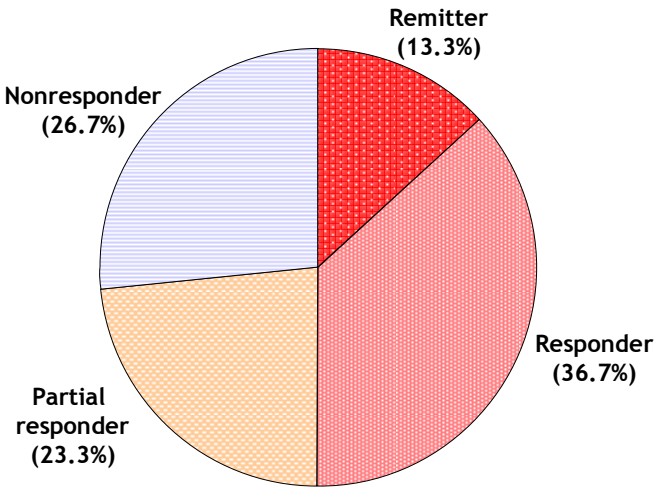

Figure 1. Clinical outcome of 8-week lamotrigine augmentation therapy in patients with treatment-resistant depression. Remission was defined as Montgomery-Åsberg Depression Rating Scale score was <5 for 2 weeks or more [15]. Responder: 50% or more reduction, Partial responder: 25% to 50% reduction, Nonresponder: 25% or less reduction in MADRS score, respectively.

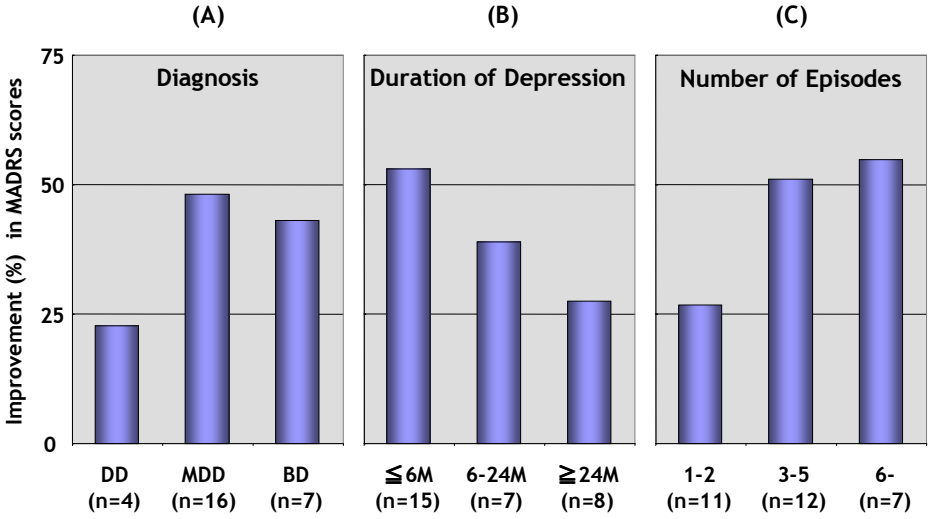

Figure 2. The effects of diagnosis of mood disorders (A), duration of unremitted period of depression (B) and number of the past mood episodes (C) on percentage improvement in Montgomery-Åsberg depression Rating Scale (MADRS) scores after 8-week lamotrigine augmentation therapy. DD: dysthymic disorder, MDD: major depressive disorder, BD: Bipolar disorder.

