Original Article

Electroconvulsive therapy, depression severity and mortality: Data from the Danish National Patient Registry

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Abstract

Background: The effects of electroconvulsive therapy are usually estimated from changes in depression scales from studies with relatively small patient samples. Larger patient samples can be achieved from epidemiological registers, which provide information on other social and clinical predictors, results and risks.

Aims: To examine whether depression severity predicts the use of electroconvulsive therapy, risk of re-hospitalization, suicidal behaviour and mortality following electroconvulsive therapy in patients with major depression.

Methods: A cohort of 92,895 patients diagnosed with single or recurrent depression between 2005 and 2016 in the Danish National Patient Registry was followed for electroconvulsive therapy and adverse outcomes. Associations between electroconvulsive therapy and outcomes were analysed using Cox regression.

Results: A total of 5004 (5.4%) patients were treated with electroconvulsive therapy. Depression severity was the strongest predictor of electroconvulsive therapy. Electroconvulsive therapy was used more frequently above age 70, in those better educated or married, whereas comorbid alcohol abuse or history of prior stroke at study entry were associated with lower rates. Electroconvulsive therapy was associated with lower mortality. The adjusted hazard ratio for the association between electroconvulsive therapy and suicide in patients with mild depression was 6.99 (3.30–14.43), whereas it was 1.10 (0.55–2.20) in those with severe depression and psychotic symptoms. A similar pattern was seen for emergency contacts and attempted suicide.

Conclusions: Electroconvulsive therapy was associated with lower all-cause mortality and the relative risk for re-hospitalization and attempted and committed suicide was lowest in patients with the most severe depression. Electroconvulsive therapy is an important treatment, with significant public health benefits, for patients with severe depression.

Keywords

Electroconvulsive therapy, ECT, psychotic depression, depression severity, patient registry

Introduction

Electroconvulsive therapy (ECT) is an effective treatment for patients with severe or medication-resistant depression, including those with psychotic features (Husain et al., 2008). In fact, remission rates are higher and occur earlier in psychotic depressed patients compared to nonpsychotic depressed patients (Petrides et al., 2001). However, in most studies, remission has been estimated based on changes in depression scales in relatively small patient samples, with some, or unreported, loss to follow-up and large heterogeneity across studies (Haq et al., 2015). Larger patient samples can be achieved from epidemiological registers, but these do not provide direct measures of response or remission. Instead, they rely on available proxies such as suicide, suicide attempts, death or hospital readmission. A recent study of 2486 patients treated with ECT at nine United States (US) general hospitals between 2015 and 2017 (Slade et al., 2017) indicated that ECT was associated with reduced short-term psychiatric inpatient readmissions among inpatients with severe affective disorders, but this study did not evaluate the influence of psychotic features, or whether readmissions differed compared to patients not treated with ECT. A large study of case records of patients who died from natural causes within a month of ECT showed no association with ECT treatment (total n = 99,728 treatments) (Ostergaard et al., 2014). Two meta-analyses (Duma et al., 2019; Torring et al., 2017) and recent cohort studies (Blumberger et al., 2017; Dennis et al., 2017) have shown that ECT is associated with a low likelihood of immediate or short-term death, and the few available studies have indicated that

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patients treated with ECT compared to other patients have decreased long-term mortality from all, and natural, causes (Avery and Winokur, 1976; Munk-Olsen et al., 2007; Philibert et al., 1995). However, no studies have examined whether depression severity influences the effect of ECT on health outcomes.

Thus, the aim of this study was to examine the importance of depression severity as a predictor of the use of ECT and on the risk of re-hospitalization, suicidal behaviour and mortality in a large, nation-wide sample of all patients with a first-time hospital diagnosis of major depression. We tested the hypothesis that indicators of depression severity would be strong predictors of ECT use, whereas the influence of social factors would attenuate after multiple adjustments. We also hypothesized that ECT would be associated with higher rates of re-hospitalization, suicidal behaviour and mortality.

