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Regular Article

One-year rehospitalization rates of patients with first-episode bipolar mania receiving lithium or valproate and adjunctive atypical antipsychotics

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Aim: We compared the 1-year rehospitalization rates of first-episode bipolar manic patients who were discharged while being treated with lithium or valproate in combination with an atypical antipsychotic.

Methods: We investigated the rehospitalization status of first-episode bipolar manic patients who were discharged between 1 January 2003 and 31 December 2010 while they were taking lithium or valproate in combination with aripiprazole, olanzapine, quetiapine, or risperidone. Rehospitalization rates during a 1-year period after discharge were compared between the group receiving lithium plus an atypical antipsychotic and the group receiving valproate plus an atypical antipsychotic using the Kaplan–Meier method. A Cox regression model was used to analyze covariates hypothesized to affect time to rehospitalization.

Results: The rehospitalization rate was 17.3% during the 1-year follow-up period. We found significant differences in the rehospitalization rates of patients in the lithium (23.1%) and the valproate (13.3%) groups using the Kaplan–Meier formula. According to Cox proportional hazards regression analysis, higher Clinical Global Impression–Bipolar Version–Severity score at discharge ($P = 0.005$) and lithium treatment ($P = 0.055$) contributed to the risk of rehospitalization.

Conclusion: Treatment with valproate and an atypical antipsychotic can be more effective than treatment with lithium and an atypical antipsychotic in preventing rehospitalization during the 1 year after hospitalization due to a first manic episode in patients with bipolar I disorder. Higher Clinical Global Impression–Bipolar Version–Severity scores at discharge also negatively affected rehospitalization rates.

Key words: bipolar disorder, lithium, manic, readmission, valproate.

BIPOLAR DISORDER IS a highly prevalent lifelong neuropsychiatric syndrome characterized by recurrent mood episodes.[1] Up to 40% of patients who respond to initial treatment suffer relapses within the first year,[2] and most investigators agree that repeated episodes present a significant problem.[3]

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Hence, prevention of mood episodes through the maintenance phase of treatment is critical for improving the long-term outcomes of bipolar patients.

The majority of treatment guidelines include lithium in their recommendations for first-line maintenance therapy.[4–7] However, alternatives to lithium are clearly needed for the maintenance treatment of bipolar disorder. Undesirable side-effects, adverse reactions, a narrow therapeutic index, and the increased risk of toxicity with overdose can make lithium therapy less than ideal for many patients.[8] A search for adjunctive and alternative treatments revealed evidence that other medications have mood-stabilizing properties. Valproate has been used in the maintenance treatment of bipolar disorder for the past 5 decades. Based on the hypothesis that mania may result from the depletion of inhibitory neurotransmitters, such as GABA, it was postulated that the GABAergic effect of valproate may be therapeutic.[9] Valproate is increasingly prescribed for both acute episodes and maintenance.[10,11] Moreover, both valproate and lithium are recommended as first-line maintenance treatments following an episode of mania or hypomania.[12]

However, clinicians often wonder whether to select valproate or lithium to treat patients with bipolar disorder. A few previous studies found lithium and valproate to be similarly effective in the maintenance treatment of bipolar disorder.[13–15] However, other studies reported results favoring lithium[16] or valproate.[17] In the context of these mixed results on the relative strengths and weaknesses of lithium and valproate, combination therapy has become the standard of care for the treatment of bipolar disorder.[8] Yet, it is somewhat surprising that only a limited number of studies comparing the use of lithium and valproate in combination with atypical antipsychotics have been conducted. Hence, we performed this study to compare the 1-year rehospitalization rates associated with lithium and valproate when each was given along with an atypical antipsychotic to patients with bipolar I disorder who had been discharged after hospitalization due to an initial manic episode.

METHODS

Subjects

In this retrospective investigation, we reviewed the medical records of patients who were hospitalized in the psychiatric ward of six university hospitals and one psychiatric hospital in Korea from January 2003 to December 2010 due to an initial manic episode. The patients were at least 20 years of age and were clinically diagnosed according to DSM-IV criteria with bipolar I disorder at the index hospitalization. To examine the effects of specific medication regimens on rehospitalization rates, all patients included in this study had been discharged on lithium or valproate along with an adjunctive atypical antipsychotic (aripiprazole, olanzapine, risperidone, or quetiapine). All participants had at least 12 months of follow-up care and continued to receive the same combination regimen they were on at discharge. The following exclusion criteria were used: (i) pharmacological treatment for a psychiatric disorder before the index hospitalization; (ii) severe medical conditions; (iii) axis I or axis II psychiatric disorders other than bipolar I disorder; (iv) medication noncompliance for more than 1 month; and (v) admission for reasons other than a manic or hypomanic episode at index hospitalization, including social reasons or diagnostic purposes.

