Predictors of a Shorter Time to Hospitalization in Patients with Bipolar Disorder: Medication during the Acute and Maintenance Phases and Other Clinical Factors

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Objective: The present study was conducted to compare the effects of pharmacological treatments during the acute and maintenance phases of mood episodes, sociodemographic, and clinical characteristics between a shorter time to hospitalization group (<12 months) and a longer time to hospitalization group (≥12 months).
Methods: The discharge medication for the first hospitalization was considered the acute treatment and the medication used during the week prior to the second hospitalization at the outpatient clinic was considered the maintenance treatment. Additionally, the charts were reviewed to examine a variety of demographic and clinical characteristics.
Results: Patients in the shorter time to hospitalization group were more likely to be unmarried and/or unemployed, have had a previous hospital admission for a mood episode, and have used antidepressant during the acute phase than those in the longer time to hospitalization group. Patients in the shorter time to hospitalization group were also less likely to use olanzapine, serotonin–norepinephrine reuptake inhibitors, or mood stabilizer monotherapy as a maintenance treatment than were patients in the longer time to hospitalization group.
Conclusion: Predictors for shorter time to hospitalization were associated with number of previous hospital admissions for a mood episode, being unmarried and/or unemployed, and antidepressant use during the acute phase.

KEY WORDS: Acute; Hospitalization; Maintenance; Medication; Prescriptions.

INTRODUCTION

Bipolar disorders are characterized by high rates of recurrence.[1] In fact, over 90% of patients with a bipolar disorder experience a recurrence during their lifetimes and half of all patients will suffer a second episode within 1 year of recovery from a mood episode.[2] The 1-year recurrence rate for bipolar disorder patients ranges from 35-57%, with the heterogeneity being due to differences in the patients' psychopathologies, the available pharmacotherapies, and the definition of recurrence (e.g., including or not including minor depressive episodes or hypomania.[3-5] The frequent recurrences of bipolar disorders are associated with poorer functioning, psychiatric and medical comorbidities, and increased odds of suicidality, disability, unemployment, and re-hospitalization.[6]

These high rates of re-hospitalization in patients with bipolar disorder may be due to the complexity of the underlying biological mechanisms, severity of the psychopathology, lack of efficacy of current pharmacological treatments, and/or other sociodemographic factors.[7,8] Thus, the genetic, biological, clinical, and social factors that are associated with the recurrence of mood episodes can be considered to be predictors of recurrence. To investigate clinical factors, many studies have employed randomized pharmacotherapy trials and pharmacological interventions, in conjunction with psychosocial therapies, to determine their efficacies but it is difficult to generalize the findings of randomized clinical trials to real clinical environments due to a variety of selection biases. For example, the inclusion of only bipolar I or II patients, and/or

the exclusion of patients with severe psychopathologies, those who are in need of hospitalization, and those with highly prevalent comorbid disorders, substance use disorders, anxiety disorders, or cognitive disorders may influence the findings. Likewise, medications that affect the accurate evaluation of clinical efficacy and/or trials that involve only monotherapies (because most patients in clinical settings are prescribed multiple medications) could affect the interpretation of the results. Therefore, observational and naturalistic studies of psychopharmacological treatments may further the current understanding of the recurrence of bipolar disorders in real clinical practice.

The aim of the present study was to compare the effects of pharmacological treatments in real clinical practice, during the acute and maintenance phases of mood episodes, between groups categorized by time to hospitalization: a shorter time to hospitalization group (<12 months) and a longer time to hospitalization group (≥12 months). This study also examined the associations between duration of hospitalization and sociodemographic and clinical characteristics. It was hypothesized that the characteristics that would act as predictors of hospitalization would include age, sex, environmental factors, education, marital status, employment, family history of psychiatric diseases, psychiatric comorbidity, bipolar type (I, II, or not otherwise specified), polarity of the episode, number of mood episodes, and number of hospital admissions due to a mood episode. Time to hospitalization was defined as shorter or longer ($<$ or ≥12 months, respectively) according to the time (months) from the second hospitalization (latest hospitalization in a psychiatric ward due to a mood episode) to the first hospitalization (hospitalization in a psychiatric ward just prior to second episode).

