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REGULAR ARTICLE

Shared preventive factors associated with relapse after a response to electroconvulsive therapy in four major psychiatric disorders

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Aim: The efficacy of electroconvulsive therapy (ECT) has been established in psychiatric disorders but the high rate of relapse is a critical problem. The current study sought preventative factors associated with relapse after a response to ECT in a continuum of four major psychiatric disorders.

Methods: The records of 255 patients with four psychiatric disorders (83 unipolar depression, 60 bipolar depression, 91 schizophrenia, 21 schizoaffective disorder) were retrospectively reviewed.

Results: The relapse-free rate of all patients at 1 year was 56.3% in the four psychiatric disorders without a difference. As a result of univariate analysis, three items could be considered as preventative factors associated with relapse: a small number of psychiatric symptom episodes before an acute course of ECT, the use of mood stabilizers, and the use of maintenance ECT. Multivariate analysis was performed, keeping age, sex, and diagnosis constant in addition to the three items, and small number of psychiatric symptom episodes before an acute course of ECT ($P = 0.003$), the use of lithium ($P = 0.025$), the use of valproate ($P = 0.027$), and the use of maintenance ECT ($P = 0.001$) were found to be significant preventative measures against relapse.

Conclusion: The use of mood stabilizers, such as lithium and valproate, and maintenance ECT could be shared preventive factors associated with relapse after a response to ECT in four major psychiatric disorders.

Keywords: *electroconvulsive therapy, lithium, maintenance electroconvulsive therapy, preventive measures, valproate.*

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Electroconvulsive therapy (ECT) is a neuromodulatory treatment for psychiatric disorders and its efficacy has been clinically well established. ECT induces generalized seizure activity in the brain by electrical stimulation and symptomatic improvement is mediated by yet-to-be-detailed biological mechanisms. While ECT is highly effective on specific symptoms, such as catatonia and acute psychotic episodes for mood disorders and schizophrenia, there is a high rate of relapse and preventing relapse is an important clinical objective. Pharmacotherapy and maintenance ECT have been used to prevent relapse – there are reports that lithium plus either nortriptyline or venlafaxine[1,2] and maintenance ECT[3–5] are effective against depression.

Major psychiatric disorders, such as schizophrenia, depression, and bipolar disorder, have more in common than previously thought. Not only are the underlying genetics shared between disorders, mutations and modifications associated with particular genes also work in concert to manage brain signaling and genome function later in life.[6–9] While various taxonomies exist to delineate psychiatric disorders, there is the concept in which schizophrenia, schizoaffective disorder, bipolar disorder, and depression are viewed as a continuum of psychiatric disorders.[10] As ECT shows efficacy in patients with similar symptoms, such as catatonia, acute psychosis, and abnormal affect[11] in both mood disorders and schizophrenia, it is possible that there could be shared factors associated with relapse. Therefore, in the current study, the four disorders were integrated as one and preventative factors associated with relapse for the four major psychiatric disorders were identified by retrospective analysis of patients' medical records.

Methods

Patients

Patients were recruited from southern Hiroshima Prefecture and all outpatients and inpatients were treated at the National Hospital Organization (NHO) Kure Medical Center. Patients included in the current study: (i) were diagnosed with unipolar depression, bipolar depression, schizophrenia, or schizoaffective disorder based on the ICD-10 guideline independently by at least two trained psychiatrists through direct interview and a systematic review of patients' medical records (the diagnoses were confirmed at the end of each investigation); (ii) received an acute course of ECT between July 2005 and December

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2016 at the NHO Kure Medical Center; and (iii) responded to the acute course of ECT. Exclusion criteria included: (i) diagnosed with delusional disorder; (ii) known to have a substance abuse problem, personality disorder, or preexisting neurological disorder, such as Parkinson's disease or dementia; and (iii) did not respond to an acute course of ECT. If a patient received two or more acute ECT courses during the study period, the observation period was defined as the time since completing the first acute ECT course. The observation period of maintenance ECT was defined as that from the last day of the acute ECT course before maintenance ECT – the earlier acute ECT course was excluded from the observation period.

ECT is often prescribed when a patient exhibits episodes of severe major depression, psychosis, and catatonia or has shown insufficient improvement with prescribed pharmacotherapy treatment. All patients had received at least one trial of medication before starting ECT and were nonresponders to such treatment. A clinical psychiatrist recommended ECT to each patient according to standards outlined by the American Psychiatric Association (APA) task force[12] and based on the patient's urgency and severity of illness.

Patients' medical records were used to obtain data for the current study. Patient information was kept confidential and anonymous. The ethics committees of the NHO Kure Medical Center approved the current retrospective study.

