



## Research paper

# Rehospitalization and suicide following electroconvulsive therapy for bipolar depression—A population-based register study



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## A B S T R A C T

**Background:** Electroconvulsive therapy (ECT) is effective in bipolar depression, but relapse is common. The aim of the study was (i) to identify prognostic factors (ii) and to determine the impact of pharmacological approaches on the risk for rehospitalization or suicide.

**Methods:** This register study analyzed data from individuals treated with inpatient ECT for bipolar depression. Subjects were identified using the Swedish National Patient Register between 2011 and 2014 and the Swedish National Quality Register for ECT. Other national registers provided data on psychopharmacotherapy, socio-demographic factors, and causes of death. The endpoint was the composite of rehospitalization for any psychiatric disorder, suicide attempt or completed suicide (RoS). Cox regression was used to calculate hazard ratios in univariate and multivariate models.

**Results:** Data from 1255 patients were analyzed. The mean period of follow-up was 346 days.

A total of 29%, 41%, and 52% of patients reached RoS at 3, 6, and 12 months post-discharge. A history of multiple psychiatric admissions, lower age, and post-discharge treatment with antipsychotics or benzodiazepines was associated with RoS.

**Limitations:** Indication bias may have affected the results.

**Conclusions:** A history of multiple hospital admissions and lower age are key predictors of the composite of rehospitalization or suicide in patients treated with ECT for bipolar depression. Lithium might be effective. By contrast, antipsychotics and benzodiazepines were associated with increased risk, but possibly this finding was influenced by indication bias.

## 1. Introduction

Bipolar affective disorder is a life-long, recurrent condition characterized by episodes of depression and mania. Despite treatment advances, affected individuals often report lower quality of life indices than patients with unipolar depression, anxiety disorders, substance abuse, or chronic pain (Jansen et al., 2013). Relapse in bipolar affective disorder is common, with rates of 33–42% reported within 1 year of remission (Geddes and Miklowitz, 2013; Hamilton et al., 2016; Li et al., 2014). Severe episodes

often require hospitalization and suicide occurs in approximately 15–20% of patients with bipolar disorder (Gonda et al., 2012).

Pharmacotherapy reduces relapse rates and increases time to relapse. Here, the strongest evidence for relapse prevention has been reported for lithium (Geddes and Miklowitz, 2013; Joas et al., 2017), which also reduces suicide rates (Cipriani et al., 2013) and suicide attempts (Song et al., 2017).

Lithium, valproate, and several antipsychotics prevent manic relapse (Goodwin et al., 2016). Also, lithium, lamotrigine, and quetiapine

**Abbreviations:** ADHD, Attention deficit hyperactivity disorder; CGI-I, Clinical Global Impression-Improvement scale; cECT, continuation ECT; CI, Confidence interval; ECT, Electroconvulsive therapy; HR, Hazard ratio; ICD, International Classification of Diseases; OCD, Obsessive-compulsive disorder; Q-ECT, Swedish National Quality Register for ECT; RoS, Rehospitalization or suicide; SD, Standard deviation

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may prevent depressive episodes (Goodwin et al., 2016). There is limited evidence for the ability of antipsychotics to prevent relapse after treatment for an acute episode of bipolar depression (Lindstrom et al., 2017). Moreover, the use of antidepressants in bipolar affective disorder is controversial because of a potential risk of precipitating mania or mood instability (Minnai et al., 2016; Viktorin et al., 2014). Therefore, although modern treatments for mania are usually effective, there are fewer effective options in relapse prevention of bipolar depression.

Electroconvulsive therapy (ECT) is administered to bipolar depression patients who are not improved by pharmacotherapy, or have severe symptoms such as suicidal ideation or catatonic features. ECT is associated with high remission rates, particularly in cases with short symptom duration, psychotic symptoms, or older age (Haq et al., 2015). However, few robust data are available concerning prognosis in bipolar depression patients who require ECT. Although available research suggests that lower age, single marital status, the presence of comorbid psychiatric disorders, and a higher number of ECT sessions are associated with an increased risk of relapse following a successful course of ECT for depression (Itagaki et al., 2017; Jelovac et al., 2013; Lisanby et al., 2008; Prudic et al., 2013; Rosen et al., 2016; Sackeim et al., 2001), most of the studies have investigated mixed unipolar and bipolar cohorts.

The aims of the present study were (i) to identify prognostic factors after ECT for bipolar depression and (ii) to determine the impact of pharmacological approaches on the risk of rehospitalization or suicide (RoS) in patients treated with inpatient ECT for bipolar depression in Sweden between January 2011, and December 2014.

