

ORIGINAL ARTICLE

Relationship among psychotic features, benzodiazepine receptor agonists, and rehospitalization in patients with electroconvulsive therapy-responsive major depressive disorder: A retrospective 2-year observational study

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Abstract

Aim: It is controversial whether psychotic features are a risk factor for relapse in patients with electroconvulsive therapy-responsive major depressive disorder. A recent study reported that benzodiazepine receptor agonists reduce relapse of psychotic depression. As long-term use of these agonists may induce dependence, further research is required. We examined whether psychotic features are associated with rehospitalization in electroconvulsive therapy-responsive major depressive disorder patients. We also investigated whether taking benzodiazepine receptor agonists at the end of electroconvulsive therapy was associated with rehospitalization among patients with psychotic depression.

Methods: This study included 47 hospitalized patients (22 with psychotic depression, 25 with non-psychotic depression) who had responded to electroconvulsive therapy. Rehospitalization for major depressive episodes within two years from the last session was investigated.

Results: Twenty-three subjects (49%) were rehospitalized during the two-year follow-up. Kaplan–Meier analysis revealed no difference in rehospitalization between patients with psychotic and non-psychotic depression (Log-rank $P = 0.87$). Among the 22 responders to electroconvulsive therapy with psychotic depression, there was no difference in benzodiazepine receptor agonist use at the end of electroconvulsive therapy between the rehospitalization and non-rehospitalization groups.

Conclusion: Our exploratory study found no difference in the benzodiazepine receptor agonists use at the end of electroconvulsive therapy between rehospitalization and non-rehospitalization groups in patients with electroconvulsive therapy-responsive psychotic depression. Thus, the relapse-preventing effect of these agonists in psychotic depression should be investigated in future randomized controlled trials.

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Further research is also needed to determine whether psychotic features are associated with rehospitalization in these patients.

KEYWORDS

benzodiazepines, depression, electroconvulsive therapy, psychotic disorders, recurrence

1 | INTRODUCTION

Major depressive disorder (MDD) with psychotic features, termed psychotic depression, is defined as an episode of MDD that includes delusions and/or hallucinations, according to the Diagnostic & Statistical Manual of Mental Disorders, fifth edition (DSM-5).¹ A previous meta-analysis showed that the lifetime prevalence of psychotic depression was 0.35%–1.0%. In psychiatric clinical practice, psychotic depression is not rare. A meta-analysis showed that the median proportion of psychotic depression among patients with depression was 28%, and among hospitalized patient with depression, it was 42%. In addition, psychotic depression is associated with more severe depressive symptoms,² increased hospitalization,³ a higher relapse rate,^{3,4} higher suicide frequency,⁵ more financial dependency,³ and reduced quality of life⁶ compared with non-psychotic depression. Therefore, it is crucial that the condition be diagnosed early and prompt, and appropriate therapeutic intervention is provided.

Electroconvulsive therapy (ECT) is an effective treatment for psychotic depression, with a response rate of 76%–89%^{7,8} and is recommended as first-line treatment in several guidelines.^{9–12} Although psychotic features predict the response to ECT among patients with MDD,^{2,13} it is not clear whether psychotic features pose a risk of relapse in patients with MDD who are responsive to ECT, as the results of previous studies were inconsistent. Flint et al. reported that psychotic depression had a higher risk of recurrence than did non-psychotic depression,⁸ whereas Wagenmakers et al. and Birkenhäger et al. reported that it had a lower risk.^{14,15} Furthermore, prior studies have set the primary endpoint at recurrence, but given that psychotic depression is one of the severe subtypes of MDD, for which guidelines recommend inpatient treatment,^{10,11} a study setting the primary endpoint at rehospitalization would be beneficial for psychiatrists, patients with psychotic depression, and caregivers.

