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# Characteristics and prognosis of patients with bipolar disorder who had been treated for depression: a pilot study

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Abstract

In this study, we aimed to clarify the outcome a change of treatment due to diagnosis change to bipolar disorder (BD) in patients who had been treated for major depressive disorder (MDD). A mirror image study was conducted in 66 BD patients who had been treated for MDD for more than one year. Setting the date of changing diagnosis as a mirror date, the number of mood episodes observed within 12 months before and after the mirror date, history of hospitalization, and history of suicide attempt were compared in these patients. The subjects were divided into the improved group (n=36) and non-improved group (n=30), and intergroup comparisons were made on patients' attributes, items associated with mood disorders, and drugs prescribed for 6 and 12 months before and after the mirror date. The number of mood episodes after changing the diagnosis to BD as well as the percentage of patients with a history of suicide attempt decreased significantly. According to the results of a multivariate analysis, family history of psychiatric disorders was a related factor in the improved group. It is important to identify BD patients who have been treated for MDD and to adequately treat them.

**Key words :** *bipolar disorder, duration of untreated bipolar disorder, major depressive disorder, mirror image study, misdiagnosis*

## I. Introduction

According to the mental health survey, lifetime prevalence of bipolar disorder (BD) is 0.6% for bipolar type I disorder (BD-I) and 0.4% for bipolar type II disorder (BD-II) [1)]. In BD, depressive episodes account for the majority of mood episodes. Patients often visit a clinic for the first time in a depressive state and receive treatments for Major Depressive Disorder (MDD).

Xiang et al. conducted Mini-International Neuropsychiatric Interview (M.I.N.I.) with MDD patients and revealed that 20.8% of them were BD. It is difficult to make an early diagnosis of BD[2)]; it takes 3 - 10 years for a

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patient to be diagnosed with BD[3, 4].

It is important to make an appropriate diagnosis for a BD patient who has already been diagnosed with MDD. Investigations have been carried out into patient factors that suggest the presence of BD in order to make an early diagnosis. It has been reported that the following factors may be associated with BD: history of multiple mood episodes, suicide attempt, childhood trauma and hypomanic/manic switch induced by antidepressants, family history of BD and suicide attempt, early age at onset, cyclothymic temperament, current mixed state and concomitant substance abuse1 [5-8].

According to the major treatment guidelines for mood disorder, the first line drug for MDD is antidepressant, while use of mood stabilizer or antipsychotic drug is recommended for depressive episodes of BD. This indicates that BD patients who have been diagnosed with MDD and treated for this disease will not receive appropriate treatment until the diagnosis is changed. It has been reported that delay in starting treatment for BD would result in prolongation of duration of mood episodes, increased number of depressive episodes, increased number of hospitalizations, and increased incidence of suicide attempt [9, 10]. Thus, it is well known that prognosis of patients who receive delayed treatment for BD is poor. However, there are hardly any reports investigating whether or not prognosis improves in BD patients whose treatment has been changed from one for MDD to another for BD. In this study, we reveal the outcome associated with the treatment change due to the diagnostic change to BD.

## II. Patients and methods

The study included 248 patients who visited the outpatient psychiatric clinics of three institutions which have psychiatric wards and handle emergency outpatients, and who were diagnosed with BD-I or BD-II according to the Diagnostic and Statistical Manual of Mental Disorders-IV-TR( DSM-IV-TR) during the period between June, 2018 and November, 2018. According to a retrospective investigation based on the patients' medical charts, it was found that for 175 patients, diagnosis other than BD had been changed to BD during the treatment. There were no patients with cyclothymic disorder or those with BD not otherwise specified (BD-NOS) in this patient group. A total of 78 patients, including those who could not be followed as their charts had been discarded or those whose diagnosis was changed within one year after the first mood episode were excluded from the study. Out of 97 patients who could be followed baced on their medical charts, 31 who previously had been diagnosed with dysthymic disorder (n = 8), schizophrenia (n = 5), anxiety disorder (n = 10), somatoform disorder (n = 1), dissociative disorder (n = 1), or personality disorder (n = 6) were excluded so that only patients who had been treated with MDD would be left. Finally, 66 patients were included in the analysis set.