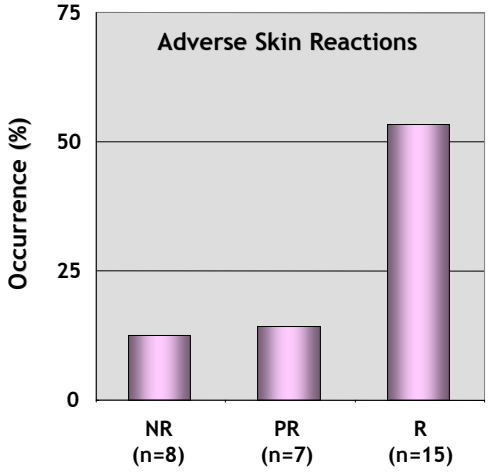

Figure 3. The effects of clinical response on adverse skin reactions during lamotrigine augmentation therapy. Skin reactions include facial redness, general itching, deteriorated acne and benign exanthema. NR: nonresponders, PR: partial responders, R: responders.

Factors Affecting Response to LTG

Fig.2 illustrates the effects of diagnosis of mood disorders, duration of unremitted period of depression and number of the past mood episodes on percentage improvements in MADRS scores after the 8-week LTG augmentation therapy.

The average percentage improvements were 22.7±42.6% in DD, 48.1±31.1% in MDD and 43.1±34.1% in BD for MADRS and 19.5±25.8% in DD, 30.1±33.7% in MDD and 46.6±51.5% in BD for GAF although no significant difference was observed among the three different diagnosis groups. The treatment response gradually diminished as the duration of the present depressive episode became prolonged (Fig.2), *i.e.*, 53.1±28.5% for ≦6 months, 39.0±35.8% for 6-24 months and 27.5±37.3% for ≧24 months in the percentage improvements in MADRS scores.

However, there was no significant correlation between duration of depression and treatment response to LTG (r_S= -0.241, p=0.199).
Meanwhile, as the numbers of the past mood episodes increased, treatment response to LTG became greater (26.8±34.9% in 1-2 episodes, 51.1±30.7% in 3-5 episodes and 54.8±14.4% in 6 or more episodes regarding the improvements in MADRS scores), as shown in Fig.2. This was also supported by a significant correlation between the numbers of the past episodes and the percentage improvement in MADRS (r_S=0.423, p=0.019).

Adverse Skin Reactions

Mild adverse skin reactions developed in 10 patients (33.3%). These skin reactions include facial redness (1 case), general itching (2 cases), deteriorated acne (3 cases) and benign exanthema (4 cases). All of these cases temporarily needed the LTG dosage to remain unchanged for a short-term or to be reduced slightly although rechallenge of slower titration was usually possible after a 2 week interval.
Interestingly, out of the 10 cases with adverse skin reactions, 9 were females, and 8 were treatment responders to LTG (Fig.3). Incidences of any skin reactions were 9/14 (64.3%) in females and 1/16 (6.25%) in males, showing the significant gender difference (Fisher's exact test, p=0.0014). Provided that the cut-off value was defined as 50% improvement in MADRS scores for treatment response, the occurrence of adverse skin reactions was higher in responders (8/15: 53.3%) than in nonresponders (2/15: 13.3%) (Fisher's exact test, p=0.049). Subjects with these adverse effects had significantly (p=0.028) greater number of coadministered psychotropics (4.3±1.4) than those without them (2.8±1.2).
Apart from skin symptoms, 4 patients each suffered from one of the following during our study - hypersomnia, hallucination, diarrhea, and back pain. The symptoms were all minor and self-limited, and the affected subjects managed to complete the study.