Methods

Study population

All citizens in Denmark with a first-time hospital contact due to single episode or recurrent depression between 1 January 2005 and 31 December 2015 were included in this study. In total, 93,118 in- or outpatients over 10 years of age were identified by record linkage with the Danish National Patient Registry (DNPR) (Schmidt et al., 2015) using the International Classification of Diseases (ICD) version 10 (F32.0–F32.3 or F33.0–F33.3) among patients with no prior admission for manic episodes (F30), bipolar disorder (F31), schizophrenia (F20) or chronic, atypical or non-specified affective disorders (F34, F38 or F39). In total, 223 patients were excluded from the analyses because of missing data on date of birth, or because they were younger than 10 years old, leaving 92,895 patients for analysis.

Measures

ECT (treatment). In Denmark ECT is administered at 21 hospital departments and the mean number of patients treated per year is around 1700, corresponding to a treatment rate of 3.6 per 10,000 inhabitants. Depression is the main indication for ECT treatment (approximately 75%) (Hundrup et al., 2016). From the DNPR we also retrieved information on all ECTs registered for patients; ECT treatment was counted from the date of first ECT. The codes and classifications have been described in detail elsewhere (Hundrup et al., 2016). The number of ECTs was counted from study entry until censoring.

Subsequent outcomes. We studied the following outcomes, which we considered proxy measures for treatment response: re-hospitalization with major depression as main diagnosis as inpatient or emergency ward patient, suicide attempts, suicide and all-cause mortality. Information on re-hospitalizations was obtained from the DNPR. This included data on date of admission, diagnosis and patient type (inpatient (full or daytime), outpatient, or emergency). *Suicide attempt* was defined as a discharge diagnosis of T39, T42, T43, X60–X84 (excluding X65) in the DNPR. We also used the contact code for 'deliberate self-harm' (code 4), but as this code is not used consistently, we also used three groups of poisoning (T39, T42, T43), which are most often deliberate self-poisoning. Mortality data were retrieved from the Causes of Death Registry. *Suicide* was defined as a main or contributory diagnosis of X60–X84 (excluding X65) in the Causes of Death Registry.

Depression severity, sociodemographic and clinical covariables. Depression severity was categorized as: mild (ICD-10: F32.0, F33.0), moderate (ICD-10; F32.1, F33.1) or severe depression with psychotic features (ICD-10: F32.3, F33.3) or without psychotic features (ICD-10; F32.2, F33.2). From the DNPR we also obtained information on whether the patients were diagnosed with depression at psychiatric or medical ward inpatient (full or daytime), outpatient or emergency contact. Because many of those diagnosed with depression in an emergency room were admitted as inpatients afterwards, we decided to collapse these entities into one, and use a dichotomized variable indicating patient type as either 'inpatient' (fulltime hospitalization, day-treatment or emergency room contact) or 'outpatient' (seen in hospital clinics). Besides these indicators of depression severity, the following sociodemographic and clinical variables measured at the first hospital contact (baseline) were included: gender, age, level of education, marital status, comorbid alcohol abuse, personality disorder, history of stroke and attempted suicide as well as medication and number of hospitalizations 1 year before study entry. Information on gender, age, ethnicity and marital status was obtained from the Danish Civil Registration system, whereas data on highest achieved educational level was from the Population's Education register, which is based on reports from all educational institutions in Denmark. Educational level was categorized into three groups (low, middle and high). Information on prescription use of psychotropic drugs the year before study entry (drugs for anxiety, insomnia, depression, psychosis and relapse prevention) was obtained from the Danish National Prescription Registry using Anatomical Therapeutic Chemical codes.