Data source

Collected data included demographic variables, clinical variables, and maintenance psychotropic-related variables. Demographic and clinical variables included age, sex, age of onset of illness, number of mood or psychotic episodes (excluding current episode), number of ECT sessions, subtype of schizophrenia or schizoaffective disorder, and imipramine (IMI)-equivalent and chlorpromazine (CPZ)-equivalent dose[13] before and after the course of ECT.

Each patient's symptoms were assessed prior to the first ECT session and the day after the last ECT session by the same trained psychiatrist, who was different from the clinician making the initial diagnosis. The Hamilton Depression Rating Scale 21 (HDRS) was used for evaluating depressive symptoms of mood disorders. The Brief Psychiatric Rating Scale (BPRS) was used for evaluating psychotic symptoms of schizophrenia and schizoaffective disorder. Scores for the Clinical Global Impressions – Severity (CGI-S) Scale, Clinical Global Impressions – Improvement (CGI-I) Scale, and Global Assessment of Functioning (GAF) were obtained from all patients. Responders to an acute course of ECT were defined as patients with a CGI-I Scale score $\leqq 3$ after the course of ECT. Each patient was subsequently evaluated by the same trained psychiatrist regularly at intervals of no less than 4 weeks. The time to recurrence/relapse was defined as the time between the date of the final ECT session and the date of an evaluation at which patients had a CGI-I score $\geqq 6$ that was maintained for at least 1 week (over two consecutive visits) or if they required psychiatric rehospitalization for depressive, manic, mixed, psychotic states, or catatonia. Recurrence/relapse is usually distinguished by the presence/absence of an achievement of full remission or the duration of remission. For the current study, recurrence and relapse were consolidated as 'relapse.' The starting point of the current investigation was the last day of acute ECT. The study end-point for the relapse group was the time to relapse and the study end-point for the relapse-free group was 1 year (52 weeks) after the final acute ECT session.

Data from patients who later moved out of the hospital's recruitment area, died, or were not readmitted within a year were treated as censored cases for Cox regression analysis. The daily dosages of the treatment drugs at the end of the investigation were calculated. Follow-up data were collected up until December 2017.

Acute course of ECT procedures

Acute courses of ECT were performed at NHO Kure Medical Center and according to a previous report.[14,15] A modified ECT method with the cooperation of an anesthesiologist was used. Without premedication, patients were anesthetized with intravenous thiamylal sodium (2–3 mg/kg) and suxamethonium chloride (0.5–1.0 mg/kg). The ECT device was a Thymatron System IV brief-pulse square-wave apparatus (Somatics Inc., Lake Bluff, IL, USA). Electrodes were positioned at the bilateral frontotemporal region. Because the majority of patients demonstrated life-threatening or treatment-resistant illness, bilateral frontotemporal electrodes were used. Only one adequate seizure was required for each session, which was defined as an electroencephalographic seizure lasting >25 s with a high-amplitude, regular slow-wave and postictal suppression. The initial stimulation was set to one-half of the patient's age.[16] If an adequate electroencephalographic seizure occurred in one session, the same stimulation was subsequently used. When a missed or an inadequate seizure occurred, the patient was restimulated with 1.5–2 times the initial stimulus. The maximum number of stimulations for each treatment session was two. ECT was administered at a maximum of three times per week. If any adverse effects (e.g., cognitive dysfunction, delirium) occurred, then the frequency of the ECT schedule was reduced to once or twice per week, or ECT was terminated. Based on APA guidelines, acute ECT was continued until the patient was asymptomatic or until the psychiatrist judged that the patient had received the maximum possible benefit from treatment.

After the purpose and procedure of ECT was fully explained, written informed consent was obtained from the patient or their family members prior to the first ECT session.

Maintenance ECT procedures

Maintenance ECT is used to preserve remission and prevent relapse after symptomatic improvement obtained with an acute ECT course. The APA has defined 'continuation ECT' as that which occurs within 6 months of acute treatment to prevent relapse, whereas 'maintenance ECT' is that which continues beyond 6 months to prevent recurrence (of a new episode of illness).[12] The distinction between the two treatments is often arbitrary, however, and the terms are often interchanged.[17] For the current study, the term 'maintenance ECT' will be used. An APA Task Force Report (2001)[12] established indications for maintenance ECT for patients who respond to an acute ECT course when one of the following has occurred: (i) pharmacotherapy alone is not effective in treating index episodes or in preventing relapse or recurrence; (ii) pharmacotherapy cannot be safely administered; or (iii) the patient prefers ECT and the patient or surrogate consenter agrees to the patient's receiving maintenance ECT. The patient must be capable, with the assistance of others, of complying with the treatment plan. Maintenance ECT was discussed at the discretion of the attending physician according to APA guidelines. Maintenance ECT was conducted in accordance with acute ECT, taking into consideration risks, such as delirium, after ECT and it was conducted during hospital admission, on average, for 3 days and 2 nights. ECT was, in principle, to be performed once during the hospital stay. The stimulus energy of the final session of acute ECT was maintained and continued. Maintenance ECT was in principle to be performed once a month, but if the symptoms were stable, the interval was extended up to 3 months.