Recently, it was reported that use of benzodiazepine receptor agonists (BzRA) could reduce relapse and recurrence in patients with psychotic depression.¹⁶ However, this previous study did not provide details of BzRA hypnotics or benzodiazepine (BZ) anxiolytics, or information on insomnia symptoms. Numerous studies have demonstrated that residual insomnia pose a major risk of relapse in patients with MDD.^{17–20} Thus, the result of the previous study may have been influenced by the improving effects of BzRA hypnotics on residual insomnia. Because BzRA can elicit a variety of adverse effects, including dependence, the relapse-preventive effects of BzRA in patients with psychotic depression, should be investigated in the

light of residual insomnia. However, the results of the previous study have not been confirmed to date.

In this study, we conducted a retrospective observational study to examine whether psychotic features are associated with rehospitalization two years after completing ECT in patients with MDD who responded to ECT. In addition, we explored whether patients taking BzRA or BzRA hypnotics had lower rehospitalization rates two years after completing ECT than those not taking them among patients with ECT-responsive psychotic depression.

2 | METHODS

2.1 | Study design, setting, and population

This study was a retrospective observational study. Consecutive patients with MDD admitted to our hospital between January 1, 2010, and August 31, 2021, and who responded to ECT were included. If ECT was performed more than once on a patient with MDD during the study period, only data from the first instance were included. In our hospital, acute ECT is performed only in an inpatient setting. Additionally, continuous ECT for MDD has not been performed at our hospital to date.

The diagnosis of MDD with or without psychotic features was based on the DSM, Fourth Edition, Text Revision, until May 2013, and on the DSM-5 after June 2013. Exclusion criteria were a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder (BD), neurocognitive disorder, substance use disorder, and personality disorder. Response was defined as >50% improvement in the Japanese version of the 17-item GRID Hamilton Depression Rating Scale (HAMD17) after ECT.²¹ Subjects were followed for up to 2 years (until May 31, 2022) to determine if they were rehospitalized for MDD with a depressive symptom severity score of 8 or higher on HAMD17. If the follow-up was interrupted due to transfer to other hospitals or interruption of hospital visits due to the patient's decision, it was considered to be censored. In addition, patients with MDD in remission after ECT (ECT remitters, defined as a HAMD17 score of ≤7) were examined in the same way.

The following information was extracted from the electronic medical records: age, sex, psychotic features based on DSM criteria, days from last ECT to rehospitalization (up to 2 years), severity of depressive symptoms measured by HAMD17 before and after ECT, residual insomnia at the end of ECT (≥1 for difficulty falling asleep, mid-morning awakening, or early morning awakening in HAMD17), residual anxiety at the end of ECT (≥1 for anxiety psychic or somatic



in HAMD17), number of ECT sessions during hospitalization, duration of current depressive episode (month), whether it was a first or a recurrent major depressive episode, history of ECT prior to this hospitalization, educational history, marital status, and employment status. Information on psychotropic drugs use (hypnotics, anxiolytics, clonazepam, antidepressants, antipsychotics, and lithium) at the end of ECT and at last observation up to 2 years was also extracted. Hypnotics comprised BzRA hypnotics (benzodiazepine [BZ] and non-benzodiazepine hypnotics), melatonin receptor agonist (MRA), and orexin receptor antagonist (ORA). Anxiolytics consisted of BZ anxiolytics and tandospirone. A BZ anxiolytic prescribed before bedtime was considered a BzRA hypnotic because BZ anxiolytics are sometimes used as hypnotics in clinical practice. For the same reason, clonazepam was considered a hypnotic when prescribed before bedtime and BZ anxiolytic when prescribed in other times. BzRA comprises BzRA hypnotics and Bz anxiolytics.

2.2 | ECT procedure

ECT was performed twice a week in the operating room under general supervision by an anesthesiologist. The treatment instrument used was a Somatics short pulse square wave therapy machine, Thymatron System IV (Somatics, LLC, Lake Bluff, IL, USA). All cases had bilateral electrode placement, and the half-age method was used for initial stimulus dose setting. Efficacy was judged by electroencephalography, and if seizures were inadequate, the stimulation dose was multiplied by 1.5. The intravenous anesthetic used was propofol 1.4–2.0 mg/kg, and the muscle relaxant was suxamethonium chloride 1.0 mg/kg. The number of treatments ranged from 6 to 12. The treatment was terminated at the attending physician's discretion when remission or symptom improvement reached a plateau.