METHODS

Patients

The medical charts of the patients included in the present study were retrospectively reviewed. All patients were diagnosed by a board-certified psychiatrist using a clinical interview in accordance with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) and the DSM fifth edition (DSM-5) for bipolar disorder (bipolar I, II, or not otherwise specified) between January 2002 and December 2015 at St. Mary's Hospital, College of Medicine at The Catholic University of Korea in Seoul, Korea. The second

hospitalization was considered to be any mood episode that led to a hospitalization between 2002 and 2015. If a patient experienced more than one hospitalization during the study period, only the data from the last admission were analyzed. The inclusion criteria for the present study were as follows: (1) a current diagnosis of bipolar disorder based on the DSM-IV-TR and DSM-5 criteria, (2) at least two hospitalization due to a mood episode, and (3) information about medication at discharge after the first hospitalization, and from the outpatient clinic prior to the second hospitalization. The exclusion criteria for the present study were as follows: (1) insufficient data about past neuropsychiatric history; (2) recent onset of an organic brain lesion that could influence mood symptoms or medication; and/or (3) diagnosis of a thought disorder, such as schizophrenia.

The charts of 416 patients with either bipolar I or II disorder were analyzed at baseline; 36 cases were excluded because they were a first-onset episode and 172 cases were excluded based on the abovementioned criteria. Thus, a total of 208 inpatients diagnosed with bipolar disorder were enrolled in the present study and subsequently categorized into two groups based on the time to hospitalization: a shorter time to hospitalization group (<12 months) and a longer time to hospitalization group (≥12 months).

Assessments

The time to hospitalization (months) was defined as the duration between the first hospitalization and the second hospitalization.

To evaluate the effects of pharmacological treatments in real clinical practice during the acute and maintenance phases between the re-hospitalization groups, the discharge medication at the first hospitalization was considered to be the acute treatment and the medication used during the 1 week just prior to the second hospitalization at the outpatient clinic was considered to be the maintenance treatment. The pharmacological treatments included mood stabilizers (lithium, valproate, lamotrigine, and others), antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole, and others), and antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], noradrenergic and specific serotonergic antidepressants [NaSSAs], and others). Additionally, to evaluate the prescription patterns during the acute and maintenance phases, the prescriptions for discharge medication during the first hospitalization, and for the outpatient clinic just prior to the sec-

ond hospitalization, were reported. Combination therapies with mood stabilizers, antipsychotics, and antidepressants, and monotherapy with mood stabilizers, antipsychotic, or antidepressants, were also compared between the groups.

The patient charts were reviewed to examine a variety of demographic and clinical characteristics including age at onset, age at admission, sex, education, marital status, employment, family history of psychiatric disorders (particularly family history of mood disorders and bipolar disorders), comorbidities, bipolar disorder type, index episode polarity, first episode polarity, number of mood episodes (total number of mood episodes, number of depressive episodes, number of manic/hypomanic episodes, and number of mixed episodes), and number of hospital admissions for mood episodes (total number of hospital admissions for mood episodes, number of hospital admissions for depressive episodes, number of hospital admissions for manic/hypomanic episodes, and number of hospital admissions for mixed episodes). Subsequently, the associations between duration of hospitalization and these sociodemographic and clinical characteristics were analyzed.

Statistical Analysis

All statistical analyses were carried out using SAS for Windows software ver. 9.2 (SAS Institute, Cary, NC, USA). The chi-squared tests or Fisher's exact test were used to analyze categorical variables and t-tests were used to analyze continuous variables. A logistic regression analysis was conducted to identify the factors associated with time to hospitalization: demographic information, clinical characteristics, and medication from and prior to the second hospitalization were included as independent variables, and time to hospitalization (<12 months or ≥ 12 months) included as the dependent variable. p-values <0.05 were considered to indicate statistical significance and p values between 0.05 and 0.10 were considered to indicate a trend towards significance.