Use of clozapine

Clozapine is indicated for treatment-resistant schizophrenia and acute ECT is indicated for patients who do not respond to clozapine. However, because clozapine was only approved for use in Japan in 2009, the number of patients prescribed clozapine in Japan is much smaller than that found elsewhere.[18] There were few patients who were prescribed clozapine within our database, so these patients were excluded from further analysis.

Treatment during follow-up period after acute ECT course

All patients were treated with medication to prevent relapse after an acute ECT course. The attending psychiatrist selected the type and

dosage of antidepressants, antipsychotics, mood stabilizers, and/or maintenance ECT on a case-by-case basis. During the study period, all patients received supportive psychotherapy. However, cognitive behavior therapy was not utilized.

Statistical analyses

Comparisons for continuous variables were conducted by using the unpaired *t*-test (Mann–Whitney *U*-test when appropriate) to compare between unipolar and bipolar depression, schizophrenia, and schizoaffective disorder. Comparisons for categorical variables within each psychiatric disorder were conducted by the χ^2-test. Continuous variables were conducted by post hoc test and Tukey's test. The cumulative probability of surviving without relapse was calculated using the Kaplan–Meier technique. Cox regression analysis was used to identify factors associated with relapse via univariate and multivariate analyses. Sex (base: male sex), diagnosis (hazard ratio of unipolar depression = 1), use of antidepressants, use of antipsychotics, use of mood stabilizers, and use of maintenance ECT (no use = 0, use = 1) were analyzed as categorical variables. Age at acute ECT, age at onset of illness, number of mood or psychotic episodes, number of acute ECT sessions per treatment, CGI-S, CGI-I, GAF, IMI- and CPZ-equivalent dose, HDRS, and BPRS were analyzed as continuous variables. Univariate analyses were conducted, and factors with a trend toward statistical significance ($P < 0.10$), sex, age, and diagnosis (adjusted hazard ratio of unipolar depression = 1) were subsequently examined by multivariate analysis. Two-tailed *P*-values < 0.05 were considered to be statistically significant. The statistical analyses were carried out on a personal computer (IBM Japan Corporation, Tokyo, Japan) using SPSS version 22.0 for Windows.

Results

Participants

During the study period, 280 patients received an acute course of ECT and of these, 255 (91.1%) were responders and 25 (8.9%) were nonresponders. Variables such as age, sex, number of acute ECT, and diagnosis were not significantly different between responders and nonresponders. A total of 255 patients with psychiatric disorders (83 unipolar depression, 60 bipolar depression, 91 schizophrenia, 21 schizoaffective disorder) fit the current inclusion criteria and were subsequently analyzed. ECT-induced hypomanic, but not manic, changes were experienced by 13 patients with unipolar depression during acute ECT course. Ten patients subsided at the end of acute ECT course and euthymia was maintained until the end of each investigation. Therefore, these patients were diagnosed with unipolar depression. Three patients remained hypomanic at the end of each investigation. Therefore, they were diagnosed with bipolar depression. Two patients had comorbidity for generalized anxiety disorder (unipolar: 1, bipolar: 1), and two patients had comorbidity for somatization disorder (unipolar: 1, bipolar: 1). The severity of the comorbidities was mild. Cox regression analysis was not performed on these comorbidity factors due to the small sample size. Out of 255 patients, 72 patients dropped out of the study within a year (68 transferred to another hospital, three discontinued treatments, and one died due to physical illness) and were treated as censored cases for the purpose of Cox regression analysis. Twenty-three patients received maintenance ECT for the first time after an acute ECT course (unipolar depression: 4; bipolar depression: 3; schizophrenia: 10; schizoaffective disorder: 6). Cognitive functioning in patients suspected of cognitive dysfunction was assessed using the Hasegawa Dementia Rating Scale – Revised, before and after ECT. If a patient demonstrated transient cognitive dysfunction, such as ECT-induced amnesia, the patient was periodically assessed until recovery. None of the patients demonstrated persistent cognitive dysfunction after an acute course of ECT.

All patient characteristics and comparisons are summarized in Table 1. Concerning 'age at acute ECT (years),' patients with schizophrenia were significantly younger than those with unipolar depression and bipolar depression, and those with schizoaffective disorder were significantly younger than those with unipolar depression. Concerning 'age at onset of illness (years),' patients with schizophrenia and schizoaffective disorder were significantly younger than those