Statistical analysis

First, we examined associations of depression severity, sociodemographic and clinical variables with first-time ECT using Cox proportional hazard regression models (expressed as hazard ratio (HR) and 95% confidence intervals). Patients were followed from study entry (the date of first registered depression diagnosis) until date of first ECT, emigration, death or end of follow-up (31 October 2016), whichever came first. Secondly, we also used Cox proportional hazard regression models to study the associations between first ECT and each study outcome in separate models. In these analyses, patients were followed from study entry until the date of first registration of outcomes of interest (re-hospitalization, attempted and committed suicide and all-cause mortality), emigration, death, or end of follow-up (31 October 2016), whichever came first. To account for potential immortal time bias, ECT was entered as time-dependent variables, so that individuals initiating treatment changed exposure status from non-exposed to exposed at the date of first ECT. To explore if any risk varied during follow-up, we specifically examined the rates for the first 365 days and more than 365 days after first ECT by splitting the data on follow-up time. Potential interactions with depression severity and ECT were first explored in stratified

analyses and tested by including an interaction term using likelihood ratio tests. This showed a significant interaction for emergency contacts and suicidal behaviour and consequently, we presented stratum-specific estimates. To illustrate the potential impact of depression severity on the outcomes, a combined variable with depression severity and ECT was analysed. The proportional hazard assumption was examined graphically and was not found to be violated. The analyses were performed in STATA_15.

Results

Depression severity and ECT

Of the 92,895 patients, 5004 (5.4%) were treated with ECT (Table 1). The first ECT was administered after a median of 35 days (interquartile range (IQR) 9–223 days) since first admission. The median number of ECT sessions was 10 (IQR 7–16). Table 1 also gives the crude and mutually adjusted estimates (HR) for the associations of depression severity and other covariates with ECT. Depressed patients treated with ECT were more often older than 70 years, better educated and married. ECT was also associated with baseline treatment with drugs for depression, lithium or drug for anxiety or insomnia. We explored whether ECT use and predictors of ECT varied when analyses were stratified according to depression severity. This showed that ECT was initiated much earlier in patients with severe depression (Supplementary Table 1), whereas predictors of ECT use were relatively similar (Supplementary Table 2).

ECT and subsequent re-hospitalization, suicidal behaviour and mortality

During follow-up 29,236 (31.7%) patients were readmitted as inpatients, whereas an additional 10,330 (11.1%) had at least one emergency ward contact. A total of 598 (0.6%) patients committed suicide and 3923 (4.2%) attempted suicide. In total, 12,211 (13.1%) patients died during follow-up between 2005 and 2016. Supplementary Table 3 shows mean follow-up and number of outcomes in patients treated with ECT or not. After adjustment for age, ECT was associated with higher risk of re-hospitalization and suicidal behaviour, but with lower all-cause mortality. The risk of re-hospitalization was higher during the first year than at later follow-up (Table 2). Adjustment for the potential confounding covariables attenuated the HR (last column in Table 2). Next, we stratified the analyses according to depression severity (Table 3). This showed that the HRs for re-hospitalization and all-cause mortality were similar across the four categories of depression severity. However, the risk of an emergency contact or suicidal behaviour in patients treated with ECT seemed to decrease with depression severity. Thus, the adjusted hazard ratio for the association between ECT and suicide in patients with mild depression was 6.99 (3.30–14.43), whereas it was 1.10 (0.55–2.20) in those with severe depression with psychotic symptoms. A similar pattern was seen for emergency contacts and attempted suicide (Table 3). Although the HRs for mild depression were imprecisely estimated due to the few outcomes in the ECT group, the interaction terms were significant. The non-parallel lines for ECT versus non-ECT in Figure 1 illustrate these interactions graphically.

Discussion

In this register-based cohort study of patients with a first-time hospital contact diagnosis of single or recurrent depression, we found, as expected, that ECT was used most often in patients with more severe depression. This aligns with the recommendations in the guidelines on the indications for ECT (American Psychiatric Association, 2001) and the well-known particularly high rates of response/remission in psychotic depression (Petrides et al., 2001). Also, higher use in the elderly is well justified, because ECT works particularly well in this age group (Spaans et al., 2015).

Contrary to our hypothesis, we found that independent of depression severity, patients with lower education or unmarried status were less likely to receive ECT. Inequality in ECT prescription by socioeconomic status has been described in the US (Case et al., 2012; Magid and Rohland, 2016), but is somewhat surprising to find in Denmark where there is free and equal access to all treatment. This may reflect more support and trust of psychiatric care in married, well-educated patients or the prescribing physician's conceptualization of the nature of the condition in those patients.