Ethics

The present study was conducted according to the guidelines of the Declaration of Helsinki and approval to conduct the chart reviews was obtained from the Institutional Review Board. Because this was a retrospective study and the data were collected during routine psychiatric examinations and treatment, the board determined that obtaining informed consent was unnecessary.

RESULTS

Demographic and Clinical Characteristics during the Second Hospitalization

The distributions of patients that met the DSM criteria for bipolar disorders are shown in Table 1. Of the patients included in the final analysis, 73 patients (35.1%) were included in in the shorter time to hospitalization group and 135 patients (64.9%) were included in the longer time to hospitalization group.

Several significant differences between the groups, in terms of demographic characteristics and psychiatric histories, were identified including marital status, employment, total number of hospital admissions, and number of hospital admissions for a depressive episode. Although a trend towards significance was identified, such that patients in the shorter time to hospitalization group were more likely to be unmarried ($p=0.061$) compared to those in the longer time to hospitalization group, this difference was not statistically significant. Employment ($p=0.004$) significantly differed between the groups, such that patients in the shorter time to hospitalization group were significantly more likely to be unemployed than those in the longer time to hospitalization group. The groups also differed significantly in terms of number of hospital admissions due to mood episodes ($p=0.049$) and depressive episodes ($p=0.033$) and the shorter time to hospitalization group had more lifetime hospital admissions due to mood episodes (4.92 ± 3.70 vs. 3.97 ± 2.29, respectively; $p=0.049$) and depressive episodes (1.73 ± 2.56 vs. 1.03 ± 1.37, respectively; $p=0.033$) than those in the longer time to hospitalization group. No significant differences were found between the groups in terms of age, sex, familial affective loading, comorbidity, bipolar type, index episode polarity, first episode polarity, or number of mood episodes.

Medications during the Acute and Maintenance Phases

The medications used by the patients during the acute phase are summarized in Table 2. The shorter time to hospitalization group had a lower rate of lithium use than the longer time to hospitalization group (35.6% vs. 49.6%, respectively; $p=0.052$) but this difference was not statistically significant. Similarly, the shorter time to hospitalization group had a lower rate of using more than two different antipsychotics compared to the longer time to hospitalization group (35.6% vs. 49.6%, respectively; $p=0.052$) but this difference was also not statistically significant. The groups also significantly differed in terms of antidepressant use ($p=0.028$), especially that of SSRIs, with

Table 1. Demographic and clinical characteristics of the patients

Characteristic	Shorter time to hospitalization (n=73)	Longer time to hospitalization (n=135)	Significance
Age (yr)			
At admission	39.08±15.74	40.12±14.09	0.628
Onset	30.95±13.91	28.95±11.33	0.295
Sex (female)	40 (54.8)	82 (60.7)	0.406
Education (yr)	13.51±3.68	14.13±3.10	0.195
Marital status			0.061[†]
Unmarried	34 (46.6)	41 (30.4)	
Married	31 (42.5)	78 (57.8)	
Divorce, separation, widowed	8 (11.0)	16 (11.9)	
Employment			0.004*
Unemployed	38 (52.1)	40 (29.6)	
Employed	19 (26.0)	62 (45.9)	
Housewives or students	16 (21.9)	33 (24.4)	
Family history of psychiatric diseases	23 (31.5)	54 (40.0)	0.226
Mood disorders	19 (26.0)	41 (30.4)	0.509
Bipolar disorders	4 (5.5)	12 (8.9)	0.423
Comorbidity	9 (12.3)	23 (17.0)	0.369
Personality disorders	7 (9.6)	9 (6.7)	0.450
Others	3 (4.1)	14 (10.4)	0.116
Bipolar I	62 (84.9)	118 (87.4)	0.618
Index episode			0.403
Depressive	26 (35.6)	36 (26.7)	
Manic/hypomanic	44 (60.3)	93 (68.9)	
Mixed	3 (4.1)	6 (4.4)	
First episode			0.934
Depressive	24 (32.9)	42 (31.1)	
Manic/hypomanic	47 (64.4)	90 (66.7)	
Mixed	2 (2.7)	3 (2.2)	
No. of episodes	5.79±4.00	5.33±3.18	0.364
Depressive	2.15±2.77	1.72±1.93	0.189
Manic/hypomanic	3.49±3.19	3.50±2.92	0.994
Mixed	0.15±0.54	0.06±0.24	0.175
No. of hospital admission	4.92±3.70	3.97±2.29	0.049*
Depressive	1.73±2.56	1.03±1.37	0.033*
Manic/hypomanic	2.99±3.22	2.73±2.43	0.525
Mixed	0.12±0.44	0.07±0.26	0.383