## 2. Methods

### 2.1. Study design

In this register-based observational study, subjects were identified using the Swedish National Patient Register. Inclusion criteria were: (i) inpatient management in a Swedish psychiatric hospital between January 2011, and December 2014 (index admission); (ii) discharge diagnosis of bipolar disorder, current episode depressed (F31.3–5) according to International Classification of Diseases (ICD)–10 criteria (Socialstyrelsen, 1997); and (iii) treatment with ECT for bipolar depression during the index admission. In cases of multiple admissions during the period of observation, only data concerning the first admission were analyzed. Clinical and socio-demographic data for the included subjects were obtained from the Swedish National Quality Register for ECT (Q-ECT); the Swedish Prescribed Drug Register; the Longitudinal Integration Database for Health Insurance and Labour Market Studies; and the Swedish Causes of Death Register. Statistics Sweden provided a key based on national personal identification numbers to enable linkage. Patients were followed from date of discharge until rehospitalization, suicide or non-suicidal death, or the end of the observation period (December 31, 2014). Analyses were performed to determine predictors of the composite endpoint: RoS. Factors of interest were socio-demographic variables, treatment prior to index admission, symptom severity, number of ECT sessions during index admission, and post-ECT psychopharmacotherapy.

### 2.2. Data sources and variables

The Swedish National Patient Register is a mandatory register of all public and private hospital admissions in Sweden. The register was established in 1964 and since 1987 it has very high coverage. Currently, more than 99% of all hospital discharges are registered (Ludvigsson et al., 2011). Validation studies have shown that 85–95% of the diagnoses in this register are valid (Ludvigsson et al., 2011). Information in the register includes the dates and length of hospital admissions, diagnoses, ECT treatment, and compulsory care.

Patients assigned one or more of the following ICD-10 diagnoses before or during index admission were classified as having a comorbid

psychiatric disorder: (i) anxiety disorder (F41); (ii) obsessive-compulsive disorder (OCD) (F42); (iii) attention deficit hyperactivity disorder (ADHD) (F90); (iv) autism (F84.1 or F84.5); (v) personality disorder (F60); (vi) or substance abuse (F10-F16 and F18-F19).

The Swedish National Quality Register for ECT (Q-ECT) was established in 2008 and became nationwide in 2011. The coverage increased from 31.1% of all patients treated with ECT in 2011, to 78.6% in 2012, and 89.8% in 2015 (Nordenskjold, 2017). The Q-ECT was accessed to complement the Swedish Patient Register data on dates for ECT and compulsory care. Variables derived from the Q-ECT were number of ECT sessions, index- or continuation-ECT (cECT) series, stimulus parameters, seizure duration, and response to ECT. cECT was defined as ECT sessions planned to take place once a week or less frequently. Response status was derived from the Clinical Global Impression-Improvement scale (CGI-I) within one week after index ECT. The CGI-I is a seven-point scale used by the clinician to evaluate response to treatment. A score of 1 indicates “very much improved”, and a score of 2 indicates “much improved”. For the purposes of the present study, response to ECT was defined as a CGI-I score of 1 or 2 (Guy, 1976). Missing Q-ECT data are indicated in Table 2.

The Swedish Prescribed Drug Register was established in its current form in 2005. The register records all medicines prescribed by a physician and collected from a pharmacy for outpatient use for all residents in Sweden (Wallerstedt et al., 2016). For the purposes of the present analyses, psychopharmacological treatments were categorized into the following nine groups: lithium, lamotrigine, antipsychotics (with the exception of quetiapine, alimemazine, and levomepromazine), quetiapine, valproate, antidepressants, benzodiazepines, anxiolytics (hydroxyzine, prometazine, alimemazine, levomepromazine, and buspirone), and central stimulants. Treatment prior to index admission was defined as medicines collected between 2005 and 1 day preceding index admission. In the Swedish health insurance system, medicines that are collected every 3 months or less are charged at the lowest possible cost. Therefore, post-discharge treatments were defined as psychopharmacological agents collected by a patient during index admission and within 100 days of discharge. In cases where the patient was rehospitalized, or died within 100 days of discharge, information on medicines collected immediately prior to index admission was included to ensure that the total number of days prior to and post admission always equaled 100.

The Longitudinal Integration Database for Health Insurance and Labour Market Studies contains information concerning education, marital status, and number of children in the household. All Swedish residents aged 16 years and above are included (SCB, 2016). Individuals who cohabit with a partner were classified as being in a relationship, irrespective of legal marital status. Individuals living in the same household as children aged 19 years or below were classified as having children. Some register data were missing from this database for the present cohort (2–5 cases, depending on the variable). These patients were imputed to the largest category for the respective variable.

The Causes of Death register includes information on dates and causes of death for all Swedish residents since 1961. In this study, deaths were classified as suicidal or non-suicidal.

### 2.3. Study endpoint (RoS)

The endpoint of the study was defined as the composite of rehospitalization for any psychiatric disorder (chapter F), rehospitalization due to a suicide attempt (T36-65, X6–84, or Y1-34), or completed suicide (X6-84 Y1-34). This endpoint is referred to as rehospitalization or suicide, RoS.

### 2.4. Statistical analyses

A Kaplan–Meier estimator was used to calculate the probability of remaining without reaching RoS. Cox regression analysis was used to identify variables associated with RoS. Both univariate and multivariate

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