### 1. Demographic and clinical characteristics of subjects

Patients' clinical information was investigated retrospectively based on medical charts. The medical charts were structured and used the same sheet of clinical information each patient's visit in multi-sites. The survey items included patients' information such as sex,

family history of psychiatric disorders, and age at the first visit to the psychiatric clinic. The items associated with mood episodes included the age when diagnosis was changed to BD, age at onset of the first mood episode, subtypes of BD (BD-I or BD-II), duration of undiagnosed bipolar disorder (DUBD) and symptomatic states when diagnosis was changed (depressive, hypomanic/manic, mixed, euthymic state). Finally, for drug therapies, the following items were investigated for 6 months and 12 months before and after the mirror date: prescription and dosage of antidepressants, lithium, antiepileptic drugs (AEDs) and antipsychotic drugs (APs). The dosage of antidepressants or APs was assessed using imipramine (IMP) or chlorpromazine (CP) converted value, respectively[11].

**2. Outcome**

A mirror image study was conducted to compare outcomes obtained for the same amount of time before and after changing the treatment[12]. Although a mirror image study can be affected by expectation bias or natural course of the disease, this method was used in this study in order to evaluate conditions which reflect actual clinical settings. Hence, by defining a mirror date as the day when diagnosis was changed from MDD to BD, clinical information including the number of episodes, history of hospitalization, and history of suicide attempt during 12 months before and after the mirror date were investigated for each patient. The mirror date was confirmed by each of the attending physicians based on the medical charts.

In this study, the primary outcome was the number of mood episodes during 12 months before and after the mirror date, and the secondary outcomes were the hospitalization rate and suicide attempt rate during 12 months before and after the mirror date. Self-harm was also included in the history of suicide attempt. The mood episodes were evaluated by two evaluators (E.H. and K.F.) based on descriptions of medical charts according to DSM-IV-TR. Evaluations were considered valid only when both evaluators agreed.

**3. Statistical analysis**

The Wilcoxon signed-rank test was used for comparisons of the primary outcome, the number of mood episodes within 12 months before and after the mirror date, and for comparisons of dosage of lithium as well as dosage of antidepressants and APs (equivalent conversion) at 6 months or 12 months before and after. For the secondary outcomes, history of hospitalization and history of suicide attempt within 12 months before and after the mirror date as well as prescription of each drug and antidepressant monotherapy at 6 months or 12 months before and after, comparisons were made using the McNemar's test. Upon analysis, history of hospitalization, history of suicide attempt, and prescription of each drug were classified as follows: (1) For history of hospitalization, the patients were categorized into two groups, "hospitalized at least once" and "none", and (2) for history of suicide attempt and prescription of each drug, the patients were categorized into the two groups "present" and "absent".

Secondly, in order to evaluate factors associated with decreased mood episodes, patients were categorized into the improved group (patients whose the number of mood episodes decreased after the diagnostic

change, or those with no episodes eithers before or after the diagnostic change; n = 36) or the non-improved group (patients with increased number of mood episodes after the diagnostic change or those with no change in the number of mood episodes before and after the diagnostic change; n = 30), based on the number of mood episodes within 12 months before and after the mirror date: comparisons were then made between the two groups for the patients backgrounds and drug therapy before and after changing the diagnosis. If dependent variables were measured on the nominal scale, the $\chi^2$ test [sex, family history of psychiatric disorders, BD subtypes, prescription of antidepressants (6 months after, 12 month before and after), antidepressant monotherapy (6 and 12 months before), prescription of lithium (6 and 12 months after), prescription of AEDs (6 and 12 months before and after), prescription of APs (6 and 12 months before and after)] was used. And the Fisher's exact test [status when the diagnosis changed, suicide attempt 12 months before the mirror date, prescription of antidepressants (6 months before), prescription of antidepressant monotherapy (6 and 12 months after), prescription of lithium (6 and 12 months before)] was used.