As expected, ECT was associated with higher rates of re-hospitalization and suicidal behaviour even after adjustment for a number of social and clinical determinants. However, the relative risk varied with depression severity, with the lowest HR among patients with the most severe depression. Because increased severity of depression is known to be associated with increased risk of suicide (Hawton et al., 2013), this probably reflects the particular efficacy of ECT for more severe depression, especially the psychotic subtype. Hence, an HR for the association between ECT and suicidal behaviour close to one, observed in patients with psychotic depression, indicates that ECT is most effective in this group of patients, or that the risk estimate is less biased from residual confounding. Thus, by repeating the analyses with patients stratified according to depression severity, we aimed to reduce the heterogeneity, and thereby potential risk, of confounding by indication within strata.

Normally ECT is not offered to patients with mild depression as reflected in the few ECTs in this group. The 'mild' category is probably due to diagnostic uncertainty, hence the long time to first treatment (Supplementary Table 1). Although predictors of ECT did not vary with depression severity, we cannot exclude that the few patients having ECT in the 'mild group' represent a more selected sample from this very heterogenous group and that some of the difference in HRs could be due to residual confounding and lack of precision.

Furthermore, ECT was associated with a decreased rate of all-cause mortality, even after adjusting for a number of patient characteristics and clinical variables. This was contrary to our hypothesis, but appears to be a consistent finding in register-based ECT studies (Avery and Winokur, 1976; Munk-Olsen et al., 2007; Philibert et al., 1995). It may be due to confounding from selection of healthier patients for ECT (Bharadwaj and Grover, 2007), but could, in theory, be causally mediated through effects on disease mechanisms (Avery and Winokur, 1976; Kranaster et al., 2019).

The strength of this study is the use of nation-wide population-based registers in a country with free access to healthcare, which provided us with a large, relatively unselected group of patients. The Danish person identification numbers make it

Table 1. Association (hazard ratios and 95% confidence intervals (CI)) between depression severity, other baseline characteristics and subsequent electroconvulsive therapy (ECT) in patients with single episode or recurrent depression.

	Total number	Number treated with ECT. n (%)	Crude hazard ratio (95% CI)	Mutually adjusted Hazard ratios (95% CI)
Total	92,895	5004 (5.4)		
Severity of depression				
Mild	20,879	348 (1.7)	1	1
Moderate	52,254	1726 (3.3)	1.99 (1.78–2.24)	1.81 (1.61–2.05)
Severe without psychotic	15,014	1762 (11.7)	7.49 (6.68–8.41)	5.53 (4.91–6.20)
Severe with psychotic symptoms	4748	1168 (24.6)	17.38 (15.42–19.59)	10.75 (9.51–12.15)
Type of admission				
Outpatient	52,606	1197 (2.2)	1	1
Inpatient	35,285	3807 (9.7)	4.51 (4.22–4.81)	3.85 (3.60–4.11)
Type of contact				
Somatic	12,161	184 (1.51)	1	1
Psychiatric	80,753	4820 (5.97)	3.86 (3.33–4.48)	4.49(3.86–5.24)
Number of hospitalizations				
1	53,368	2173 (4.1)	1	1
2–4	32,868	2383 (7.3)	1.83 (1.73–1.94)	1.34 (1.26–1.42)
5+	6659	448 (6.7)	1.79 (1.61–1.98)	1.16 (1.04–1.29)
Comorbid personality disorder				
No	89,867	4833 (5.4)	1	1
Yes	3028	171 (5.7)	1.03 (0.89–1.21)	1.00 (0.85–1.15)
Comorbid alcohol abuse				
No	85,087	4692 (5.5)	1	1
Yes	7808	312 (4.0)	0.71 (0.63–0.79)	0.63 (0.56–0.71)
Prior suicide attempt				
No	85,105	4574 (5.4)	1	1
Yes	7790	430 (5.5)	1.00 (0.96–1.11)	0.98 (0.88–1.08)
Prior stroke				
No	88,711	4791 (5.4)	1	1
Yes	4184	213 (5.1)	1.01 (0.88–1.16)	0.72 (0.64–0.84)
Drugs for depression (N06A)				
No	32,518	1129 (3.5)	1	1
Yes	60,377	3875 (6.4)	1.85 (1.74–1.98)	1.33 (1.25–1.51)
Drugs for psychosis (N05A) (N05AX)				
No	82,081	4068 (5.0)	1	1
Yes	10,814	936 (8.7)	1.81 (1.69–1.94)	1.15 (1.06–1.23)
Lithium				
No	92,581	4933 (5.3)	1	1
Yes	314	71 (22.6)	4.81 (3.81–6.01)	3.10 (2.48–4.00)
Drugs for anxiety and insomnia				
No	60,706	2105 (3.5)	1	1
Yes	32,189	2899 (9.0)	2.68 (2.53–2.83)	1.45 (1.31–1.54)
Sociodemographic variables				
Gender				
Men	34,837	1998 (5.7)	1	1
Women	58,058	3006 (4.2)	0.89 (0.84–0.94)	1.01 (0.95–1.06)
Age at baseline (years)				
10–29	29,504	561 (1.9)	1	1
30–49	31,833	1605 (5.0)	2.66 (2.43–2.95)	1.76 (1.68–1.97)
50–69	18,321	1719 (9.4)	5.25 (4.77–5.78)	3.03 (2.79–3.42)
70–101	13,237	1119 (8.5)	5.15 (4.66–5.71)	4.71 (4.13–5.57)