Values are presented as mean±standard deviation or number (%).
*$p<0.05$, [†]$0.05 \leq p<0.10$.

Table 2. Medication during the acute phase

Variable	Shorter time to hospitalization (n=73)	Longer time to hospitalization (n=135)	Significance
Mood stabilizers	58 (79.5)	118 (87.4)	0.129
Lithium	26 (35.6)	67 (49.6)	0.052[†]
Valproate	26 (35.6)	52 (38.5)	0.680
Lamotrigine	12 (16.4)	23 (17.0)	0.912
Others	9 (12.3)	13 (9.6)	0.546
≥2 mood stabilizers	11 (15.1)	19 (14.1)	0.846
Antipsychotics	62 (84.9)	115 (85.2)	0.961
Olanzapine	8 (11.0)	22 (16.3)	0.296
Risperidone	8 (11.0)	22 (16.3)	0.296
Quetiapine	27 (37.0)	40 (29.6)	0.279
Aripiprazole	9 (12.3)	14 (10.4)	0.667
Others	17 (23.3)	24 (17.8)	0.340
≥2 antipsychotics	11 (15.1)	9 (6.7)	0.050[†]
Antidepressants	24 (32.9)	26 (19.3)	0.028*
SSRIs	19 (26.0)	17 (12.6)	0.015*
SNRIs	2 (2.7)	5 (3.7)	>0.999
NaSSAs	5 (6.8)	2 (1.5)	0.053[†]
Others	5 (6.8)	6 (4.4)	0.522
≥2 antidepressants	7 (9.6)	5 (3.7)	0.117
MS+AP+AD	11 (15.1)	11 (8.1)	0.121
MS+AP	41 (56.2)	90 (66.7)	0.134
MS+AD	5 (6.8)	7 (5.2)	0.757
AP+AD	2 (2.7)	5 (3.7)	>0.999
Monotherapy	13 (17.8)	17 (12.6)	0.307
MS	1 (1.4)	6 (4.4)	0.425
AP	7 (9.6)	8 (5.9)	0.330
AD	5 (6.8)	3 (2.2)	0.132

Values are presented as number (%).
SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; NaSSAs, noradrenergic and specific serotonergic antidepressants; MS, mood stabilizer; AP, antipsychotics; AD, antidepressants.
*$p<0.05$, [†]$0.05 \leq p<0.10$.

Table 2. There were no significant differences between the groups in terms of the percentage of patients receiving each type of prescription pattern.

The medications used by the patients during the maintenance phase are summarized in Table 3. The use of mood stabilizers did not significantly differ between the groups but the shorter time to hospitalization group had a lower rate of olanzapine use than the longer time to hospitalization group (8.2% vs. 17.0%, respectively; p=0.080); however, this difference was not statistically significant. The use of more than two different antipsychotics was significantly higher in the shorter time to hospitalization group than the longer time to hospitalization group (13.7% vs. 5.2%, respectively; p=0.032) and the frequency of SSRI prescriptions was higher in the shorter time to hospitalization group compared to the longer time to hospitalization group (28.8% vs. 16.3%, respectively; p=0.034). Additionally, SNRIs were prescribed less often to patients in the shorter time to hospitalization group compared to

higher rates in the shorter time to hospitalization group compared to the longer time to hospitalization group (26.0% vs. 12.6%, respectively; p=0.015). Although there was a trend towards patients in the shorter time to hospitalization group having a higher rate of NaSSA use compared to those in the longer time to hospitalization group (6.8% vs. 1.5%, respectively; p=0.053), this difference was not statistically significant. Additionally, there were no differences between the groups in terms of the percentage of patients receiving mood stabilizers, other than lithium and antipsychotics. The prescription patterns during the prior episode for the shorter time to hospitalization and longer time to hospitalization groups are also presented in

