

Factors Associated with Doses of Mood Stabilizers in Real-world Outpatients with Bipolar Disorder

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Objective: Several evidence-based practice guidelines have been developed to better treat bipolar disorder. However, the articles cited in these guidelines were based on clinical or basic studies with specific conditional settings and were not sufficiently based on real-world clinical practice. In particular, there was little information on the doses of mood stabilizers.

Methods: The MULTicenter treatment SURvey on BIpolar disorder in Japanese psychiatric clinics (MUSUBI) is a study conducted to accumulate evidence on the real-world practical treatment of bipolar disorder. The questionnaire included patient characteristics such as comorbidities, mental status, treatment period, Global Assessment of Functioning (GAF) score, and details of pharmacological treatment.

Results: Most patients received mood stabilizers such as lithium (n = 1,317), valproic acid (n = 808), carbamazepine (n = 136), and lamotrigine (n = 665). The dose of lithium was correlated with age, body weight, number of episodes, depression and GAF. The dose of valproic acid was correlated with body weight, number of episodes, presence of a rapid cycle and GAF. The dose of carbamazepine was correlated with age, mania, and the presence of a rapid cycle. The dose of lamotrigine was correlated with the number of episodes, depression, mania, psychotic features, and the presence of a rapid cycle. Doses of coadministered mood stabilizers were significantly correlated, except for the combination of valproic acid and lamotrigine.

Conclusion: The dose of mood stabilizers was selectively administered based on several factors, such as age, body composition, current mood status and functioning. Further prospective studies are required to confirm these findings.

KEY WORDS: Bipolar disorder; Mood stabilizers; Nationwide study; Real world; Dose.

INTRODUCTION

For the treatment of bipolar disorders, mood stabilizers are still categorized as a first-line treatment for manic and depressive episodes and the maintenance phase [1]. A previous network meta-analysis demonstrated that lithium, valproic acid (VPA), and lamotrigine (LTG) but not carbamazepine (CBZ) were more effective than placebo

and that the tolerability of CBZ was inferior to that of placebo [2]. However, the findings of this study are difficult to apply in the context of real-world clinical practice. The International College of Neuropsychopharmacology Treatment Guidelines for Bipolar Disorder (CINP-BD) has recently recommended that monotherapy with aripiprazole, asenapine, cariprazine, paliperidone, quetiapine, risperidone or VPA is a first-line treatment for manic patients [3]. Monotherapy with quetiapine, lurasidone or olanzapine-fluoxetine combination is the first-line treatment for depressive patients, and monotherapy with lithium, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone or risperidone long-acting injectables was a

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first-line treatment in maintenance therapy [3]. In addition, the Canadian Network for Mood and Anxiety Treatments (CANMAT 2018) has recently suggested that monotherapy with lithium or divalproex is recommended as a first-line treatment for acute mania [4]. Quetiapine and lurasidone monotherapy are recommended as first-line options for bipolar depression [4]. Lithium, LTG and divalproex are recommended options for the maintenance phase [4]. The Korean Medication Algorithm Project for Bipolar Disorder (KMAP-BP) [5], which was the most recent guideline for bipolar disorder, suggested that the preferred first-step strategies were VPA, lithium, olanzapine and quetiapine for acute mania; lithium, VPA, LTG, aripiprazole, and quetiapine for depression; and a combination of mood stabilizers and atypical antipsychotics for maintenance. However, there is little information on adequate doses of mood stabilizers for the treatment of bipolar disorders, although the therapeutic reference ranges are 0.5–1.2 mmol/L for lithium, 50–100 µg/ml for VPA, 4–10 µg/ml for CBZ and 1–6 µg/ml for LTG [6].

A previous study suggested that the doses of mood stabilizers tend to be adjusted based on clinical response, including adverse effects. There were negative associations between serum levels of VPA and short-term delayed recall and working memory. A positive association was suggested between the serum level of lithium and working memory [7]. Although therapeutic drug monitoring (TDM) applications for neuropsychiatric agents aim to assist clinicians in enhancing the safety and efficacy of treatment, most patients do not apply for TDM in the treatment of bipolar disorders in Japan [8]. Most side effects can be transient or dose related and can be managed by optimizing drug doses to the lowest effective dose [9]. In addition, the optimal dose of mood stabilizers might have been influenced by other clinical conditions, such as age, sex, psychiatric features, comorbid symptoms and other mood stabilizers.

More than 90% of all patients with mood disorders in Japan are outpatients, 30% of whom are treated at the clinics of Japanese Association of Neuro-Psychiatric Clinics members [10]. Therefore, we aimed to search for potential factors associated with the optimal doses of mood stabilizers in stable outpatients in good practical situations.