(Continued)

Table 1. (Continued)

	Total number	Number treated with ECT. n (%)	Crude hazard ratio (95% CI)	Mutually adjusted Hazard ratios (95% CI)
Educational status				
Basic	38,792	1633 (4.2)	1	1
Middle	34,321	2113 (6.2)	1.47 (1.38–1.57)	1.30 (1.22–1.39)
High	13,342	1027 (7.7)	1.86 (1.72–2.01)	1.36 (1.27–1.48)
Unknown	6440	231 (3.4)	0.87 (0.76–1.00)	0.77 (0.65–0.90)
Marital status				
Married	31,818	2585 (8.1)	1	1
Unmarried	41,943	1280 (3.1)	0.36 (0.34–0.38)	0.83 (0.77–0.90)
Divorced	11,004	562 (5.1)	0.62 (0.56–0.68)	0.68 (0.62–0.74)
Widowed	7462	52 9(7.1)	0.94 (0.85–1.03)	0.82 (0.74–0.91)

Table 2. Hazard ratios and 95% confidence intervals (CI) for associations between electroconvulsive therapy (ECT) and re-hospitalization, suicidal behaviour and all-cause mortality in 92,895 patients with first time single episode or recurrent depression.

Outcome	Not treated with ECT N (rate per 1000 py)	Treated with ECT N (rate per 1000 py)	Age adjusted hazard ratio (ECT vs no ECT)	Age adjusted hazard ratio follow up 0–1 years (ECT vs no ECT)	Age adjusted hazard ratio follow up 1– 11.3 years (ECT vs no ECT)	Adjusted hazard[c] ratio follow up 0– 11.3 years (ECT vs no ECT)
In patient re-hospitalization[a]	28,092 (73.0)	1144 (147.0)	1.83 (1.73–1.95)	2.24 (2.08–2.42)	1.39 (1.26–1.53)	1.34 (1.26–1.43)
Re-admission at emergency clinic[a]	9709 (21.7)	621 (34.4)	2.39 (2.20–2.60)	2.45 (2.20–2.81)	2.32 (2.05–2.64)	2.22 (2.04–2.43)
Suicide attempts[a]	3653 (8.3)	270 (11.9)	2.34 (2.07–2.66)	2.25 (1.81–3.22)	2.37 (2.03–2.77)	1.90 (1.66–2.08)
Suicide[b]	495 (1.0)	103 (3.8)	3.82 (3.07–4.76)	4.48 (2.28–6.14)	3.45 (2.55–4.67)	2.49 (1.98–3.14)
All-cause mortality[a]	11,409 (22.8)	809 (29.6)	0.72 (0.67–0.77)	0.81 (0.65–0.96)	0.70 (0.64–0.76)	0.81 (0.74–0.88)

py: person years.
[a]Followed from 2005 through October 2016; [b]followed from 2005 through 2014; [c]adjusted for age, gender, education, marital status, patient type, comorbid alcohol abuse, personality disorder, previous stroke, drugs for depression, psychosis, anxiety, insomnia and relapse prevention.