Lastly, in order to investigate the primary outcome, namely, the factors associated with decreased number of mood episodes, logistic regression analysis (forced entry) was performed using two groups, the improved group and non-improved group (“improved group = 1”, “non-improved group = 0”) as dependent variables, as well as age when diagnosis was changed, age at onset of the first mood episode, DUBD, BD subtypes, family history, and use of antidepressants 6 and 12 months after the diagnostic change as covariates. For statistical analysis, SPSS 22.0 J for Windows (IBM®) was used. The significance level was set to 5% in all analyses, and p-values were obtained in numbers.

**4. Ethical considerations**

This study was reviewed and approved by the Ethics Committee of Iwate Medical University School of Medicine (No.MH2018-013) and ethics committees of each institution and conducted following Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research in Japan. It was guaranteed that patients could have an opportunity to refuse participation in the study. This was stated in the information disclosure document regarding this study.

## III. Results

**1. Study sample**

A total of 66 BD patients who had been treated for MDD were included in the study. The clinical information is presented in Table 1. Out of all subjects, BD-I 28.8% and BD-II 71.2%, and 33.0% had a family history of psychiatric disorders. After the onset of the first mood episode, it took 61.0 months (33.8 - 124.0) until they received the diagnosis of BD.

**2. Drug therapy after diagnostic change** (Table 2)

By setting the date of diagnostic change as a mirror date, the rate of antidepressant prescription and its dose had significantly decreased after diagnostic change at both 6 months and 12 months. The majority of patients who received antidepressants after the diagnostic change had been diagnosed with BD-II (6 months BD-I: n = 6, 17.1%, BD-II: n =

Table 1. Demographic and clinical characteristics of subjects

| | N or median | % or range |
|---|---|---|
| Sex (Male) (%) | 30 | 45.5 |
| Family history (%) | 22 | 22 |
| Age at first mood episode (years) | 46.0 | 32.0-54.0 |
| Age at first visit to psychiatric clinic (years) | 46.5 | 33.0-54.0 |
| Age at diagnostic change (years) | 53.5 | 42.8-60.0 |
| DUBD (months) | 61.0 | 33.8-124.0 |
| Bipolar disorder subtypes (%) | | |
| BD-I | 19 | 28.8 |
| BD-II | 47 | 71.2 |
| Status at diagnostic change (%) | | |
| Depressive state | 14 | 21.2 |
| Hypomanic/Manic state | 37 | 56.1 |
| Mixed state | 8 | 12.1 |
| Euthymic state | 7 | 10.6 |

BD-I, Bipolar disorder type I; BD-II, Bipolar disorder type II; DUBD, Duration of undiagnosed bipolar disorder.

Table 2. Drug Treatments for 6 months and 12 months before and after the mirror date

| | 6 months | | | | | 12 months | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before | | After | | | Before | | After | | |
| | N or median | % or range | N or median | N or median | p-value | N or median | % or range | N or median | N or median | p-value |
| Antidepressants (%) | 57 | 86.4 | 35 | 53.0 | <0.001 | 53 | 80.3 | 34 | 51.5 | 0.001 |
| IMP equivalents (mg) | 128.2 | 50.0-200.0 | 12.5 | 0.0-100.0 | <0.001 | 106.3 | 37.5-178.1 | 12.5 | 0.0-75.0 | <0.001 |
| Monotherapy (%) | 33 | 50.0 | 6 | 9.1 | <0.001 | 34 | 51.5 | 4 | 6.1 | <0.001 |
| Lithium (%) | 2 | 3.0 | 10 | 15.2 | 0.021 | 1 | 1.5 | 12 | 18.2 | 0.003 |
| Dose range (mg) | 0.0 | 0.0-0.0 | 0.0 | 0.0-0.0 | 0.009 | 0.0 | 0.0-0.0 | 0.0 | 0.0-0.0 | 0.002 |
| AEDs (%) | 17 | 25.8 | 53 | 80.3 | <0.001 | 15 | 22.7 | 51 | 77.3 | <0.001 |
| APs (%) | 14 | 21.2 | 28 | 42.4 | 0.003 | 14 | 21.2 | 28 | 42.4 | 0.004 |
| CP equivalents (mg) | 0.0 | 0.0-0.0 | 0.0 | 0.0-162.5 | 0.002 | 0.0 | 0.0-0.0 | 0.0 | 0.0-200.0 | 0.002 |

AEDs, antiepileptics drugs; APs, antipsychotic drugs; CP, chlorpromazine; IMP, imipramine.