Table 1. Patient characteristics and comparisons

	Unipolar depression (n = 83) Mean ± SD	Bipolar depression (n = 60) Mean ± SD	Schizophrenia (n = 91) Mean ± SD	Schizoaffective disorder (n = 21) Mean ± SD	*P*-value
Age at acute ECT (years)	65.6 ± 11.6	59.6 ± 16.7	49.5 ± 14.9	51.6 ± 16.3	<0.001†
Age at onset of illness (years)	58.8 ± 12.6	51.0 ± 17.6	30.9 ± 15.4	33.5 ± 13.2	<0.001†
Number of episodes before acute ECT	1.52 ± 1.98	3.00 ± 3.90	4.88 ± 3.78	7.19 ± 11.2	<0.001†
Number of acute ECT sessions per course	8.96 ± 3.78	8.52 ± 4.02	9.86 ± 3.53	12.3 ± 10.10	0.044†
CGI-I after acute ECT	1.71 ± 0.63	1.73 ± 0.58	2.32 ± 0.54	1.90 ± 0.63	<0.001†
HDRS before acute ECT	28.7 ± 6.61¶	29.7 ± 6.86¶	—	—	0.399‡
HDRS after acute ECT	4.31 ± 2.01¶	4.85 ± 2.27¶	—	—	0.137‡
BPRS before acute ECT	—	—	49.7 ± 8.50¶	52.5 ± 6.26¶	0.154‡
BPRS after acute ECT	—	—	26.9 ± 8.19¶	28.3 ± 5.55¶	0.329§
IMI-equivalent dose before acute ECT (mg/day)	147.1 ± 112.1	66.9 ± 99.4	7.4 ± 30.2	27.4 ± 64.1	
IMI-equivalent dose after acute ECT (mg/day)	125.6 ± 108.5	64.5 ± 92.9	5.1 ± 22.1	19.6 ± 57.6	
CPZ-equivalent dose before acute ECT (mg/day)	57.2 ± 106.7	151.6 ± 233.1	1106.9 ± 618.5¶	977.2 ± 442.1¶	
CPZ-equivalent dose after acute ECT (mg/day)	38.6 ± 69.2	145.9 ± 207.5	829.0 ± 620.6¶	616.7 ± 407.4¶	

†Comparison among four groups by the Kruskal–Wallis test.
‡Comparisons between two groups by unpaired *t*-test.
§Comparisons between two groups by Mann–Whitney *U*-test.
¶Comparison between scores at pre-ECT and those at post-ECT by Wilcoxon signed-rank test.
BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impressions Improvement Scale; CPZ, chlorpromazine; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale-21; IMI, imipramine.

with unipolar depression and bipolar depression. Concerning 'number of episodes before an acute course of ECT,' the number of episodes in patients with unipolar depression was significantly less than those with other disorders, and the number of episodes in patients with bipolar depression was significantly less than that in patients with schizophrenia and schizoaffective disorder. In patients with schizophrenia, the degree of improvement in CGI-I after acute ECT was significantly lower than in other disorders. After acute ECT, HDRS scores in patients with unipolar depression and bipolar depression and BPRS scores in patients with schizophrenia and schizoaffective disorder were significantly improved, and CPZ-equivalent (mg/day) doses in patients with schizophrenia and schizoaffective disorder were significantly decreased. The number (%) of women with the disorders was 52 (62.7%) for unipolar depression, 48 (80.0%) for bipolar depression, 58 (63.7%) for schizophrenia, and 21 (95.2%) for schizoaffective disorder, with significantly greater proportions of women in the bipolar depression and schizoaffective disorder groups. In the bipolar depression group, 24 patients (40.0%) out of 60 were diagnosed as having bipolar I. Schizophrenia subtypes (n = 91) consisted of 35 (38.5%) catatonic patients, 10 (11.0%) undifferentiated patients, 32 (35.2%) patients with paranoia, 10 (11.0%) hebephrenic patients, and four (4.4%) residual patients. Schizoaffective disorder subtypes (n = 21) consisted of 13 (61.9%) depressive-type patients, six (28.6%) bipolar-type patients, and two (9.5%) unspecified patients.

Patient characteristics and comparisons in the use of maintenance ECT are summarized in Table 2. CGI-I after acute ECT showed a significant difference among the groups. After acute ECT, BPRS scores in patients with schizophrenia and schizoaffective disorder were significantly improved and CPZ-equivalent doses in patients with schizophrenia and schizoaffective disorder were significantly decreased. In bipolar depression patients, one patient out of three (33.3%) was diagnosed as having bipolar I. Schizophrenia subtypes (n = 10) consisted of five (50.0%) catatonic patients, four (40.0%) patients with paranoia, and one (10.0%) hebephrenic patient. Schizoaffective disorder subtypes (n = 6) consisted of five (83.3%) depressive-type patients and one (16.7%) bipolar-type patient.

Relapse-free rate in four psychiatric disorders (Fig. 1)

The relapse-free rate of all patients at 1 year was 56.3% (unipolar depression: 55.1%, bipolar depression: 54.7%, schizophrenia: 57.9%, schizoaffective disorder: 57.7%). There was no statistically significant difference in the relapse-free rate among these psychiatric disorders (P = 0.992).