Table 3. Adjusted[a] hazard ratios and 95% confidence intervals (CI) for the association between electroconvulsive therapy (ECT) and re-hospitalization, suicidal behaviour and all-cause mortality in relation to depression severity in patients with first time single episode or recurrent depression.

Outcome/exposure	Mild	Moderate	Severe without psychotic features	Severe with psychotic features
In patient re-hospitalization/ ECT vs no ECT	1.63 (1.17–2.34)	1.63 (1.44–1.86)	1.54 (1.39–1.74)	1.46 (1.29–1.65)
Re-admission at emergency clinic/ ECT vs no ECT	3.43 (2.45–2.79)	2.48 (2.12–2.90)	2.27 (1.97–2.61)	1.81 (1.47–2.23)
Suicide attempts/ ECT vs no ECT	2.69 (1.65–4.50)	2.42 (1.95–3.00)	2.06 (1.65–2.56)	1.40 (0.99–1.99)
Suicide/ ECT vs no ECT	6.99 (3.30-14.43)	3.37 (2.31–4.91)	2.84 (1.95–4.15)	1.10 (0.55–2.20)
All-cause mortality/ ECT vs no ECT	0.92 (0.71–1.14)	0.83 (0.73–0.95)	0.96 (0.85–1.09)	0.70 (0.58–0.82)

[a]Adjusted for age, gender, education, marital status, patient type, comorbid alcohol abuse, personality disorder, previous stroke, drugs for depression, psychosis, anxiety, insomnia and relapse prevention.

possible to link individual patient data with different registers and obtain complete data on ECT and follow-up information for hospital admissions and death. This also allowed us to include a reference group of patients not treated with ECT, which previous studies of readmission and suicide following ECT have lacked. The Danish medical registers contain accurate information on specific diagnoses and mortality, however, information on effectiveness of treatments in terms of intermediate outcomes, such as changes in symptom severity, is limited. Thus, our measure of re-hospitalization could not discriminate between readmissions due to recurrence or worsening of depression, or readmission, for example, for maintenance ECT. To account for this, we restricted our analyses to inpatient or emergency contacts. Furthermore, the outcomes might also reflect the general quality of care. In the analyses we also adjusted for several potential confounding factors, but we cannot preclude the possibility of residual confounding associated with the selection of patients for ECT. All data were register based and the information on education, depression severity and comorbidities at baseline might not fully capture the patients' social status, social relations, symptom severity and