2.3 | Statistical analysis

Continuous variables are expressed as median (25%–75% percentile). To examine differences between the rehospitalized and non-rehospitalized groups, we performed a Mann–Whitney U test for continuous variables and a chi-squared test or Fisher's exact test for categorical variables. The event-free survival length was determined from the date of last ECT to rehospitalization up to two years. Cumulative incidence curves were derived using the Kaplan–Meier method, and differences between the curves were analyzed using the log-rank test. Statistical analyses were performed with SPSS Statistics 28.0 (IBM Corp. Armonk, NY, USA). Values of $P < 0.05$ (two-sided) were considered significant.

2.4 | Ethical issues

This study was approved by the Ethical Committee for Human Research of Akita University (No. 2521), which also exempted the

study from the requirement of informed consent because the study involved de-identified data acquired during routine care of the patient. This study was conducted in accordance with the Declaration of Helsinki.

3 | RESULTS

During the study period, 65 patients with MDD underwent ECT. For all patients, organic diseases were ruled out by brain computed tomography or magnetic resonance imaging. No patients met the exclusion criteria for comorbid mental disorders. Of the 65 patients, six patients were excluded for the following reasons: in four, response/remission could not be determined because HAM-D data were not available in the electronic medical records, and in two, outcomes could not be followed because they were transferred to other hospitals immediately after ECT. Among 59 patients, 80% (47/59) responded to ECT and 51% (30/59) had ECT in remission. Of 47 ECT responders, 23 (49%) were rehospitalized during the 2-year follow-up, nine (19%) had completed the period without rehospitalization, and 15 (32%) were censored during the period. Of 30 ECT remitters, 17 (57%) were readmitted within two years after ECT, seven (23%) had completed the period without rehospitalization, and six (20%) were censored during the period. All rehospitalized patients had a HAMD17 score of 8 or higher, and the mean $\pm$ standard deviation of HAMD17 was 21.7 ± 8.6 points. Diagnosis was not changed to BD or schizophrenia during the 2-year follow-up in any of the subjects.

Table 1 shows the clinical characteristics of the subjects included in this study. The subjects were mostly middle and old-aged, with a median age of 65 years, (first quartile 51–third quartile 73 years), and 72% of the subjects were women. Of the subjects, 47% had psychotic depression and 15% had a history of ECT. One patient in the non-rehospitalized group was taking Bz anxiolytics before bedtime, which were thus considered BzRA hypnotics. No patients took clonazepam and tandospirone. The rehospitalization group had a significantly higher proportion of women and a higher proportion of individuals taking BzRA hypnotics than the non-rehospitalization group, but there were no significant differences between the two groups in terms of other items, such as severity of depressive symptoms before ECT and after completing ECT, and psychotropic drugs.

Figure 1 shows the cumulative incidence of rehospitalization in ECT responders with or without psychotic features. Kaplan–Meier analysis showed no difference in rehospitalization rates between patients with psychotic depression and those with non-psychotic depression (Log-rank $P = 0.87$). We also examined whether rehospitalization differed according to the presence or absence of psychotic features in patients with MDD who went into remission with ECT ($N = 30$), but found no significant differences between the two groups (Log-rank $P = 0.848$).