Table 3. Medication during the maintenance phase

Variable	Shorter time to hospitalization (n=73)	Longer time to hospitalization (n=135)	Significance
Mood stabilizers	56 (76.7)	109 (80.7)	0.494
Lithium	22 (30.1)	56 (41.5)	0.107
Valproate	26 (35.6)	56 (41.5)	0.409
Lamotrigine	11 (15.1)	31 (23.0)	0.176
Others	10 (13.7)	10 (7.4)	0.142
≥2 mood stabilizers	11 (15.1)	26 (19.3)	0.451
Antipsychotics	60 (82.2)	112 (83.0)	0.888
Olanzapine	6 (8.2)	23 (17.0)	0.080†
Risperidone	8 (11.0)	21 (15.6)	0.361
Quetiapine	28 (38.4)	38 (28.1)	0.131
Aripiprazole	9 (12.3)	13 (9.6)	0.546
Others	16 (21.9)	22 (16.3)	0.317
≥2 antipsychotics	10 (13.7)	7 (5.2)	0.032*
Antidepressants	29 (39.7)	43 (31.9)	0.255
SSRIs	21 (28.8)	22 (16.3)	0.034*
SNRIs	1 (1.4)	12 (8.9)	0.036*
NaSSAs	3 (4.1)	3 (2.2)	0.425
Others	9 (12.3)	15 (11.1)	0.793
≥2 antidepressants	5 (6.8)	10 (7.4)	0.882
MS+AP+AD	14 (19.2)	12 (8.9)	0.032*
MS+AP	36 (49.3)	60 (44.4)	0.501
MS+AD	6 (8.2)	18 (13.3)	0.271
AP+AD	3 (4.1)	6 (4.4)	>0.999
Monotherapy	13 (17.8)	35 (25.9)	0.185
MS	2 (2.7)	17 (12.6)	0.019*
AP	6 (8.2)	12 (8.9)	0.870
AD	5 (6.8)	6 (4.4)	0.522

Values are presented as number (%).
SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; NaSSAs, noradrenergic and specific serotonergic antidepressants; MS, mood stabilizer; AP, antipsychotics; AD, antidepressants.
*$p < 0.05$, †$0.05 \leq p < 0.10$.

the longer time to hospitalization group (1.4% vs. 8.9%, respectively; $p=0.036$). Table 3 also presents the prescription patterns during attendance at outpatient clinics prior to the second hospitalization for both times to hospitalization groups. The shorter time to hospitalization and longer time to hospitalization groups significantly differed in terms of the use of combination therapy with mood stabilizers, antipsychotics, and antidepressants (19.2% vs. 8.9%, respectively; $p=0.032$) and mood stabilizer monotherapy (2.7% vs. 12.6%, respectively; $p=0.019$).

Predictors of Short-term Hospitalization in Patients with Bipolar Disorder

The logistic regression analysis conducted in the present study included significant variables and revealed that there were several independent factors associated with the time to hospitalization for episodes of bipolar disorders. The final regression model that evaluated both groups is presented in Table 4. Patients in the shorter time to hospitalization group were less likely to be married (odds ratio [OR], 0.452; 95% confidence interval [CI], 0.216-0.947) or be employed (OR, 0.375; 95% CI, 0.176-0.801) compared to those in the longer time to hospitalization group. Additionally, patients in the shorter time to hospitalization group were more likely to have had a previous hospital admission for a mood episode (OR, 1.156; 95% CI, 1.024-1.306) and to have used antidepressants during the acute phase (OR, 2.961; 95% CI, 1.261-6.954) than those in the longer time to hospitalization group.