Outcome measures and predictors

This study compared two treatment groups (lithium plus an atypical antipsychotic versus valproate plus an atypical antipsychotic), and time to rehospitalization was regarded as the outcome measure. Demographic and clinical characteristics, including age, sex, psychotic features, prior depressive episodes, adjunctive atypical antipsychotic, duration of index hospitalization, and Global Assessment of Functioning (GAF) and Clinical Global Impression–Bipolar Version–Severity (CGI-BP-S)[18] scores at the index admission and discharge were also investigated.

Statistical analyses

Independent *t*-tests and χ^2-tests were performed to compare the demographic and clinical characteristics of the lithium and valproate groups. Kaplan–Meier survival analysis was used to determine time to rehospitalization due to any type of mood episode, due to a manic or a mixed episode, and due to a depressive episode within 1 year after discharge. A forward multivariate Cox proportional hazards regression model was employed to analyze the factors predictive of rehospitalization. Variables for which a significant

difference between lithium and valproate groups were observed were included in the proportional hazard analyses. When the Pearson's correlation coefficient between variables was 0.60 or higher, only the variable judged to be clinically more important was entered into the multivariate model. All statistical tests were two-tailed, and statistical significance was set at 0.05.

Ethics

The Institutional Review Board (IRB) reviewed and approved the protocol, and the study was conducted in accordance with good clinical practices and the Helsinki Declaration. Our IRB waived patient-specific informed consent for this confidential chart review and anonymous reporting of aggregate data.

RESULTS

Demographic and clinical characteristics

During the study period (January 2003–December 2010), a total of 485 patients were hospitalized for first-episode bipolar mania, and 76.1% of these patients ($n = 369$) were treated with an atypical antipsychotic and lithium or valproate. Of these, 115 patients were excluded by the selection criteria. A total of 254 patients diagnosed with bipolar I disorder were eligible for analysis (Table 1). One hundred eleven (44.1%) were male, and the participants' mean age was 36.4 ± 12.8 years. Lithium and an atypical antipsychotic were prescribed for 104 patients (40.9%), and valproate and an atypical antipsychotic were prescribed for 150 patients (59.1%).

Table 1. Clinical and demographic characteristics of the study sample

	Total ($n = 254$)	LIT+AAP ($n = 104$)	VAL+AAP ($n = 150$)	*P*-value
Age (years), mean (SD)	36.4 (12.8)	35.6 (12.4)	36.9 (13.1)	0.436
Male, *n* (%)	111 (43.7)	41 (39.4)	70 (46.7)	0.252
Years in education, mean (SD)	11.9 (3.5)	12.1 (3.2)	11.7 (3.7)	0.317
Psychotic features, *n* (%)	142 (55.9)	60 (57.7)	82 (54.7)	0.633
Presence of prior depressive episode, *n* (%)	148 (58.3)	57 (54.8)	91 (60.7)	0.352
Duration of index hospitalization (days), mean (SD)	39.1 (22.6)	38.4 (17.5)	39.6 (25.6)	0.639
GAF score, mean (SD)				
At index hospitalization	33.5 (7.6)	33.8 (7.2)	33.2 (7.8)	0.511
At discharge from index hospitalization	61.6 (8.7)	61.8 (8.3)	61.5 (9.0)	0.770
CGI-BP-S score, mean (SD)				
At index hospitalization	5.4 (0.7)	5.5 (0.6)	5.4 (0.8)	0.283
At discharge from index hospitalization	3.1 (0.7)	3.1 (0.7)	3.0 (0.7)	0.292
Combined atypical antipsychotics, *n* (%)				
Aripiprazole	31 (12.2)	9 (8.7)	22 (14.7)	0.311
Olanzapine	68 (26.8)	26 (25.0)	42 (28.0)	
Quetiapine	80 (31.5)	33 (31.7)	47 (31.3)	
Risperidone	75 (29.5)	36 (34.6)	39 (26.0)	
Mean daily dose on discharge (mg/day), mean (SD)				
Mood stabilizer		1063.1 (215.3)	959.8 (252.6)	
Aripiprazole	22.1 (7.0)	18.9 (7.4)	23.4 (6.6)	0.106
Olanzapine	17.4 (5.4)	16.4 (5.6)	18 (5.3)	0.260
Quetiapine	567.2 (239.7)	578.8 (247.8)	559 (236.1)	0.719
Risperidone	4.3 (1.7)	4.2 (1.9)	4.3 (1.6)	0.779
Haloperidol equivalent dose on discharge (mg/day), mean (SD)†	6.7 (2.6)	6.6 (2.8)	6.9 (2.5)	0.344

†Haloperidol equivalent doses were calculated with the formula by Andreasen *et al.*[19]
AAP, atypical antipsychotic; CGI-BP-S, Clinical Global Impression-Bipolar Version Severity; GAF, Global Assessment of Functioning; LIT, lithium; SD, standard deviation; VAL, valproate.