Of the 22 patients with psychotic depression who responded to ECT, 12 were taking BzRA, 10 were taking BzRA hypnotics, and 6 were taking BZ anxiolytics at the end of ECT. At the last observation or rehospitalization, 14 were taking BzRA, one had stopped taking



TABLE 1 Clinical characteristics of the subjects

	Rehospitalization group (N = 23)	Non-rehospitalization group (N = 24)	P value
Age, year	64.0 (51.0, 73.0)	67.0 (51.25, 72.5)	0.59
Sex ^a			0.049*
Female	20/23 (87.0%)	14/24 (58.3%)	
Male	3/23 (13.0%)	10/24 (41.7%)	
Psychotic symptoms ^a	11/23 (47.8%)	11/24 (45.8%)	>0.99
HAMD before ECT	27.0 (21.0, 38.0)	26.0 (18.25, 30.0)	0.22
HAMD after completing ECT	5.0 (3.0, 8.0)	6.5 (4.25, 8.75)	0.31
Residual insomnia ^a	13/23 (56.5%)	17/24 (70.8%)	0.37
Duration of current depressive episode (month)	5.0 (3.0, 11.0)	6.5 (5.0, 12.0)	0.17
Past major depressive episodes ^a	18/23 (78.3%)	20/24 (83.3%)	0.72
Onset of MDD (age)	54.0 (40.0, 66.0)	52.0 (40.5, 67.0)	0.88
History of ECT ^a	3/23 (13.0%)	4/24 (16.7%)	>0.99
Cohabitants ^a	19/23 (82.6%)	22/24 (91.7%)	0.42
Spouse ^a	20/23 (87.0%)	21/24 (87.5%)	>0.99
Education ^b			0.76
Junior high school graduate	7/23 (30.4%)	6/24 (25.0%)	
High school graduate	13/23 (56.5%)	13/24 (54.2%)	
College graduate	3/23 (13.0%)	5/24 (20.8%)	
Occupation ^b			0.13
Student	0/23 (0%)	0/24 (0%)	
Employed	3/23 (13.0%)	9/24 (37.5%)	
Retired	14/23 (60.9%)	12/24 (50.0%)	
None	6/23 (26.1%)	3/24 (12.5%)	
Total number of ECT sessions performed (times)	7.0 (5.0, 10.0)	8 (6.25, 10)	0.15
Psychotropic drug use at the end of ECT			
Antidepressants ^a	21/23 (91.3%)	22/24 (91.7%)	>0.99
Antipsychotics ^a	16/23 (69.6%)	20/24 (83.3%)	0.32
Lithium ^a	1/23 (4.3%)	0/24 (3.8%)	0.49
Anxiolytics at the end of ECT			
BZ anxiolytic ^a	4/23 (17.4%)	5/24 (20.8%)	>0.99
Hypnotics at the end of ECT			
Any of the hypnotics ^a	21/23 (91.3%)	19/24 (79.2%)	0.42
BzRA hypnotics ^a	18/23 (78.3%)	11/24 (45.8%)	0.036*
MRA ^a	4/23 (17.4%)	7/24 (29.2%)	0.49
ORA ^a	4/23 (17.4%)	6/24 (25.0%)	0.72
BzRAs at the end of ECT ^a	18/23 (78.3%)	13/24 (54.2%)	0.13

Notes: values are presented as median (interquartile range) or number [%]. P values with significant results are labeled with an asterisk.