Patients in the shorter time to hospitalization group were also less likely to use olanzapine (OR, 0.305; 95%

Table 4. Final logistic regression model between the groups to determine predictors of a shorter time to hospitalization in patients with bipolar disorders

Variable	Significance	OR†	95% CI for OR
Marital status			
Unmarried vs. married	0.035*	0.452	0.216-0.947
Unemployment vs. Housewives or students	0.216	0.485	0.154-1.525
Employment			
Unemployment vs. Employed	0.011*	0.375	0.176-0.801
Unemployment vs. Divorce, separation, widowed	0.179	0.557	0.237-1.309
No. of hospital admissions	0.019*	1.156	1.024-1.306
Medication of acute phase			
Antidepressants	0.013*	2.961	1.261-6.954
NaSSAs	0.093†	7.800	0.711-85.611
Medication of maintenance phase			
Olanzapine	0.036*	0.305	0.100-0.926
SNRIs	0.028*	0.090	0.010-0.773
Prescription patterns of maintenance phase			
Mood stabilizer monotherapy	0.044*	0.185	0.036-0.958

OR, odds ratio; CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; NaSSAs, noradrenergic and specific serotonergic antidepressants.
*$p < 0.05$, †$0.05 \leq p < 0.10$.

CI, 0.100-0.926) or SNRIs (OR, 0.090; 95% CI, 0.010-0.773) as a maintenance treatment than were patients in the longer time to hospitalization group. In terms of prescription patterns during the maintenance phase, patients in the shorter time to hospitalization group were less likely to use a mood stabilizer monotherapy (OR, 0.185; 95% CI, 0.036-0.958) than patients in the longer time to hospitalization group. However, patients in the shorter time to hospitalization group were more likely to use combination therapy that included mood stabilizers (OR, 0.185; 95% CI, 0.036-0.958) than were patients in the longer time to hospitalization group.

DISCUSSION

The primary objective of the present study was to compare the effects of pharmacological treatments for bipolar disorder in real clinical practice during the acute and maintenance phases of the disease. Additionally, the demographic and clinical characteristics of the shorter time to hospitalization and longer time to hospitalization groups were compared. The present study found that 35.1% of patients experienced a re-hospitalization within 12 months and that 64.9% of patients had a time to hospitalization that was longer than 12 months; this finding is similar to those of previous studies.[3,9]

Patients in the shorter time to hospitalization group were more likely to be unmarried and/or unemployed than those in the longer time to recurrence group, which is consistent with the findings of Tohen *et al*.[9] who found that a lower premorbid occupational status was associated with a shorter time to relapse. There are three possibilities that may explain this result. First, patients in the shorter time to hospitalization group may have experienced more frequent hospitalization during their lifetime, which is important because individuals with frequent hospitalization have a lower functional status and a lower quality of life among all patients with bipolar disorders.[10] It has been suggested that patients who experience frequent hospitalizations are more likely to have incomplete remissions, and that this type of severe psychopathology is related to poorer functional outcomes.[11] Second, marriage and employment emerged as important predictors of short-term hospitalization, which indicates that a supportive social environment may be mediated by self-esteem.[12] The families and co-workers of bipolar patients can provide supportive and stable environments and this type of well-functioning social milieu may act as a non-pharmacological alternative treatment for patients.[13] Third, these

findings highlight the importance of social rehabilitation and/or education for the family of patients with bipolar disorders. Improvements in the social abilities of bipolar patients, including the adaptation of family and work environments, can prevent the frequent recurrence of symptoms in patients and lead to better long-term outcomes.[10] Therefore, treatments for bipolar patients should include a psychosocial approach that includes the patients as well as their families.

