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Factors associated with relapse after a response to electroconvulsive therapy in unipolar versus bipolar depression

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ABSTRACT

Background: While electroconvulsive therapy (ECT) treatment for depression is highly effective, the high rate of relapse is a critical problem. The current study investigated factors associated with the risk of relapse in mood disorders in patients in which ECT was initially effective.

Method: The records of 100 patients with mood disorders (61 unipolar depression, 39 bipolar depression) who received and responded to an acute ECT course were retrospectively reviewed. Associations between clinical variables and relapse after responding to acute ECT were analyzed. The Ethics Committee of NHO Kure Medical Center approved the study protocol.

Results: After one year, the percentage of relapse-free patients was 48.7%. There was no significant difference between patients with either unipolar or bipolar depression who were relapse-free (unipolar: 51.1%, bipolar: 45.5%, P=0.603). Valproate maintenance pharmacotherapy in unipolar depression patients was associated with a lower risk of relapse compared to patients without valproate treatment (multivariate analysis, hazard ratio: 0.091; P=0.022). Lithium treatment, reportedly effective for unipolar depression following a course of ECT, tended to lower the risk of relapse (hazard ratio: 0.378; P=0.060). For bipolar depression, no treatment significantly reduced the risk of relapse.

Limitations: The current findings were retrospective and based on a limited sample size.

Conclusions: The relapse-free rate was similar between unipolar and bipolar depression. Valproate could have potential for unipolar depression patients as a maintenance therapeutic in preventing relapse after ECT.

1. Introduction

Electroconvulsive therapy (ECT) is a highly effective acute treatment for severe forms of depression characterized by attempted suicide, catatonia, and resistance or intolerance to pharmacotherapy (American Psychiatric Association, 2001; Bailine et al., 2010; Sienaert et al., 2009). Even in patients with at least 1 failed medication trial, therapeutic effects of ECT appears in 58% of patients (Haq et al., 2015). Furthermore, ECT is highly efficacious for bipolar depression as well as unipolar depression (Haq et al., 2015; Schoeyen et al., 2015).

Although ECT is effective for both unipolar and bipolar depression, there is a high relapse rate for patients responding to an acute course of ECT (Kellner et al., 2006; Sackeim et al., 2001). In major depressive disorder, relapse rates within 12 months have been reported to be between 38 and 64%, even with pharmacotherapy following ECT (Birkenhager et al., 2004; Huuhka et al., 2004; Prudic et al., 2004; Rasmussen et al., 2009; Sackeim et al., 2001). In bipolar depression, the 12-month relapse rate was about 50%, with continuous pharma-

Abbreviations: ECT, Electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale-21; CGI-I, Clinical Global Impressions Improvement; IMI, imipramine; CPZ, chlorpromazine; SGA, second-generation antipsychotic; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor

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cotherapy, after a course of ECT (Medda et al., 2013). Therefore, in order to prevent relapse, robust clinical predictors associated with relapse after ECT for depression are needed.

A number of factors that could lead to relapse following ECT for depression have been suggested, including symptom resistance to medication, residual symptoms, female gender, psychosis, and comorbid conditions (Medda et al., 2013). Also, maintenance pharmacotherapies, including imipramine, nortriptyline, a combination of nortriptyline and lithium, and a combination of venlafaxine and lithium, appear to prevent relapse following ECT for unipolar depression (Atiku et al., 2015; Jelovac et al., 2013; Kellner et al., 2006; Prudic et al., 2013; Sackeim et al., 2001; van den Broek et al., 2006). In bipolar patients after an acute course of ECT, the risk of relapse was significantly decreased with post-ECT maintenance treatment of mood stabilizers and without reinstatement of antidepressants (Minnai et al., 2016). However, there is currently a dearth of information concerning the effect of maintenance pharmacotherapy following ECT for both unipolar and bipolar depression. To develop better treatment regimens for unipolar and bipolar depression, it is crucial to compare and contrast prognosis and predictors of relapse after ECT. The current retrospective study evaluated factors that could influence the risk of relapse in unipolar and bipolar depression after an efficacious course of ECT.

2. Methods

2.1. 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: 1) were diagnosed with unipolar depression or bipolar depression based on the International Classification of Diseases (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, 2) received an acute course of ECT between July 2005 and December 2013 at the NHO Kure Medical Center and 3) responded to the acute course of ECT.

Patients that were excluded were: 1) diagnosed with schizophrenia or schizoaffective disorder, 2) known to have a substance abuse problem, personality disorder, or preexisting neurological disorder such as Parkinson's disease or dementia and 3) did not respond to an acute course of ECT. If two or more acute ECT courses were received by the same patient during the study period (2005–2013), the observation period was defined as the time since completing the first acute ECT course.

Electroconvulsive therapy 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 received at least one trial of medication before starting ECT treatment and were nonresponders to such treatment. A clinical psychiatrist recommended ECT to each patient according to standards outlined by the American Psychiatric Association task force (American Psychiatric Association, 2001) and based on the patient's urgency and severity of illness.

Patient medical records were used to obtain data for the current study. Patient information was kept confidential and anonymous. The ethics committees of the study centers approved the current retrospective study.

2.2. Data source

Collected data included demographic variables, clinical variables, and maintenance psychotropic-related variables. Demographic and clinical variables included age, gender, age of onset of illness, number of mood episodes (excluding current episode), number of ECT sessions, and imipramine (IMI) equivalence and chlorpromazine (CPZ) equivalence (Inada and Inagaki, 2015) before the course of ECT. The classification of antipsychotics into first-generation antipsychotic and second-generation antipsychotic (SGA) categories was according to the literature (Tandon et al., 2008).

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, using the Hamilton Depression Rating Scale-21 (HDRS) and the Clinical Global Impressions Improvement (CGI-I) Scale score, which could be used for evaluation of not only the depressive state but also manic and mixed states. Responders to an acute course of ECT were defined as patients with a 50% decrease in HDRS, and 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 relapse/recurrence 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 re-hospitalization for depressive, manic, and mixed states. Recurrence/relapse is usually distinguished by the presence/absence of an achievement of full remission or the duration of remission. For the analysis in the current study, the two terms were consolidated as "relapse". The starting point of the current investigation was the last day of acute ECT treatment. The study end point for the relapse group was the time to relapse and the study end point for the relapse-free group was one year (52 weeks) after the final 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 drugs at the end of the investigation were calculated. Follow-up data were collected up until December 2014.

2.3. ECT treatment procedures

Electroconvulsive therapy treatments were performed at our facility and according to a previous report (Shibasaki et al., 2015). A modified ECT method with the cooperation of an anesthesiologist was used. Without premedication, patients received intravenous thyamylal sodium (2–3 mg/kg) and suxamethonium chloride (0.5–1.0 mg/kg) for anesthesia. The ECT device was the Thymatron System IV brief-pulse square-wave apparatus (Somatics Inc., Lake Bluff, IL, USA). Electrodes were positioned at the bilateral front-temporal region. 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 stimulus dose was set to one-half of the patient's age (Petrides and Fink, 1996). If an adequate electroencephalographic seizure occurred in one session, the stimulus energy of the next session was kept the same. When a missed or an inadequate seizure occurred, the patient was restimulated with 1.5–2 times the stimulus energy. The maximum number of stimulations for each treatment session was two. Electroconvulsive therapy 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 American Psychiatric Association guidelines, ECT was continued until the patient was asymptomatic or when the psychiatrist judged that the patient 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.