29, 82.9%; 12 months: BD-I: n = 10, 29.4%, BD-II: n = 24, 70.6%). Meanwhile, the percentage of patients who received lithium and its dose, as well as the percentage of patients who received AEDs, significantly increased at 6 months and 12 months. Similarly, the percentage of patients treated with APs and the dose significantly also increased at both months.

### 3. Treatment outcomes for BD patients who had been treated for MDD (Table 3)

After changing the treatment from MDD to BD in BD patients, the primary outcome, the number of mood episodes, significantly decreased [1.00 times (0.75 - 1.25) vs 1.00 times (0.00 - 1.00), p = 0.011)]. The percentage of patients with the secondary outcome, history of suicide attempt, also significantly

Table 3. Patient outcomes in 12 months before and after the mirror date

| | BD diagnosis | | | | |
|---|---|---|---|---|---|
| | Before | | After | | |
| | N or median | % or range | N or median | % or range | p-value |
| Number of mood episodes | 1.00 | 0.75-1.25 | 1.00 | 0.00-1.00 | 0.011 |
| Hospitalized for a mood episode (%) | 11 | 16.7 | 8 | 12.1 | 0.581 |
| Attempted suicide (%) | 8 | 12.1 | 1 | 1.5 | 0.016 |

Table 4. Patient attributes and clinical information in the improved group and non-improved group

| | BD diagnosis | | | | |
|---|---|---|---|---|---|
| | Before | | After | | |
| | N or median | % or range | N or median | % or range | p-value |
| Sex (male) (%) | 16 | 44.4 | 14 | 46.7 | 1.00 |
| Family history (%) | 17 | 51.5 | 5 | 21.7 | 0.03 |
| Age at first mood episode (years) | 47.5 | 37.3-55.5 | 44.0 | 29.8-51.5 | 0.17 |
| Age at first visit to psychiatric clinic (years) | 49.0 | 38.3-56.3 | 45.0 | 31.5-52.5 | 0.14 |
| Age at diagnostic change (years) | 54.5 | 45.3-60.0 | 51.0 | 36.5-60.0 | 0.27 |
| DUBD (months) | 64.0 | 22.5-105.8 | 42.0 | 26.8-149.8 | 0.84 |
| History of suicide attempt during 12 months before diagnostic change (%) | 4 | 11.1 | 4 | 13.3 | 1.00 |
| History of Hospitalization during 12 months before diagnostic change (%) | 5 | 13.9 | 6 | 20.0 | 0.51 |
| Bipolar disorder subtypes (%) | | | | | |
| BD-I | 9 | 25.0 | 10 | 33.3 | 0.59 |
| BD-II | 27 | 75.0 | 20 | 66.7 | |
| Status at diagnostic change (%) | | | | | |
| Depressive state | 6 | 16.7 | 8 | 26.7 | |
| Hypomanic/Manic state | 19 | 52.8 | 18 | 60.0 | 0.30 |
| Mixed state | 5 | 13.9 | 3 | 10.0 | |
| Euthymic state | 6 | 16.7 | 1 | 3.3 | |

BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; DUBD, duration of undiagnosed bipolar disorder.

decreased (12.1% vs 1.5%, p = 0.016). There was no significant difference in terms of the percentage of patients with history of hospitalization (16.7% vs 12.1%, p = 0.581).