The present study also found that a greater number of hospital admissions due to mood episodes increased the risk of a shorter time to hospitalization by 1.156-fold. This result corresponds well with the findings of previous studies, which reported that the rate of relapse leading to a hospitalization increases commensurate with an increasing number of previous bipolar episodes.[14] A hospital admission for a mood episode typically indicates the occurrence of a severe mood episode. These types of severe cases, where attempts should be made to achieve complete remission of symptoms (including aggressively targeting residual mood symptoms), are associated with episodes of a longer duration and more severe psychopathology, and exhibit mixed features, which are all predictors of hospitalization.[11,15]

In terms of medication prescribed during the acute phase of a bipolar episode, antidepressant use appeared to increase the risk of a shorter time to hospitalization by 2.961-fold in the present study. There are two possible interpretations of this finding. First, antidepressant use in patients with bipolar disorders is associated with a poorer course of illness, an increased risk of a mood switch to a hypomanic, manic, or mixed state, and increased episode frequency or the induction of rapid cycling in bipolar patients.[16] Second, clinicians choose which antidepressant will be used despite the risk of switching, whether or not the index episode had a severe psychopathology, and whether or not there were residual depressive symptoms, even though a patient may have received the standard therapeutic regimen. Thus, it is important to consider that the use of antidepressants in the present study occurred during the acute phase of a bipolar episode rather than during the maintenance phase. These findings indicate that, although antidepressant use during the acute phase of a bipolar episode is a common treatment option for the short-term amelioration of symptoms, it may be a risk factor for a shorter time to hospitalization.

In terms of medication prescribed during the maintenance phase of bipolar disorder, the present study found that olanzapine use was related to a decreased risk of a

shorter time to hospitalization by 0.305-fold. The present findings are similar to those of previous studies, which found that olanzapine was more efficacious than a placebo for the prevention of manic and depressive relapses during the maintenance phase, and was non-inferior to lithium and valproate.[17,18]

Regarding prescription patterns during the maintenance phase, mood stabilizer monotherapy appears to be protective against a shorter time to hospitalization. Although a combination therapy of mood stabilizers and antipsychotics is preferred during the acute phase of a bipolar episode, many clinicians try to prescribe a monotherapy with only one of these drugs for safety and adherence purposes during bipolar maintenance. Pharmacological treatments during bipolar maintenance should prevent manic and depressive relapse, reduce residual symptoms, suicidal risk, cycling frequency, and mood instability, and improve functioning.[19,20] However, the independent use of a mood stabilizer or an antipsychotic as a treatment for bipolar disorder during the maintenance phase is currently debated in terms of their pharmacological effectiveness. Because many patients experience re-hospitalization under this prescription pattern, the use of a monotherapy may be advised if mood stability is maintained with a mood stabilizer alone. This may be because patients undergoing mood stabilizer monotherapy have less serious psychopathologies and a less severe course of illness compared to those who require combination therapy.

These findings are in contrast to those of Salvadore *et al.*[21] who showed that venlafaxine confers a higher risk for a treatment-emergent affective switch, often from depression to (hypo) mania compared to SSRIs or other second-generation antidepressants. In the present study, SNRIs were associated with a decreased risk of a shorter time to hospitalization by 0.090-fold, which is consistent with previous findings. For example, recent long-term hospitalization prevention studies with venlafaxine found very low hospitalization rates not only over the first year but, surprisingly, over the second year of maintenance as well.[22]

The present study had several limitations. First, this was a retrospective study and the possibility of reviewer bias needs to be considered. Additionally, this retrospective study did not assess residual mood symptoms or other clinical features. Second, this study included only inpatients who may have had more severe psychopathologies. Although the definition for time to hospitalization was stated very clearly to reduce reviewer bias, it is possible that mild-to-moderate cases, which may have pro-

vided more information about predictors of recurrence, were excluded from the study.

Taken together, the present findings indicate that the use of antidepressants during the acute phase of a bipolar episode may shorten the time to hospitalization. On the other hand, the uses of olanzapine and SNRIs during the maintenance phase, and a maintenance phase prescription pattern that includes mood stabilizer monotherapy, could act as protective factors against re-hospitalization. In terms of the associations between the duration of hospitalization and sociodemographic and clinical characteristics, being unmarried and/or unemployed could shorten the time to hospitalization. Additionally, in terms of the clinical factors, a greater number of past severe mood episodes that required hospital admission may shorten the time to hospitalization. However, clinical information on predictors of the frequent hospitalization of bipolar disorders remains insufficient with respect to illness severity and the long-term course. Thus, future research needs to be conducted to confirm the present findings.

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