METHODS

Study Design and Subjects

Joint research (the MULTICENTER treatment SURvey on BIpolar disorder in Japanese psychiatric clinics, MUSUBI) was conducted between the Japanese Association of Neuro-Psychiatric Clinics and the Japanese Society of Clinical Neuropsychopharmacology to accumulate evidence on the real-world practical treatment of bipolar disorder in Japan. The method and design of MUSUBI has been described previously [11]. The MUSUBI is a cross-sectional study in which a questionnaire was administered at 176 outpatient clinics belonging to the Japanese Association of Neuro-Psychiatric Clinics from September to October 2016 [11]. Patients diagnosed with bipolar disorder based on the International Classification of Diseases, 10th edition criteria (World Health Organization, 1992) and treated at these clinics were included in this study.

This study protocol was reviewed and approved by the institutional review board of the ethics committee of the Japanese Association of Neuro-Psychiatric Clinics (ID: 20160822). This study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. Prior to the initiation of the study, the study protocol was reviewed and approved by the institutional review board of the ethics committee of the Japanese Association of Neuro-Psychiatric Clinics. Since this was a retrospective medical record survey, the informed consent requirement was exempted, but we instead released information on this research so that patients were free to opt out [11].

Study Procedures

Clinical psychiatrists were asked to complete a questionnaire about patients with bipolar disorder by performing a retrospective medical record survey. The questionnaire included patient characteristics (age, sex, height, weight, academic background, mental status), treatment period, Global Assessment of Functioning (GAF) score, and details of pharmacological treatment. We mailed 20 copies of this questionnaire to each outpatient clinic and analyzed the responses. This study focused on antidepressant prescriptions for bipolar disorder patients and their profiles.

Table 1. Characteristics of subjects receiving mood stabilizers

Variable	Lithium (n = 1,317)	Valproic acid (n = 808)	Carbamazepine (n = 136)	Lamotrigine (n = 665)
Age (yr)	51.7 ± 13.7	50.8 ± 13.2	52.6 ± 12.5	46.9 ± 12.5
Sex (male = 1, female = 2)	1.5 ± 0.50	1.53 ± 0.50	1.5 ± 0.50	1.54 ± 0.499
Height (cm)	163 ± 8.7	162 ± 8.4	162 ± 8.8	163 ± 8.4
Weight (kg)	63 ± 12.6	64 ± 13.2	63 ± 13.5	62 ± 12.3
Education ^a	2.9 ± 1.1	2.7 ± 1.1	2.6 ± 1.1	3.0 ± 1.1
Current status of depression ^b	0.57 ± 0.70	0.64 ± 0.72	0.66 ± 0.70	0.77 ± 0.77
Current status of mania ^b	0.20 ± 0.46	0.25 ± 0.50	0.33 ± 0.58	0.18 ± 0.43
Current status of psychotic feature ^b	0.06 ± 0.26	0.07 ± 0.28	0.16 ± 0.39	0.09 ± 0.30
Current status of suicidal ideation ^b	0.09 ± 0.31	0.13 ± 0.38	0.17 ± 0.40	0.16 ± 0.41
Current status of substance use ^b	0.05 ± 0.23	0.06 ± 0.27	0.10 ± 0.32	0.06 ± 0.26
Current status of rapid cyler ^b	0.12 ± 0.33	0.13 ± 0.34	0.20 ± 0.40	0.14 ± 0.34
Global assessment of functioning ^c	0.88 ± 0.78	0.97 ± 0.78	1.07 ± 0.79	0.98 ± 0.78
Total number of episode	8.5 ± 6.2	8.1 ± 6.1	11.0 ± 7.0	7.0 ± 5.6
Number of mood stabilizers	1.4 ± 0.55	1.5 ± 0.58	1.8 ± 0.70	1.4 ± 0.58
Number of antidepressants	0.45 ± 0.65	0.46 ± 0.66	0.46 ± 0.74	0.46 ± 0.69
Number of antipsychotics	0.61 ± 0.70	0.67 ± 0.74	0.76 ± 0.77	0.71 ± 0.69
Number of anxiolytics	0.39 ± 0.57	0.39 ± 0.56	0.42 ± 0.58	0.42 ± 0.60
Number of hypnotics	0.85 ± 0.82	0.84 ± 0.80	0.99 ± 0.85	0.89 ± 0.87
Daily dosage (mg/day)	559 ± 245	519 ± 270	363 ± 197	159 ± 100
Range (mg/day)	25–1,500	100–1,600	50–1,000	5–600
Co-administered dosage (mg)				
Lithium	-	579 ± 249, n = 266	616 ± 255, n = 61	649 ± 260, n = 198
Valproic acid	538 ± 267, n = 266	-	677 ± 273, n = 31	552 ± 285, n = 77
Carbamazepine	406 ± 192, n = 61	340 ± 183, n = 31	-	268 ± 194, n = 19
Lamotrigine	177 ± 103, n = 198	111 ± 68, n = 77	234 ± 119, n = 19	-

Values are presented as mean ± standard deviation.