**4. Intergroup comparisons between the improved group and non-improved group**

According to the comparisons made between the two groups on the patients' backgrounds (Table 4), the percentage of patients with a family history of psychiatric disorders was significantly higher (51.5% vs 21.7%, p = 0.030). No difference was observed in the age at onset of the first mood episode [47.5 years (37.3 - 55.5) vs 44.0 years (29.8 - 51.5), p = 0.17], DUBD [64.0 months (22.5 - 105.8) vs 42.0 months (26.8 - 149.8), p = 0.84], and the percentage of patients with a history of suicide attempt during the 12 months before changing the diagnosis (11.1% vs 13.3%, p =

Table 5. Comparisons of drug therapies before and after diagnostic change

| | Drug therapy before diagnostic change | | | | | Drug therapy after diagnostic change | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 6 months before | | | | | 6 months after | | | | |
| | Improved group (n = 36) | | Non-improved group (n = 30) | | | Improved group (n = 36) | | Non-improved group (n = 30) | | |
| | N or median | % or range | N or median | % or range | p-value | N or median | % or range | N or median | % or range | p-value |
| Antidepressants (%) | 25 | 89.3 | 25 | 83.3 | 0.72 | 17 | 47.2 | 18 | 60.0 | 0.29 |
| IMP equivalents (mg) | 106.3 | 50.0-196.9 | 141.3 | 37.5-218.8 | 0.84 | 0.0 | 0.0-37.5 | 50.0 | 0.0-112.5 | 0.17 |
| Monotherapy (%) | 18 | 50.0 | 15 | 50.0 | 1.00 | 3 | 8.3 | 3 | 10.0 | 1.00 |
| Lithium (%) | 2 | 7.1 | 0 | 0.0 | 0.50 | 5 | 13.9 | 5 | 16.7 | 1.00 |
| Dose range (mg) | 0.0 | 0.0-0.0 | 0.0 | 0.0-0.0 | 0.19 | 0.0 | 0.0-0.0 | 0.0 | 0.0-0.0 | 0.85 |
| AEDs (%) | 10 | 35.7 | 6 | 20.0 | 0.40 | 29 | 80.6 | 24 | 80.0 | 0.47 |
| APs (%) | 9 | 32.1 | 5 | 16.7 | 0.55 | 17 | 47.2 | 11 | 36.7 | 0.46 |
| CP equivalents (mg) | 0.0 | 0.0-3.8 | 0.0 | 0.0-0.0 | 0.48 | 0.0 | 0.0-200.0 | 0.0 | 0.0-150.0 | 0.42 |
| | 12 months before | | | | | 12 months after | | | | |
| | Improved group (n = 36) | | Non-improved group (n = 30) | | | Improved group (n = 36) | | Non-improved group (n = 30) | | |
| | N or median | % or range | N or median | % or range | p-value | N or median | % or range | N or median | % or range | p-value |
| Antidepressants (%) | 21 | 75.0 | 26 | 86.7 | 0.35 | 17 | 47.2 | 17 | 56.7 | 0.47 |
| IMP equivalents (mg) | 81.3 | 9.4-159.4 | 137.5 | 56.3-190.6 | 0.28 | 0.0 | 0.0-75.0 | 18.8 | 0.0-112.5 | 0.37 |
| Monotherapy (%) | 17 | 47.2 | 17 | 56.7 | 0.45 | 2 | 5.6 | 2 | 6.7 | 1.00 |
| Lithium (%) | 1 | 3.6 | 0 | 0.0 | 1.00 | 4 | 11.1 | 8 | 26.7 | 0.12 |
| Dose range (mg) | 0.0 | 0.0-0.0 | 0.0 | 0.0-0.0 | 0.36 | 0.0 | 0.0-0.0 | 0.0 | 0.0-400.0 | 0.12 |
| AEDs (%) | 8 | 28.6 | 6 | 20.0 | 0.77 | 27 | 75.0 | 24 | 80.0 | 0.73 |
| APs (%) | 9 | 32.1 | 5 | 16.7 | 0.55 | 17 | 47.2 | 11 | 36.7 | 0.46 |
| CP equivalents (mg) | 0.0 | 0.0-11.25 | 0.0 | 0.0-0.0 | 0.44 | 2.5 | 0.0-200.0 | 0.0 | 0.0-163.6 | 0.70 |

AEDs, antiepileptics drugs; APs, antipsychotics drugs; CP, chlorpromazine; IMP, imipramine.