Univariate analysis after response to acute ECT course in four psychiatric disorders (Table 3)

Regarding demographic and clinical factors, the number of mood or psychotic episodes before acute ECT was associated with a trend towards a lower risk of relapse (P = 0.082).

Regarding treatment factors after acute ECT, patients who were treated with maintenance ECT were at a significantly lower risk of relapse than those who were not treated with maintenance ECT (P = 0.012) and the use of mood stabilizers was associated with a trend towards a lower risk of relapse (P = 0.069).

Mood stabilizers were prescribed for 153 (60.0%) of 255 patients at the end of the current study (lithium: 91; valproate: 55; carbamazepine: 7; lamotrigine: 11; a combination of lithium and valproate: 4; a combination of lithium and lamotrigine: 6; a combination of valproate and carbamazepine: 1; a combination of lithium, valproate, and lamotrigine: 1). The attending physician selected mood stabilizers on a case-by-case basis. For example, lithium was selected in consideration of the risk of suicide, or selected for patients with emotional instability. However, when there was a history of overdose, lithium was not selected to avoid potentially serious nephropathy due to overdose. Valproate was selected for patients with decreased renal function and irritability. Lamotrigine was chosen for women who planned on pregnancy. For emotional instability with psychotic symptoms and psychomotor excitement, carbamazepine was chosen. If a patient was taking a mood stabilizer before the current episode, the attending psychiatrist either prescribed another mood stabilizer or added another mood stabilizer. For lithium, there were no statistically significant differences between patients either with or without relapse, in terms of mean dosage (relapse: 438.7 ± 215.5 mg/day; relapse-free: 420.0 ± 183.0 mg/day,

Table 2. Patient characteristics and comparisons in use of maintenance ECT

	Unipolar depression (n = 4) Mean ± SD	Bipolar depression (n = 3) Mean ± SD	Schizophrenia (n = 10) Mean ± SD	Schizoaffective disorder (n = 6) Mean ± SD	P-value
Age at acute ECT (years)	69.0 ± 11.9	70.7 ± 5.69	59.2 ± 11.8	55.8 ± 17.6	0.173†
Age at onset of illness (years)	58.8 ± 9.11	60.3 ± 11.7	37.6 ± 18.6	35.2 ± 16.1	0.077†
Number of episodes before acute ECT	2.00 ± 1.41	4.33 ± 4.51	6.50 ± 4.77	14.5 ± 18.8	0.122†
Number of acute ECT sessions per treatment	9.50 ± 4.12	8.67 ± 7.37	7.90 ± 3.45	16.0 ± 18.8	0.839†
CGI-I after acute ECT	2.00 ± 0.00	1.67 ± 0.58	2.60 ± 0.52	2.00 ± 0.63	0.046†
HDRS before acute ECT	28.8 ± 1.50	30.3 ± 2.08	—	—	0.291‡
HDRS after acute ECT	3.50 ± 1.00	3.00 ± 2.65	—	—	0.737‡
BPRS before acute ECT	—	—	51.8 ± 10.1§	53.8 ± 6.90§	0.672‡
BPRS after acute ECT	—	—	28.0 ± 7.53§	30.0 ± 5.50§	0.582‡
IMI-equivalent dose before acute ECT (mg/day)	278.1 ± 50.4	187.5 ± 187.5	7.50 ± 23.7	37.5 ± 91.9	
IMI-equivalent dose after acute ECT (mg/day)	271.9 ± 56.3	175.0 ± 188.7	1.25 ± 3.95	25.0 ± 61.2	
CPZ-equivalent dose before acute ECT (mg/day)	206.9 ± 188.6	75.8 ± 75.8	901.4 ± 752.8§	1067.1 ± 425.3§	
CPZ-equivalent dose after acute ECT (mg/day)	100.8 ± 79.5	60.6 ± 80.2	683.4 ± 690.8§	793.8 ± 427.4§	

†Comparison among four groups by the Kruskal–Wallis test.
‡Comparisons between two groups by unpaired t-test.
§Comparison between scores at pre-ECT and those at post-ECT by Wilcoxon signed-rank test.
BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impressions Improvement Scale; CPZ, chlorpromazine; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale-21; IMI, imipramine.