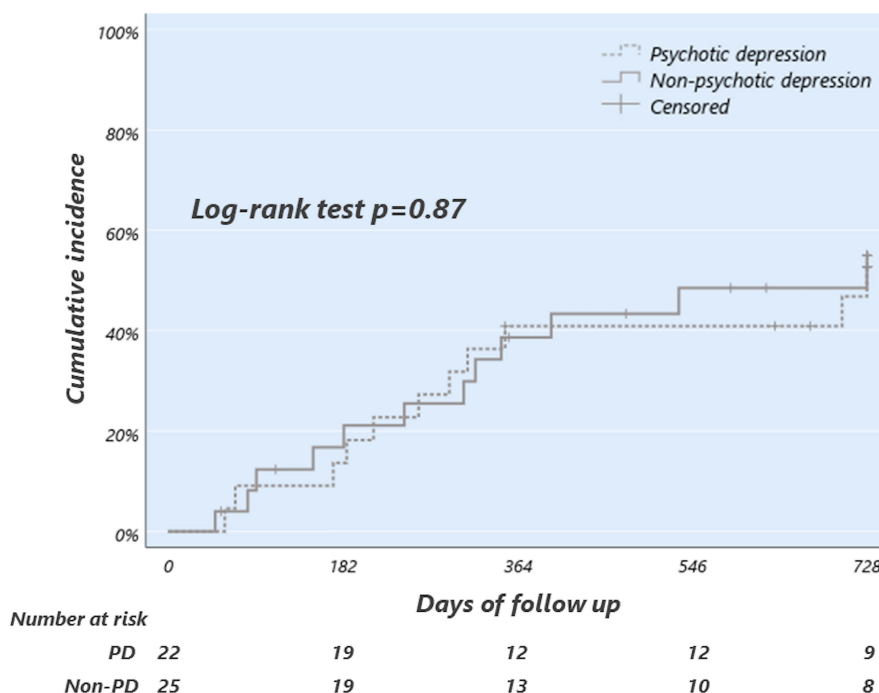
Abbreviations: BZ, benzodiazepine; BzRA, benzodiazepine receptor agonist; ECT, electroconvulsive therapy; HAMD, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder; MRA, melatonin receptor agonist; ORA, orexin receptor antagonist.

^aFisher's exact test.

^bChi-squared test.



FIGURE 1 Kaplan–Meier survival curves for time to rehospitalization associated with psychotic features in 47 patients with major depressive disorder who responded to electroconvulsive therapy. The dotted line indicates patients with psychotic depression ($N = 22$), and the solid line indicates the patients with non-psychotic depression ($N = 25$). PD, psychotic depression.



BzRA, and three had started new BzRA after completing ECT. At the last observation, 11 were taking BzRA hypnotics, one had stopped taking BzRA hypnotics, and two had started new BzRA hypnotics after completing ECT. At the last observation, 14 were taking BZ anxiolytics, and eight started BZ anxiolytics after completing ECT. Table 2 shows the clinical characteristics of patients with psychotic depression who responded to ECT. Of these patients, 50% (11/22) were rehospitalized within 2 years of last ECT. The severity of depressive symptoms before ECT was significantly higher in the rehospitalized group than in the non-rehospitalized group. However, no significant differences in all other factors were observed between the two groups, including the use of BzRA or BzRA hypnotics, at the end of ECT.

4 | DISCUSSION

No previous studies have investigated whether psychotic features are a risk factor for rehospitalization in patients with MDD who responded to ECT. In this study, rehospitalization occurred in 50% (11/22) of patients with psychotic depression and in 48% (12/25) of patients with non-psychotic depression; thus, psychotic features were not associated with rehospitalization within 2 years after ECT.

Since psychotic depression is a serious illness that often requires inpatient treatment, it is significant that we had set the primary endpoint in this study as rehospitalization, rather than relapse. In a previous prospective observational study in which ECT remitters with severe late-life depression were followed for 6 months, patients with psychotic depression were less likely to relapse than patients with non-psychotic depression (23% [9/39] vs 46% [13/28]).¹⁴ In another previous prospective observational study in which ECT responders with MDD were followed up for 6 months,