We found no significant differences between the lithium and valproate groups in age ($P = 0.436$), sex ($P = 0.252$), years of education ($P = 0.317$), or percentage of patients with histories of prior depressive episodes ($P = 0.352$). The lithium and valproate groups also did not differ with regard to GAF and CGI-BP-S scores at admission ($P = 0.511$ and $P = 0.283$, respectively) or at discharge ($P = 0.770$ and $P = 0.292$, respectively). The two treatment groups were comparable in terms of psychotic features ($P = 0.633$), duration of index hospitalization ($P = 0.639$), proportion of atypical antipsychotics adjunctively used, and mean daily lithium, valproate, atypical antipsychotic, and haloperidol-equivalent doses (Table 1).

Factors related to rehospitalization

Of the 254 patients, 44 (17.3%) were rehospitalized within 1 year after discharge from the index hospitalization due to a mood episode. Patients who were rehospitalized differed significantly from those who were not in their GAF and CGI-BP-S scores at discharge. The mean discharge GAF score (57.6 ± 6.7) of the rehospitalized group was lower than that of the group that was not rehospitalized (62.4 ± 8.8, $P < 0.001$), and the mean discharge CGI-BP-S score of the rehospitalized group (3.4 ± 0.7) was higher than that of the group that was not rehospitalized (3.0 ± 0.7, $P = 0.001$). The rehospitalized group contained a larger proportion of patients with a prior depressive episode (70.5%, $n = 31$) than the group that was not rehospitalized (55.7%, $n = 117$), but this difference was not statistically significant ($P = 0.071$). Neither the adjunctive atypical antipsychotic used ($\chi^2 = 3.625$, d.f. = 3, $P = 0.305$) nor the hospital at which the study was conducted ($\chi^2 = 11.057$, d.f. = 6, $P = 0.070$) had a significant effect on the rehospitalization rate. The groups did not differ significantly with regard to the mean daily dose of mood stabilizers ($P = 0.884$ for lithium; $P = 0.396$ for valproate) or the haloperidol-equivalent dose ($P = 0.179$). With the exception of the mood stabilizer prescribed, the groups did not differ significantly with respect to demographic and clinical characteristics.

Time to rehospitalization

Rehospitalization rates within 1 year were significantly higher in the lithium (23.1%, $n = 24$) than in the valproate group (13.3%, $n = 20$; $P = 0.044$). The rehospitalization rates due to a manic or mixed episode differed significantly between the groups: 11.5% ($n = 12$) of the lithium group and 5.3% ($n = 8$) of the valproate group ($P = 0.041$) were rehospitalized for this reason. Rehospitalization rates due to a depressive episode did not significantly differ ($P = 0.482$) between the lithium (10.6%, $n = 11$) and valproate (8.0%, $n = 12$) groups. Figure 1 shows time to rehospitalization in the two treatment groups. The mean time to rehospitalization due to any kind of mood episode was significantly shorter (log–rank = 4.7, d.f. = 1, $P = 0.031$) in the lithium (310.0 ± 10.6 days) than in the valproate (340.0 ± 5.9 days) group. At the time of rehospitalization, the mean daily haloperidol-equivalent dose of atypical antipsychotics of the valproate group (6.3 ± 2.9 mg/day) was not significantly different from the dose of the lithium group (6.1 ± 3.0 mg/day, $P = 0.574$). The mean time to rehospitalization due to a manic or mixed episode was also significantly shorter (log–rank = 4.6, d.f. = 1, $P = 0.032$) in the lithium (331.7 ± 9.0 days) than in the valproate (354.1 ± 4.1 days) group. The mean time to rehospitalization due to a depressive episode did not differ significantly