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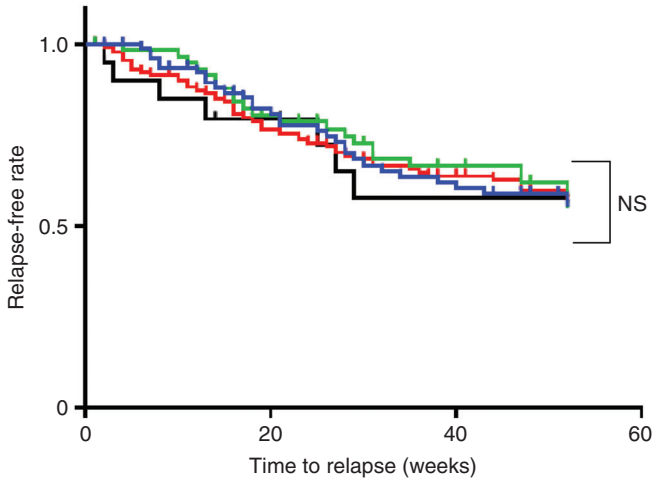

Fig.1 Kaplan–Meier cumulative survival curves for time to relapse for patients with (⊥) unipolar depression (n = 83), (⊥) bipolar depression (n = 60), (⊥) schizophrenia (n = 91), or (⊥) schizoaffective disorder (n = 21) after a response to an acute electroconvulsive therapy (ECT) course. The vertical bars on the curves indicate censored cases. NS, not significant.

P = 0.665) and blood levels (relapse: 0.52 ± 0.21 mEq/L; relapse-free: 0.48 ± 0.19 mEq/L, P = 0.461). For valproate, there were no significant differences between patients with and without relapse in terms of mean dosage (relapse: 547.6 ± 469.7 mg/day; relapse-free: 502.9 ± 231.2 mg/day; P = 0.640) and blood levels (relapse: 48.7 ± 21.0 μg/mL; relapse-free: 45.2 ± 13.4 μg/mL, P = 0.603). For carbamazepine, there were no significant differences between patients with and without relapse in terms of mean dosage (relapse: 450.0 ± 251.7 mg/day; relapse-free: 366.7 ± 251.7 mg/day; P = 0.683) and blood levels (relapse: 4.85 ± 1.50 μg/mL; relapse-free: 5.30 ± 2.43 μg/mL; P = 0.772). For lamotrigine, there were no significant differences between patients either with or without relapse in terms of mean dosage (relapse: 117.2 ± 74.1 mg/day; relapse-free: 112.5 ± 82.0 mg/day; P = 0.929).

There was no difference in the relapse-free rate between patients treated with antidepressants and those who were treated without antidepressants (P = 0.440). Antidepressants were prescribed for 57.3% of patients (tricyclic antidepressants: 21; selective serotonin reuptake inhibitors: 42; serotonin noradrenalin reuptake inhibitors: 27; other antidepressants [tetracyclic antidepressant, trazodone, mirtazapine]: 57). IMI-equivalent dose at the end of each investigation was not significantly different between patients who had relapsed and those who had not relapsed (data not shown). There was no significant difference in the relapse-free rate between patients treated with antipsychotics and those who were treated without antipsychotics (P = 0.901). Antipsychotics were prescribed for 69.0% of patients (second-generation antipsychotics: 204; first-generation antipsychotics: 55). The CPZ-equivalent dose at the end of each investigation was not significantly different between patients who had relapsed and those who had not relapsed (data not shown).

Table 3. Univariate Cox regression analyses of risk factors for relapse after a response to acute ECT

	HR (95%CI)	n	P-value
Demographic and clinical factors			
Female sex (base: male sex)	1.353 (0.821–2.229)	178	0.236
Age at acute ECT (years)	1.003 (0.990–1.016)	255	0.701
Diagnosis			
Unipolar depression	1.000	83	
Bipolar depression	0.976 (0.567–1.680)	60	0.930
Schizophrenia	1.055 (0.627–1.775)	91	0.841
Schizoaffective disorder	1.070 (0.470–2.437)	21	0.871
Age at onset of illness (years)	1.003 (0.992–1.014)	255	0.570
Number of episodes before acute ECT	1.029 (0.996–1.062)	255	0.082
Number of ECT sessions per acute treatment	1.019 (0.983–1.058)	255	0.307
CGI-S before acute ECT	1.235 (0.821–1.858)	255	0.311
CGI-S after acute ECT	1.070 (0.802–1.429)	255	0.644
CGI-I after acute ECT	1.237 (0.894–1.713)	255	0.200
GAF before acute ECT	0.988 (0.961–1.015)	255	0.378
GAF after acute ECT	0.996 (0.980–1.012)	255	0.639
Treatment factors after acute ECT			
Use of antidepressants	1.180 (0.775–1.798)	109	0.440
Use of antipsychotics	1.028 (0.661–1.600)	176	0.901
Use of mood stabilizers	0.674 (0.441–1.031)	153	0.069
Use of maintenance ECT	0.227 (0.072–0.719)	23	0.012

CGI-I, Clinical Global Impressions Improvement; CGI-S, Clinical Global Impressions Severity; CI, confidence interval; ECT, electroconvulsive therapy; GAF, Global Assessment of Functioning; HR, hazard ratio.