^aJunior high school graduate = 1, high school = 2, junior college = 3, college = 4, postgraduate degree = 5. ^bPresence = 1, absent = 0. ^cGlobal assessment of functioning (GAF) (81–100) = 0, GAF (61–80) = 1, GAF (41–60) = 2, GAF (< 41) = 3.

Statistical Analysis

The factors associated with the dose of mood stabilizers among bipolar disorder patients were examined using linear regression with forced entry. These factors included sex, height, weight, educational level, GAF score, psychiatric comorbidity, rapid cycle status, substance abuse, mood status, and total number of episodes. The dummy variables included were as follows: male = 1 and female = 2; junior high school graduate = 1, high school = 2, junior college = 3, college = 4, and postgraduate degree = 5; GAF (81–100) = 0, GAF (61–80) = 1, GAF (41–60) = 2, and GAF (< 41) = 3; depression = 1 and without depression = 0; mania = 1 and without mania = 0; psychotic feature = 1 and without psychotic feature = 0; suicidal ideation = 1 and without suicidal ideation = 0; rapid cyler = 1 and not rapid cyler = 0; and substance abuse = 1 and without substance abuse = 0. Pearson correlations were performed for association between doses of mood stabilizers. All statistical tests were based on a two-sided significance level of 0.05. The SPSS Statistics software program for

Windows, version 25.0 (IBM Japan, Tokyo, Japan), was used for all analyses.

RESULTS

Completed questionnaires on 3,213 outpatients with bipolar disorder were returned from 176 originally solicited outpatient facilities. The characteristics of the subjects are shown in Table 1. Most patients received mood stabilizers such as lithium (n = 1,317), VPA (n = 808), CBZ (n = 136), and LTG (n = 665). The dose of LTG in patients receiving VPA was significantly lower than that in patients receiving lithium and CBZ.

The dose of lithium was directly correlated with body weight and number of episodes, and GAF and was inversely correlated with age and depression (Table 2). The dose of VPA was correlated with body weight, number of episodes, presence of a rapid cycle and GAF (Table 2). The dose of CBZ was correlated with mania and was inversely correlated with age and the presence of a rapid cy-

Table 2. Partial correlation coefficients of dose of mood stabilizers prescribed in the outpatients clinics using multiple regression analysis

Variable	Lithium (n = 1,317)	Valproic acid (n = 809)	Carbamazepine (n = 136)	Lamotrigine (n = 665)
Age	-0.186***	-0.038	-0.206*	-0.003
Sex (male = 1, female = 2)	-0.047	0.004	0.076	0.042
Height	0.077	-0.017	0.163	0.062
Weight	0.115**	0.103*	-0.125	-0.003
Education periods ^a	0.045	0.055	0.193	0.007
Number of episode	0.073**	0.116**	0.049	0.084*
Presence of depression ^b	-0.070*	-0.057	0.017	-0.113*
Presence of mania ^b	0.021	0.042	0.237*	-0.082*
Presence of psychotic features ^b	0.012	-0.018	0.095	0.089*
Presence of suicidal ideation ^b	-0.031	0.026	-0.047	0.015
Presence of substance use ^b	-0.032	-0.015	-0.139	-0.005
Presence of rapid cycler ^b	0.019	0.090**	-0.203*	0.101*
Global assessment of functioning ^c	0.108**	0.072*	-0.011	0.061
R	0.328***	0.213***	0.450**	0.194*

R, multiple correlation coefficients.

^aJunior high school graduate = 1, high school = 2, junior college = 3, college = 4, postgraduate degree = 5. ^bPresence = 1, absent = 0. ^cGlobal assessment of functioning (GAF) (81–100) = 0, GAF (61–80) = 1, GAF (41–60) = 2, GAF (< 41) = 3.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Correlations between doses of mood stabilizers co-administered

Drugs	Lithium (n = 1,317)	Valproic acid (n = 808)	Carbamazepine (n = 136)	Lamotrigine (n = 665)
Valproic acid	0.254*** (n = 266)			
Carbamazepine	0.346** (n = 61)	0.454** (n = 31)		
Lamotrigine	0.139* (n = 198)	-0.038 (n = 77)	0.557** (n = 19)	

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

cle (Table 2). The dose of LTG was correlated with the number of episodes, psychotic features, and the presence of a rapid cycle and was inversely correlated with the presence of depression and mania (Table 2).