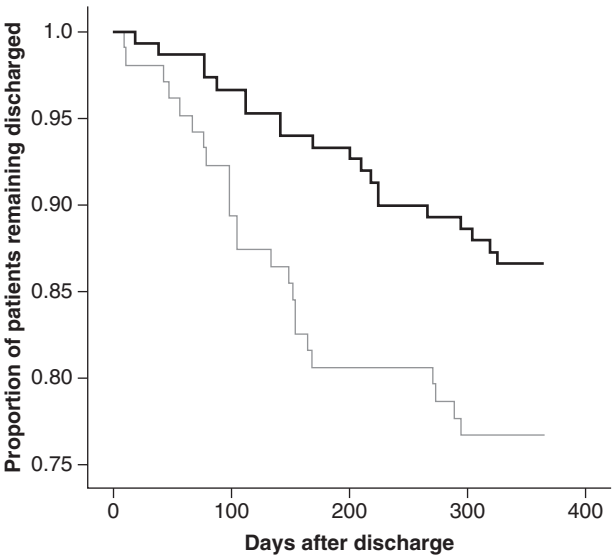

Figure 1. Time to rehospitalization in the lithium and valproate groups. The mean time to rehospitalization due to any kind of mood episode was significantly shorter (log–rank = 4.7, d.f. = 1, $P = 0.031$) in the lithium (310.0 ± 10.6 days) than in the valproate (340.0 ± 5.9 days) group. ———, Lithium + an atypical antipsychotic; ———, Valproate + an atypical antipsychotic.

Table 2. Predictive variables of rehospitalization

Dependent variables	Predictive variables	β	χ^2	Hazards ratio	*P*-value
Rehospitalization due to any mood episode	CGI-BP-S at discharge from index hospitalization	0.654	7.755	1.923	0.005**
	Absence of prior depressive episode	−0.493	2.161	0.611	0.142
	Haloperidol equivalent dose of atypical antipsychotics on discharge	−0.041	0.607	0.960	0.436
	Lithium + an atypical antipsychotic	0.585	3.696	1.796	0.055
Rehospitalization due to manic or mixed episode	CGI-BP-S at discharge from index hospitalization	0.852	5.664	2.343	0.017**
	Absence of prior depressive episode	−0.494	1.012	0.610	0.315
	Haloperidol equivalent dose of atypical antipsychotics on discharge	−0.050	0.438	0.951	0.508
	Lithium + an atypical antipsychotic	0.844	3.492	2.326	0.062
Rehospitalization due to depressive episode	CGI-BP-S at discharge from index hospitalization	0.490	2.451	1.632	0.117
	Absence of prior depressive episode	−0.486	1.120	0.615	0.290
	Haloperidol equivalent dose of atypical antipsychotics on discharge	−0.033	0.204	0.968	0.651
	Lithium + an atypical antipsychotic	0.354	0.712	1.425	0.399

*$P < 0.05$, **$P < 0.01$.
CGI-BP-S, Clinical Global Impression-Bipolar Version Severity; GAF, Global Assessment of Functioning.

(log–rank = 0.875, d.f. = 1, $P = 0.350$) between the lithium (340.6 ± 7.4 days) and valproate (350.4 ± 4.6 days) groups.

Forward Cox proportional hazards regression analysis was used to clarify the relations between differences in discharge CGI-BP-S scores, history of depressive episodes and the mean daily haloperidol-equivalent dose of atypical antipsychotics. Patients with lower discharge CGI-BP-S scores were more likely to be rehospitalized due to any kind of mood episode ($P = 0.005$) or a manic or mixed episode ($P = 0.017$, Table 2). The Cox regression showed that patients who received lithium were more likely to be rehospitalized due to any kind of mood episode ($P = 0.055$) or a manic or mixed episode ($P = 0.062$) than patients in the valproate group, but the effect of lithium treatment was not statistically significant. Rehospitalization due to a depressive episode was not associated with discharge CGI-BP-S score ($P = 0.117$), history of depressive episodes ($P = 0.290$), mean haloperidol-equivalent dose of atypical antipsychotics ($P = 0.651$) or mood stabilizer used ($P = 0.384$).

DISCUSSION

To our knowledge, this is one of the first studies comparing the rehospitalization rates for lithium or valproate given in combination with an atypical antipsychotic to bipolar I patients with first-episode mania. We found that the time before rehospitalization for any mood episode was significantly longer in patients receiving valproate plus an atypical antipsychotic than in those receiving lithium plus an atypical antipsychotic. A trend toward a significant difference between the groups was also seen with respect to rates of rehospitalization due to manic or mixed episodes. Additionally, we found that patients with bipolar I disorder who were hospitalized due to a first manic episode and who received valproate plus an atypical antipsychotic had lower 1-year rehospitalization rates for any kind of mood episode than did those who received lithium plus an atypical antipsychotic, but the difference did not reach a statistically significant level.