Multivariate analysis after response to acute ECT course in four psychiatric disorders (Table 4)

As a result of univariate analysis on items that could be considered relapse-preventative factors, three were found: a small number of psychiatric symptom episodes before acute ECT, the use of mood stabilizer, and the use of maintenance ECT. Multivariate analysis was performed keeping age, sex, and diagnosis constant, and it was found that a small number of psychiatric symptom episodes before acute ECT treatment (P = 0.003), the use of mood stabilizers (P = 0.030), and the use of maintenance ECT (P = 0.001) were significantly associated with preventing relapse. On the other hand, diagnosis was not

Table 4. Multivariate Cox regression analyses of risk factors for relapse after a response to acute ECT

	Adjusted HR (95%CI)	n	P-value
Number of episodes before acute ECT	1.067 (1.023–1.113)	255	0.002
Mood stabilizers			
Use of lithium	0.569 (0.348–0.931)	91	0.025
Use of valproate	0.512 (0.282–0.927)	55	0.027
Use of carbamazepine	0.978 (0.324–2.954)	7	0.969
Use of lamotrigine	1.343 (0.538–3.354)	11	0.528
Maintenance ECT	0.103 (0.025–0.418)	23	0.001
Age at acute ECT (years)	1.006 (0.990–1.021)	255	0.479
Female sex (base: male sex)	1.504 (0.893–2.534)	178	0.125
Diagnosis			
Unipolar depression	1.000	83	
Bipolar depression	0.898 (0.501–1.611)	60	0.718
Schizophrenia	1.122 (0.601–2.096)	91	0.718
Schizoaffective disorder	1.057 (0.379–2.944)	21	0.916

CI, confidence interval; ECT, electroconvulsive therapy; HR, hazard ratio.

associated with preventing relapse. As the use of mood stabilizers was found to be significantly associated with preventing relapse, individual agents found to be associated with preventing relapse included lithium ($P = 0.025$) and valproate ($P = 0.027$).

Relapse-free rate in use of maintenance ECT or mood stabilizers after response to acute ECT course (Fig. 2)

The relapse-free rate at 1 year was 90.0% with the use of maintenance ECT and the lack of use of mood stabilizers, 83.3% with the use of maintenance ECT and use of mood stabilizers, 57.0% with the use of mood stabilizers and lack of use of maintenance ECT, and 44.8% with the lack of use of maintenance ECT and lack of use of mood stabilizers. Relapse-free rate was significantly higher in the use of maintenance ECT and the lack of use of mood stabilizers ($P = 0.017$), in the use of both maintenance ECT and mood stabilizers ($P = 0.021$), and in the use of mood stabilizers and the lack of use of maintenance ECT ($P = 0.023$) compared with the lack of use of maintenance ECT and mood stabilizers. The relapse-free rate tended to be higher in the use of maintenance ECT and the lack of use of mood stabilizers compared to the use of mood stabilizers and the lack of use of maintenance ECT ($P = 0.066$).

Discussion

The current findings suggest that a small number of psychiatric symptom episodes before acute ECT, the use of mood stabilizers (including lithium and valproate), and the use of maintenance ECT could be shared factors associated with relapse prevention in four major disorders that respond to acute ECT. The significance of a small number of psychiatric symptom episodes before acute ECT observed in the current study is consistent with previous reports that repeated episodes correlated with the risk of relapse.[15,19] In remitted patients with mood disorders, those who had more previous episodes had a higher risk of relapse than those with fewer previous episodes, and the probability of another episode increased progressively with each successive episode.[20–22] Also, there was no significant difference in the relapse-free rate at 1 year after a response to ECT between patients with one of the four major psychiatric disorders. This may be related to the finding that the relapse-free rate in schizophrenia and schizoaffective disorder patients was as high as that of patients with mood disorders. The relapse-free rate of patients with schizophrenia and schizoaffective disorder was about 58% at 1 year. By contrast, the relapse-free rate of patients with schizophrenia in the current facility appears to be higher than other facilities. This could be because, according to patient data, 47.3% of patients with schizophrenia use mood stabilizers. Multivariate analysis demonstrated that 'diagnosis' was not significantly associated with relapse-free rate following ECT, which suggests that the four major disorders examined in the current study could be considered on a continuum, especially if limited after a response to ECT. It is possible, especially in schizophrenia, that differences in treatment outcome between the current facility and other treatment facilities could be due to the observation that the population of schizophrenia patients in the local area is not reflective of the wider population of schizophrenia patients.