patients with psychotic depression had significantly lower recurrence rates than those with non-psychotic depression (15% [4/27] vs 68% [19/28]).¹⁵ In contrast, in another previous prospective observational study of ECT responders with MDD who were followed up for 2 years, patients with psychotic depression had significantly higher recurrence rates than those with non-psychotic depression (47% [9/19] vs 15% [10/68]).⁸ Compared with these previous studies, it is unclear why the relapse rate of psychotic depression was higher in the present study. One possible reason is that few of the subjects in this study were taking lithium, which has been shown in randomized controlled trials to prevent relapse in patients with MDD who went into remission with ECT.²² Interestingly, a previous study reported that recurrence occurred faster after ECT in patients with BD than in patients with MDD, and that the group whose diagnosis changed from MDD to BD during follow-up after ECT had a higher recurrence rate than did the group whose diagnosis remained unchanged as MDD.²³ Given the possibility that this study may have included some patients whose diagnosis may change to BD in future, and given the established efficacy of lithium in preventing recurrence of all phases of BD,²⁴ the fact that few patients in this study were taking lithium may account for the higher rehospitalization rate than in previous studies.^{8,14,15} In fact, in the study conducted by Birkenhäger et al., none of the ECT responders with psychotic depression who were receiving tricyclic antidepressant and lithium combination therapy after ECT relapsed during one-year follow-up period.¹⁵ Other possible reasons is heterogeneity between studies (age, sex, duration of maintenance period, number of previous episodes, whether the subjects were ECT responders or ECT limiters, follow-up period, and different definitions of primary endpoint of recurrence or rehospitalization),²⁵ which may have influenced the differences in results between the present and previous studies. Due to the different results between



TABLE 2 Clinical characteristics of the subjects with psychotic depression who responded to electroconvulsive therapy

	Rehospitalization Group (N = 11)	Non-rehospitalization Group (N = 11)	P value
Age, year	64.0 (53, 71)	71.0 (65, 78)	0.13
Sex ^a			>0.99
Female	9/11 (81.8%)	9/11 (81.8%)	
Male	2/11 (18.2%)	2/11 (18.2%)	
HAMD before ECT	38 (29, 40)	30.0 (26, 32)	0.035*
HAMD after completing ECT	5 (3, 11)	8 (4, 9)	0.95
Residual insomnia ^a	7/11 (63.6%)	8/11 (72.7%)	>0.99
Duration of current depressive episode (month)	6 (4, 8)	6 (4, 8)	0.95
Past major depressive episodes ^a	9/11 (81.8%)	9/11 (81.8%)	>0.99
Onset of MDD (age)	59 (46, 62)	63 (50, 68)	0.48
History of ECT ^a	1/11 (9.1%)	2/11 (18.2%)	>0.99
Cohabitants ^a	8/11 (72.7%)	10/11 (90.9%)	0.59
Spouse ^a	10/11 (90.9%)	10/11 (90.9%)	>0.99
Education ^b			0.44
Junior high school graduate	4/11 (36.4%)	2/11 (18.2%)	
High school graduate	6/11 (54.5%)	6/11 (54.5%)	
College graduate	1/11 (9.1%)	3/11 (27.3%)	
Occupation ^b			0.30
Student	0/11 (0%)	0/11 (0%)	
Employed	1/11 (9.1%)	2/11 (18.2%)	
Retired	8/11 (72.7%)	9/11 (81.8%)	
None	2/11 (18.2%)	0/11 (0%)	
Total number of ECT sessions performed (times)	7 (6, 10)	8 (5, 10)	0.80
Psychotropic drug use at the end of ECT			
Antidepressants ^a	9/11 (81.8%)	9/11 (81.8%)	>0.99
Antipsychotics ^a	8/11 (72.7%)	8/11 (72.7%)	>0.99
Lithium ^a	0/11 (0%)	0/11 (0%)	NA
Anxiolytics at the end of ECT			
BZ anxiolytics ^a	3/11 (27.3%)	3/11 (27.3%)	>0.99
Hypnotics at the end of ECT			
Any of the hypnotics ^a	10/11 (90.9%)	6/11 (54.5%)	0.15
BzRA hypnotics ^a	7/11 (63.6%)	3/11 (27.3%)	0.20
MRA ^a	3/11 (27.3%)	3/11 (27.3%)	>0.99
ORA ^a	3/11 (27.3%)	2/11 (18.2%)	>0.99
BzRAs at the end of ECT ^a	7/11 (63.6%)	5/11 (45.5%)	0.67

Notes: values are presented as median (interquartile range) or number [%]. P values with significant results are labeled with an asterisk.

Abbreviations: BZ, benzodiazepine; BzRA, benzodiazepine receptor agonist; ECT, electroconvulsive therapy; HAMD, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder; MRA, melatonin receptor agonist; ORA, orexin receptor antagonist.