The results of the present study are consistent with those of previous studies in which valproate was favored over lithium for relapse prevention in bipolar patients. Lambert and Venaud conducted a comparative study of valproate versus lithium for the prophylaxis of bipolar disorders.[20] This 18-month open, randomized study reported 0.51 episodes per subject in the valproate group and 0.61 episodes per subject in the lithium group; although this difference was not statistically significant, these figures reflect a 20%

lower rate of new episodes among valproate-treated than among lithium-treated patients. Bowden *et al*.[17] conducted the first double-blind, randomized, controlled maintenance study in bipolar I disorder, which involved following patients from an index manic episode through a subsequent 52-week maintenance phase. The mean durations of survival in maintenance treatment were 198 days for the divalproex group and 152 days for the lithium group, reflecting a significant difference between the divalproex- and lithium-treated groups in favor of divalproex.

A few previous studies have compared the effectiveness of lithium and valproate monotherapy for preventing relapses of bipolar disorder. Findling *et al*.[14] reported that lithium and divalproex treatment groups did not differ in the time to symptoms of relapse or to discontinuation for any reason. Another 20-month, double-blind study comparing lithium and divalproex monotherapy[15] reported no significant differences in the time to relapse due to any kind of episode, the time to relapse due to a depressive episode, or the time to relapse due to a hypomanic/manic/mixed episode. However, these studies included pediatric bipolar patients[14] or rapid-cycling bipolar patients,[15] and methodological differences make it hard to compare the effectiveness of pharmacological treatments. Moreover, lithium monotherapy was more likely to prevent relapse than was valproate monotherapy according to a recent randomized, open-label trial.[16] However, as the trial was primarily designed to compare lithium and valproate combination therapy with lithium or valproate monotherapy, conclusions about the comparative efficacy of the two agents should be made cautiously.[16]

It is has been established that several clinical features are related to increased risk of relapse. Factors associated with shorter survival times include increased number of previous episodes, decreased interval between episodes, and persistence of affective symptoms.[21] The results from the present study showing higher discharge CGI-BP-S scores associated with a higher risk of rehospitalization also confirm previous reports that residual affective symptoms are associated with outcomes.[21]

Several possible weaknesses in our study design should be considered. The main limitations were the retrospective design and small sample. Moreover, we included only patients with at least 12 months of follow-up care who continued to receive the same combination regimen as was given at discharge. Hence, the results are most applicable to patients who can tolerate treatment with lithium or valproate in combination with an atypical antipsychotic and who are largely adherent to this regimen. Medication adherence is a well-known predictor of relapse in bipolar patients.[21] The rehospitalization rates reported in this study may be underestimates, as we excluded patients who did not receive follow-up care for 12 months. Moreover, we did not use objective adherence monitoring and could not exclude the possibility that adherence issues substantially affected relapse or rehospitalization rates. Another concern was that clinical variables that can affect rehospitalization rates, such as number of previous depressive episodes, age at onset, and number of previous psychiatric hospitalizations, were not considered. Additionally, we did not examine plasma concentrations of lithium and valproate. Hence, the lithium and valproate plasma concentrations of some patients may have been suboptimal during the follow-up period. All researchers participating in this study were members of the Committee for a Korean Medication Algorithm for Bipolar Disorder.[22] The Korean medication algorithm for bipolar disorder recommends lithium or valproate in combination with an atypical antipsychotic as the first-line strategy for acute mania. This may have affected clinical practice and contributed to the relatively even distribution of clinical variables and treatment preferences observed in the study data. Finally, we did not distinguish rehospitalizations due to the failure of acute treatment from those due to the failure of maintenance treatment. Some proportion of rehospitalized patients were experiencing a failure of acute treatment rather that a failure of maintenance treatment. However, the efficacy of lithium is comparable to that of valproate for the treatment of acute mania,[23] but about 34% more patients relapse due to any kind of mood episode while receiving lithium than while receiving valproate.[24] The results of the present study showing that valproate reduced the risk of rehospitalization are consistent with the results of a previous maintenance study.

Despite these limitations, our results indicate that treatment with valproate and an atypical antipsychotic may be more effective than treatment with lithium and an atypical antipsychotic to prolong the time to rehospitalization due to any kind of mood episode among patients with bipolar disorder I who have previously been hospitalized with their first

episode of mania. Long-term, double-blind, randomized, controlled trials are needed to elucidate the effectiveness of combination therapy with lithium or valproate and atypical antipsychotics in terms of relapse prevention.

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No conflicts of interest are declared.

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