Table 6. Factors related in the improved group

| | B | p-value | OR | 95% CI |
|---|---|---|---|---|
| Age at diagnostic change (years) | −0.24 | 0.59 | 0.79 | 0.33− 1.88 |
| Age at first mood episode (years) | 0.26 | 0.55 | 1.30 | 0.55−3.08 |
| DUBD (months) | 0.021 | 0.56 | 1.02 | 0.95−1.10 |
| BD-I (BD-II) | −0.33 | 0.67 | 0.72 | 0.16−3.25 |
| Family history of psychiatric disorder (absent) | 1.38 | 0.03 | 3.96 | 1.14−13.74 |
| Antidepressant prescription during 12 months after diagnostic change (absent) | 0.058 | 0.95 | 1.06 | 0.21−5.40 |
| Antidepressant prescription during 6 months after diagnostic change (absent) | −0.57 | 0.55 | 0.57 | 0.090−3.62 |

B= the coefficient for constant in the model
The parentheses are reference categories.
BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; DUBD, duration of undiagnosed bipolar disorder; OR, odds ratio; CI, confidence interval.

1.00). As for drug therapy after the diagnostic change, there was no statistically significant difference was observed (Table 5).

According to the results of the logistic regression analysis, family history of psychiatric disorders [OR = 3.96 (95% CI: 1.14 - 13.74), p = 0.030] was extracted as a significant variable in the improved group (Table 6).

## IV. Discussion

A mirror image study was conducted to investigate outcomes of BD patients who had been treated for MDD. According to the results, the number of mood episode and the percentage of patients with a history of suicide attempt had been reduced. It was also revealed that presence of family history of psychiatric disorders was associated with decrease in the number of mood episodes after the diagnostic change.

This study included only patients who had been treated for MDD. As the population is unique, some of the patients' attributes observed in this study may be different from those of other studies on BD. In this study, the rate of BD-II was almost 2.5 times that of BD-I. In addition, this study included BD patients who had been treated for MDD without presenting hypomanic/manic episodes for more than one year. Therefore, the population might have included more BD-II patients for whom the incidence of developing hypomanic episodes is lower than that of BD-I[13, 14].

Even after the management plan was changed from the treatment for MDD to BD, antidepressants were still prescribed for more than a half of the patients. The efficacy of antidepressants for the depressive episodes of BD is still under debate[15, 16]. There are also concerns about using antidepressants in BD; these drugs may stimulate a switch hypomania/mania and rapid cycling of episodes.

Viktorin et al. reported that in BD patients who had been treated only with antidepressants, the risk of inducing manic switch was 2.83 times higher compared to patients who were not treated with antidepressants [17].

Meanwhile, there are also some studies reporting that administration of antidepressants would not be a risk for switch to mania[15, 16]. Such differences may be attributed to the types of antidepressants being used. The risk of switching to mania is higher with tricyclic antidepressants (TCAs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) compared to Selective Serotonin Reuptake Inhibitors (SSRIs) [18, 19]. There is also a report stating that the risk of switching to mania would be reduced by concomitant use of mood stabilizers [17]. In this study, nearly a half the patient had been treated with antidepressants even after the diagnostic change. However, the percentage of patients who had been only treated with antidepressant monotherapy was below 10%; about 80% had been concomitantly using mood stabilizers (at 6 months 77.1%, 12 months 77.1%).

The number of mood episodes decreased after changing the diagnosis and treatments from MDD to BD. In previous studies, the number of mood episodes per year was about 1-2 times for both BD-I and BD-II [20, 21]. Similar data were obtained in this study, and the number was 1.00 times (0.75 - 1.25) for one year before changing the diagnosis. In this study, presence of family history of psychiatric disorders was associated with

decreased number of mood episodes after diagnostic change. In general, one of the factors associated with poor outcome in BD is family history of BD [22, 23]. It can be considered that the number of mood episodes probably decreased as our study patients were able to receive appropriate treatment.