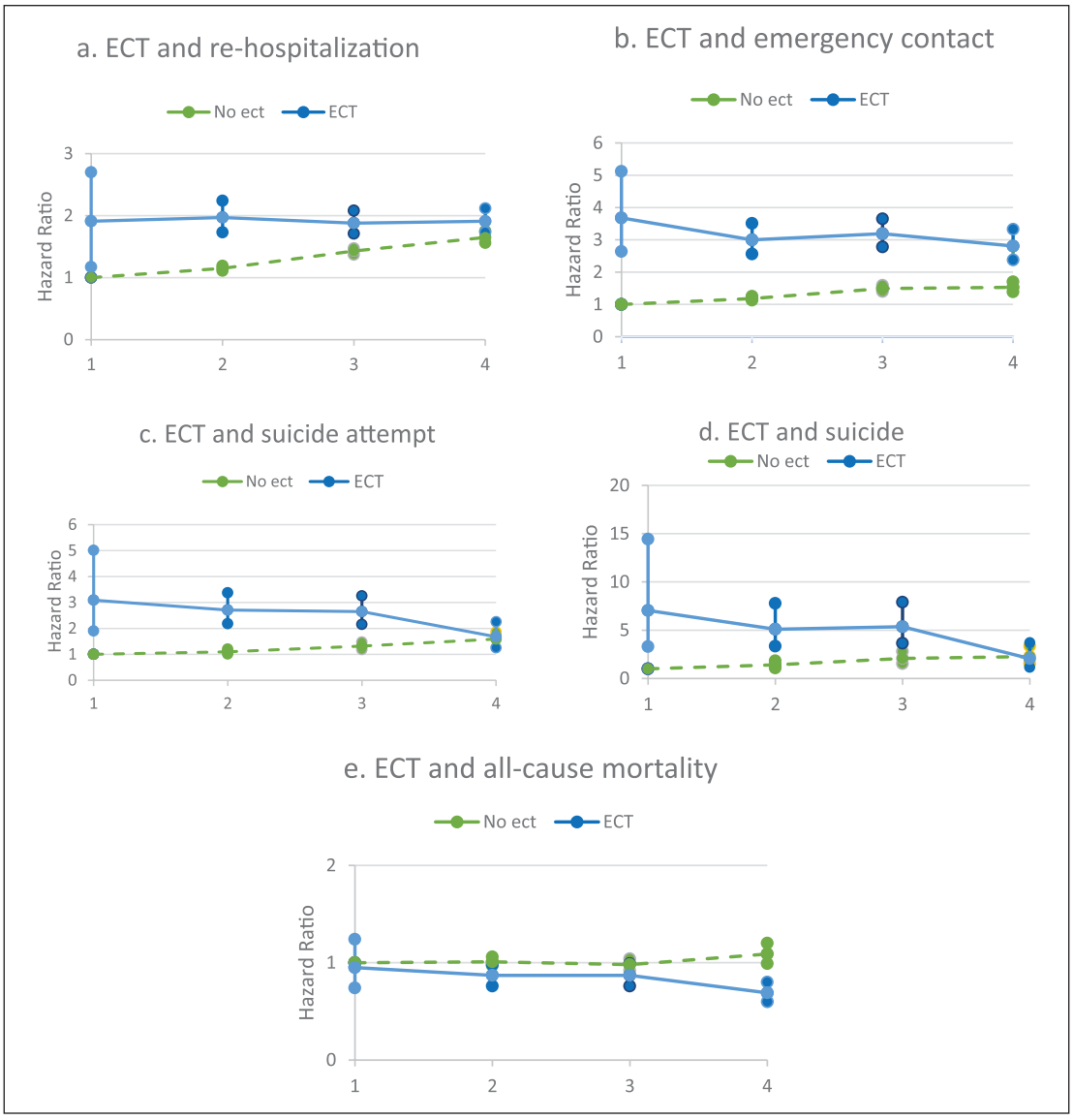

Figure 1. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) of the association between electroconvulsive therapy (ECT) and five outcomes: (a) re-hospitalization; (b) emergency contact; (c) attempted suicide; (d) committed suicide; and (e) all-cause mortality and interaction with depression severity. No ECT and mild depression was the reference and the analyses were adjusted for covariates. Depression severity (1 = mild; 2 = moderate; 3 = severe without psychotic symptoms; 4 = severe with psychotic symptoms).

somatic health status, which might influence the decision to prescribe ECT as a treatment modality and, later, the risk of hospitalization or suicidal behaviour.

In conclusion, the present study demonstrates that ECT was associated with decreased all-cause mortality, especially in the most severely depressed patients. Because ECT is, for any degree of severity, only used in the most unstable treatment resistant patients, it will be expected that ECT use compared to no use is associated with higher rates of re-hospitalization, suicide and suicidal behaviour. However, we found that the relative rates of those outcomes decreased with increasing depression severity. Finally, independent of depression severity, ECT is more commonly prescribed to married patients with higher education. These findings add to the evidence base of ECT as an important treatment, with significant public health benefits, for patients with severe depression.

Author note

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Supplemental material

Supplemental material for this article is available online.

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