^aFisher's exact test.

^bChi-squared test.



the present study and previous studies, the small sample size of the studies conducted to date, and the large heterogeneity between studies, as noted above, it is not possible to draw conclusions about whether psychotic features increase the risk of relapse or rehospitalization after successful ECT. Future meta-analyses integrating current evidence and larger-scale observational studies with more elaborate designs are warranted.

As a secondary aim, we explored whether BzRA and BzRA hypnotics are associated with rehospitalization in patients with psychotic depression who responded to ECT, given the findings of a previous study that showed that BzRA prevented relapse of psychotic depression.¹⁶ In this study, no differences were observed between the rehospitalization and non-rehospitalization groups in taking BzRA or BzRA hypnotics at the end of ECT. The results of the present study were in contrast to those of the previous study,¹⁶ suggesting that taking BzRA or BzRA hypnotics after completing ECT was not associated with subsequent rehospitalization. No firm conclusion can be drawn on whether BzRA or BzRA hypnotics are effective or not in preventing relapse in patients with psychotic depression who respond to ECT based on the findings of this small naturalistic design study. Moreover, this study included some patients who had newly started or stopped taking BzRA or BzRA hypnotics during the 2-year follow-up period after ECT. Nevertheless, this study is valuable because it demonstrated that further research is needed on the recurrence-preventive effects of BzRA on psychotic depression. Future randomized controlled trials will be needed to conclude whether BzRA or BzRA hypnotics prevent recurrence or relapse of psychotic depression, taking into account the presence or absence of residual symptoms, such as insomnia and anxiety.

This study has several limitations. First, because this study was a retrospective, observational study, the criteria for rehospitalization as a primary endpoint were not defined. However, considering that the subjects were patients with psychotic depression who responded to ECT and who made regular outpatient visits to the same physician after discharge, it is inferred that the primary endpoint was not significantly affected. Second, due to the small sample size, it was not possible to examine whether psychotic features were associated with rehospitalization in ECT responder using multivariate analysis. Third, pharmacotherapy after response to ECT varies among patients. The combination of antidepressants and lithium or the combination of antidepressants and antipsychotics may prevent recurrence of psychotic depression better than antidepressants alone.^{26,27}

In conclusion, approximately half of the patients with major depressive disorder who responded to ECT were readmitted to the hospital during the 2-year study period, regardless of the presence or absence of psychotic features. Furthermore, we report the novel finding that psychotic features were not associated with rehospitalization, contrary to previous studies showing that psychotic features are associated with the risk of relapse in MDD patients who respond to ECT. An exploratory study was also conducted to confirm the results of a previous study showing that BzRA prevents relapse of psychotic depression, but the previous findings could not be confirmed.

Further studies with a larger sample are warranted to clarify these clinical questions.

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CONFLICT OF INTEREST

Masahiro Takeshima has received lecture fees from Daiichi Sankyo Company, Sumitomo Dainippon Pharma, Meiji Seika Pharma, Viatrix Pharmaceuticals Japan, Yoshitomi Pharmaceutical, and Daiichi Sankyo Company, and research grants from Otsuka Pharmaceutical, Eisai, and Shionogi, outside the submitted work. Kazuo Mishima has received speaker's honoraria from Eisai Co., Ltd., Nobelpharma Co., Ltd., and MSD Inc., and research grants from the Japanese Ministry of Health, Labor and Welfare (19GC1012, 21GC0801) outside of the submitted work. Akise Umakoshi, Yu Itoh, Mari Yamamoto, Nana Shibata, Masaya Ogasawara, and Naoko Ayabe have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The raw data are available as Supporting Information.

ETHICS APPROVAL

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee for Human Research of Akita University, Approval No. 2521.

PATIENT CONSENT

This study was exempted from the requirement of obtaining informed consent because the study involved de-identified data acquired during routine care of the patient.

STUDY REGISTRATION

This study is not pre-registered.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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