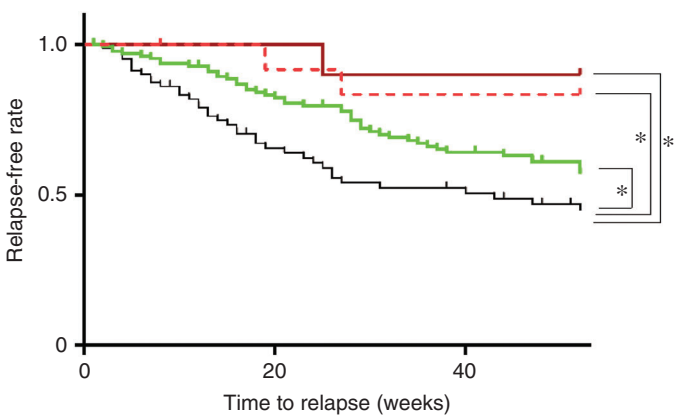

Fig.2 Kaplan–Meier cumulative survival curves for time to relapse in the use of maintenance electroconvulsive therapy (ECT) or use of mood stabilizers after a response to acute ECT course. The vertical bars on the curves indicate censored cases. *$P < 0.05$.
(—) Maintenance ECT (+) and mood stabilizers (–) ($n = 10$). (—) Maintenance ECT (+) and mood stabilizers (+) ($n = 13$). (—) Maintenance ECT (–) and mood stabilizers (+) ($n = 140$). (—) Maintenance ECT (–) and mood stabilizers (–) ($n = 92$).

It was previously reported that lithium used with antidepressant following ECT could be important in preventing relapse in patients with unipolar depression.[1] Either lithium or valproate use was associated with relapse prevention in patients with unipolar depression.[14] The use of mood stabilizers as adjunctive medications has also been associated with decreased symptoms relapse in schizophrenia patients.[15] Current treatment guidelines for schizophrenia do not directly endorse the use of mood stabilizers, but several reports suggest that mood stabilizers could be helpful in specific subpopulations of schizophrenic patients, such as those with catatonia,[23] anxiety/depression,[24] and hostility.[25] While a positive association between mood stabilizers and decreased symptoms relapse was shown in the current study, ECT is also effective for patients that show these symptoms, including catatonia, changes in affect,[11] tension, and hostility,[26] regardless of diagnosed disorder. Thus, the apparent efficacy of mood stabilizers for schizophrenia could in fact be due to ECT and it is speculated that the two treatments may share a common mechanism of action, for example, through mitochondrial-mediated synaptic plasticity.[27–29] High-quality clinical studies are needed to confirm that adjuvant medications, such as mood stabilizers, prevent symptoms relapse. If changes in neuroanatomy underlie the treatment efficacy of mood stabilizers, then perhaps noninvasive neuroimaging, such as magnetic resonance spectroscopy, could be used to demonstrate the underlying mechanism of action.

In a meta-analysis of prospective studies on maintenance ECT in unipolar depression, relapse-free rate was 79.5% at 1 year with maintenance ECT plus pharmacotherapy.[30] There are few studies on maintenance ECT in patients with only bipolar disorder – the relapse-free rate was 58% at 1 year in one prospective study on maintenance ECT.[31] According to a study of maintenance ECT in patients with schizophrenia, the relapse-free rate in the use of maintenance ECT plus antipsychotic (flupentixol) after a response to acute ECT was 60% at 6 months.[32] In the current study, the relapse-free rate in the use of maintenance ECT even with the lack of use of mood stabilizers at 1 year was as high as 90%. In addition, the current results suggest preventative factors associated with relapse in the four major disorders.

The relapse-preventive effect of a combination of a mood stabilizer and maintenance ECT following acute ECT has not been examined in the past. In the current study, mood stabilizers and maintenance ECT appear to have relapse-preventative effects by themselves, so a higher relapse-free rate could be expected when both are used together. However, as shown in Figure 2, this was not the case. The number of maintenance ECT cases examined in the current study was small and examination of more cases could show an additive effect.

Conclusions

The current study suggests that use of mood stabilizers, such as lithium and valproate, and maintenance ECT are common factors that are associated with the prevention of relapse after responding to ECT across four major psychiatric disorders.

Limitations

Limitations in the current study include: (i) a naturalistic and retrospective design, rather than a prospective, randomized controlled trial; (ii) variation in the severity of the disorders; (iii) exclusion of refractory

schizophrenia patients who received clozapine; (iv) inclusion of subjects who may have been 'refractory' (i.e., all patients in the current study received one or more trials of medication before starting ECT and were nonresponders to treatment, and most patients had experienced two or more mood or psychotic episodes); (v) use of maintenance ECT and various maintenance pharmacotherapies (because medication was selected based on the judgment of the attending psychiatrist, rather than in any systematic manner); (vi) absence of examination of other factors that could potentially affect relapse (such as adherence to medication instructions, patient recognition of the severity of their own illness, adverse life events, level of social support, and premorbid psychosocial functioning due to incomplete medical records); and (vii) basis of the current data on the findings from one hospital.

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Disclosure statement

The authors declare that they have no competing interests.

Author contributions

W.O. and M.T. conceived and designed the study; W.O. and K.I. collected the data; W.O. performed the statistical analysis; all authors contributed to the discussion; W.O. and M.T. revised the paper. All authors have read and approved the final version of this article.

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