DISCUSSION

Lithium carbonate and thyroid hormone have been used as standardized augmentation therapy for TRMD [4]. However, these agents are of only limited values from the aspects of effectiveness and tolerability. Actually, half of our subjects enrolled in the present study had been nonresponsive to lithium or valproate, another mood stabilizer. Meanwhile, LTG augmentation is currently expected as an option for the treatment of TRMD. However, despite the efficacy of LTG for relapse prevention of prevailingly depressive episodes of bipolar disorders [5], clinical indication of this drug for the acute treatment of bipolar depression or non-bipolar TRMD has not been established yet.
It is disappointing that placebo-controlled studies have revealed little efficacy of LTG monotherapy in the acute treatment of bipolar depression [9]. However, it has been generally accepted that monotherapy switches have limited effectiveness, and that combination strategies rather have more advantages over monotherapy in achieving remission [4]. LTG might be efficacious as an augmentation agent rather than as monotherapy use in treating subjects with TRMD. In fact, LTG as add-on therapy to lithium [6] or second-generation antipsychotics [7] resulted in the successful outcome for the acute treatment of bipolar depression. The present study has also shown the high rate of responders to LTG coadministration (50%), which is consistent with the aforementioned previous studies [6, 7], supporting efficacy of LTG augmentation therapy in the acute treatment of TRMD including bipolar depression.
It has been reported that at least around 200 mg/day of LTG is required in seizure control for epilepsy and relapse prevention for bipolar disorders [16]. In this study, however, the maintenance dose of LTG after the 8-week augmentation was finally 88.0 mg/day on average, which was almost the same as proposed doses in previous retrospective reports dealing with acute treatments of TRMD [17, 18]. Therefore, LTG even at lower doses than those needed for relapse prevention of bipolar disorders may have enough efficacy for the acute augmentation therapy of TRMD.
Diagnosis of mood disorders and duration of the present depression did not significantly affect treatment response to LTG augmentation in the present study. However, the possibility that large inter-individual variations in each subgroup may mask significant results cannot be entirely ruled out. Actually, the therapeutic effects of LTG in patients with DD appear to be much smaller than those with MDD or BD, leading to lower LTG response in subjects with longer duration ($\geqq$24 months) of unremitted period of TRMD (Fig.2) since DD was originally defined as a mood disorder with chronic depressive symptoms lasting for a period of at least two years. In contrast, relatively greater improvements were observed in subjects having the present depressive episode within 6 months (Fig.2). This may be at least partly supported by a previous study

[19] showing that 6 months of illness are the critical point to determine the probability of recovery from major depressive episode.

Contrary to our expectations, patients with greater number of the past mood episodes showed rather better responses to LTG in the present study (Fig.2). Similarly, patients with the past history of rapid cycling also showed greater symptom reduction after LTG augmentation. A previous report [20] also suggested the advantages of valproate and lamotrigine over lithium or carbamazepine in the treatment of rapid cycling bipolar disorder. These findings together with aforementioned plausible influential factors suggest that TRMD with more recurrences of shorter depressive episodes are the best clinical indication for LTG augmentation irrespective of unipolar/bipolar pathophysiology (MDD or BD). Early introduction of LTG may be recommended for these patients within 6 months of critical period to achieve remission.

Meanwhile, adverse skin reactions were more frequently observed in females than in males. This gender difference may result from more concern and sensitivity to these unwanted effects in female subjects mainly from cosmetic reasons. Furthermore, treatment responders to LTG augmentation showed higher occurrence of adverse skin reactions than nonresponders. Although we have no clear explanation for this, there might exist common underlying mechanisms between increased skin reactions and treatment response. From a practical point of view, the higher risk of adverse skin reactions should be warned of especially in treatment responders to LTG, though mild and temporary skin reactions do not necessarily warrant withdrawal of LTG. After development of any skin reactions, careful monitoring and temporary maintaining of dosage or reduction of LTG are necessary, which can be successfully followed by slower and more cautious titration [21].

This study is still preliminary and has several limitations, i.e., an open trial in clinical settings, relatively small-sized study, flexible-dose schedule of LTG, heterogeneity in diagnosis of mood disorders, and a short study period to confirm the efficacy for relapse prevention of TRMD. However, the present study suggests possible indication of LTG to TRMD patients with specific profiles. A larger-sized controlled study with a longer follow-up period is desirable to confirm reproducibility of this study or obtain much clearer results.

CONCLUSION

The TRMD patients with greater number of the past mood episodes and shorter duration of the present depressive episode may have benefit from LTG augmentation irrespective of diagnosis for mood disorders. However, attention should be paid to the development of adverse skin reactions rather in responders to LTG treatment.

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