There have been studies investigating presence or absence of family history of mood disorders and the response to lithium treatment. According to previous reports, there was no relationship between presence of family history and satisfactory response to lithium treatment [24].

Misra and Burns reported that 3/4 of bipolar patients who do not respond to lithium had family history of mood disorder [25]. On the other hand, there is also a report stating that patients showed excellent response to lithium if they had a family member who had been treated with lithium [26]. This suggests that response to treatment with lithium is associated with genes. In this study evaluating the dose of lithium 6 months and 12 months after the diagnostic change, it was revealed that the dose of lithium had been slightly reduced at 12 months after the diagnostic change in the improved group, while in the non-improved group, the dose administered 12 months after the mirror date was twice as high as that of 6 months after. It can be considered that many of the patients in the non-improved group might have been unresponsive to the lithium treatment. Although no detailed analysis was made in this study, further investigations will be necessary as family history of psychiatric disorders, particularly a family history of lithium treatment, might affect the number of episodes.

The rate of suicide attempts was reduced after changing to treatment for BD. According to a previous report, 20-50% of BD patients had attempted suicide at least once in their lifetime [27].

A 2 year follow up study reported that 3.66% of BD patients had attempted or committed suicide [28]. In this study, the rate of history of suicide attempt before changing the diagnosis was 12.1%, which was higher than in the above-mentioned study. The facilities targeted in this study may also be affected by having emergency outpatients. However, the rate decreased remarkably after changing the treatment plan for BD. There is a report that valproate can reduce suicide attempts [29].

Tondo et al. compared preventive effects of antidepressants, lithium, and AEDs for suicide and reported that preventive effects for attempted and committed suicide were the highest for lithium compared to AEDs or antidepressants [30]. In this study, 5 out of 7 patients (71.4%) whose number of suicide attempts decreased to 0 after the diagnostic change had been additionally treated with lithium or valproate after the changing of the diagnosis. These changes in prescription might have contributed to reducing the rate of suicide attempts.

There were five limitations in this study. All the participating institutions in this study had a psychiatric ward. The patients' attributes and the level of severity may be different for patients who visit a psychiatric clinic. The second limitation was assessment methods for mood episodes. This was a retrospective study using medical charts. Assessments were not made for all patients using clinical

assessment scales to evaluate mood episodes. The third limitation is the sample size. Among the patients whose diagnosis changed, many cases were excluded. Therefore, due to lack of parameters, detailed analyses on psychiatric family history, prescribed drugs, or concomitant use of drugs were not performed. The fourth limitation was that there was no investigation on the association with comorbidity. Lastly, we could not investigate the introduction of psychosocial therapies which are effective for relapse prevention.

## V. Conclusions

We revealed that even the patients who required a long time to be diagnosed with BD could have better outcomes such as decreased number of mood episodes or decreased suicide attempt by providing appropriate treatment for disorders. This suggests that it is important to precisely find BD patients who have been treated for MDD and to treat them in an appropriate manner.

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# 臨床経過中にうつ病から双極性障害へ診断変更になった患者の転帰調査

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要旨

うつ病から双極性障害へ診断変更後の転帰および転帰の関連因子を明らかにすることを目的とした．1 年以上大うつ病性障害として治療を受けた患者 66 名を対象にミラーイメージ試験で検証を行った．診断変更日を基準日とし，前後 12 ヵ月間の気分エピソード回数，入院歴の有無，自殺企図歴の有無を比較した．また気分エピソード改善群 (n = 36)，非改善群 (n = 30) に分け，2 群間比較をした．診断変更後，気分エピソード回数 (p = 0.011)，自殺企図歴がある患者の割合 (p = 0.016) は有意に減少した．二項ロジスティック解析で改善群出現の関連因子として精神疾患の家族歴があること [OR = 3.962, (95%CI: 1.143- 13.740), p = 0.030] が抽出された．双極性障害の診断まで時間を要した患者でも，適切な治療で良好な転帰を辿ることが分かった．