The doses of coadministered mood stabilizers were significantly correlated with the combination of VPA and LTG (Table 3).

DISCUSSION

Mood stabilizers such as lithium and anticonvulsants are still standard-of-care for the acute and long-term treatment of bipolar disorder. The results of this study showed that age, body weight, number of episodes, presence of current mood disorders, presence of rapid cycle and social adjustment are associated with the doses of mood stabilizers, and this is the first report regarding mood stabilizer dosing and its related factors in the world.

We found a significant inverse correlation between daily doses of lithium and CBZ and age. These findings are reasonable because lithium is excreted by the kidneys

[12], and renal function decreases with age [13]. In addition, CBZ is metabolized by liver enzymes, particularly CYP3A4 [12], whose activity decreases with age [14]. Therefore, serum concentrations of lithium and CBZ tend to increase with age. On the other hand, VPA and LTG are metabolized by glucuronic acid conjugation, which, unlike compared with CYPs, is not influenced by age.

Depression decreased the doses of lithium and LTG in the study. The recommended doses of lithium were 600–1,200 mg/day during the manic episode and 600–1,800 mg/day during the depressive episode [3], suggesting that the daily dose of lithium during the depressive episode should be higher than that during the manic episode. However, our findings demonstrated a lower dose of lithium in patients with depression, although the average daily dose of lithium was approximately 560 mg/day, which is low compared with the world standard recommended dose [3]. We do not have a clear explanation for this discrepancy. The recommended doses of LTG were 50–200 mg/day during depressive episodes and 50–400 mg/day during maintenance episodes [3], suggesting that

the daily dose of LTG during depressive episodes should be lower than that during maintenance episodes. Our results for LTG were in line with the guidelines [3].

The number of episodes was correlated with the doses of lithium and VPA in the study. Although the recommended doses for these mood stabilizers were not shown in the guidelines, lithium and VPA were consistently ranked as the 1st line treatments [3-5]. Therefore, lithium and VPA might be regarded as the main agents for the prevention of repeated episodes.

The presence of rapid cycling was directly correlated with the doses of VPA and LTG and inversely correlated with the dose of CBZ. CINP guidelines say that aripiprazole, quetiapine and VPA were the first-line treatments for rapid-cycling patients, and olanzapine and lithium were recommended as second-line strategies [15], but LTG was not different from placebo in the context of maintenance treatment in patients with rapid cycling [16]. On the other hand, a combination of LTG and mood stabilizers (or atypical antipsychotics) was potentially preferable during episodes of current depression according to KMAP-BP 2018 [5].

Patients who have better response to lithium are a group of patients with bipolar disorder core phenotype clinical features [17,18]. An non-episodic pattern of the mania-depression interval, high rates of comorbid conditions, rapid cycling and younger age at illness onset have been identified as potentially risk against recurrence during the lithium treatment [19-22]. Patients who have better response to VPA are characterized by the presence of pure, mixed or dysphoric mania. In addition, elder age at onset, absence of rapid cycling, absence of concurrent substance abuse and lack of response or intolerance to lithium are clinical predictors of positive outcome of treatment with VPA [23]. Patients who have better response to CBZ seems to be predicted by clinical features such as mood-incongruent psychosis and lack of response or intolerance to lithium, while contrasting findings are potentially predictive of presence of rapid cycling, severe mania and dysphoric mania [24,25]. Earlier onset of symptoms, nonepisodic course of illness, rapid cycling, comorbidity with a panic or substance use disorder, fewer hospitalizations, fewer prior medication trials and male sex may be predictors in patients who have better response to LTG [26,27].

This study has several notable limitations. First, this was

a cross-sectional study, so we could not determine causal relationships. The second limitation of this study was the lack of a structural clinical evaluation of patients, although clinical evaluation in this study was performed by doctors in charge of the patients who were well trained. Additionally, selection bias may have occurred because the subjects were not randomized. Finally, there may be problems with population heterogeneity because we did not distinguish between bipolar I and II. Thus, some inter-rater variability cannot be excluded. Further longitudinal studies are needed to confirm the detailed prescription patterns for patients with bipolar disorder in Japan.

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■ Conflicts of Interest

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