Risk of serious medical events in patients with depression treated with electroconvulsive therapy: a propensity score-matched, retrospective cohort study

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Lancet Psychiatry 2021; 8: 686–95

Published Online July 12, 2021 https://doi.org/10.1016/S2215-0366(21)00168-1

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Summary

Background Previous studies examining the risk of medical complications from electroconvulsive therapy have been confounded and this might contribute to its underuse. This study aimed to compare the risk of serious medical events, defined as those resulting in hospitalisation or death, among patients with depression who received electroconvulsive therapy versus patients who did not receive electroconvulsive therapy.

Methods This was a propensity score-matched, retrospective cohort study using linked population-based administrative health data for adults admitted to designated psychiatric facilities in Ontario, Canada, for more than 3 days with depression between April 1, 2007, to Feb 28, 2017. Electroconvulsive therapy exposure was defined as one or more physician billing procedure codes during hospitalisation. The unit of analysis was individual admissions and propensity score matching was used to match each exposed admission to an unexposed admission to estimate the average treatment effect of electroconvulsive therapy among those treated. The primary outcome was serious medical events, a composite of hospitalisation for medical (ie, non-psychiatric) reasons or non-suicide death within 30 days from electroconvulsive therapy exposure or matched date in the unexposed group. Effect modification was examined using tests of interaction for three clinically relevant prespecified subgroups (sex, presence of psychotic symptoms, and illness polarity). Secondary outcomes were medical hospitalisation and non-suicide death separately, suicide death, and specific serious medical events.

Findings In propensity score matched analyses, there were 10 016 psychiatric hospitalisation records (6628 women, 3388 men) with mean age 56·6 years (SD 16·3) and no ethnicity data available. 65 818 admissions were eligible for matching and 5008 were matched (1:1) in each exposure group. In the propensity score matched cohort, the incidence of serious medical events was 0·25 per person-year in the exposed group and 0·33 per person-year in the unexposed group (cause-specific hazard ratio 0·78 [95% CI 0·61–1·00]). Suicide death as a competing risk did not alter this finding. The risk of suicide death was significantly lower in the exposed (≤5 of 5008 admissions) versus the unexposed group (11 [0·2%] of 5008 admissions; p<0·03). Bipolar depression, compared with unipolar depression, was associated with a greater reduction in the risk of serious medical events with electroconvulsive therapy. Electroconvulsive therapy was not associated with medical hospitalisation or non-suicide death separately, nor with any specific serious medical event.

Interpretation Among individuals hospitalised with depression, we found no evidence for a clinically significant increased risk for serious medical events with exposure to electroconvulsive therapy, and the risk of suicide was found to be significantly reduced, suggesting the benefits of electroconvulsive therapy for depression outcomes might outweigh its risks in this population.

Funding Norris Scholars Award, Department of Psychiatry, University of Toronto; the Canadian Institutes for Health Research.

Introduction

Depression is a leading cause of illness and disability worldwide. Unfortunately, many individuals do not go into remission with initial treatments. In treatment-resistant depression, commonly defined as non-response to two or more medication trials of adequate dose and duration from different classes,[1] fewer than one in seven patients go into remission with additional pharmacotherapeutic strategies.[2] There is little evidence for the use of psychotherapy in treatment-resistant depression.[3] Of all treatments for treatment-resistant depression, electroconvulsive therapy is the single most effective, achieving remission in 60% of individuals.[4] As a result, electroconvulsive therapy is recommended by clinical guidelines for treatment-resistant depression or scenarios in which rapid improvement is crucial.[5]

Despite clinical guidelines recommending its use, electroconvulsive therapy is underused.[6] This underuse is probably related to stigma and concerns about side-effects.[7] Although cognitive side-effects associated with

Research in context

Evidence before this study

We searched MEDLINE using the PubMed interface from January, 1980, to Jan 21, 2021, for observational studies using the search terms: (1) electroconvulsive therapy and (2) mortality or adverse medical event, with no language restrictions. This approach identified case series of individuals receiving electroconvulsive therapy as well as comparative studies of individuals receiving versus individuals not receiving electroconvulsive therapy. Case series identified mortality as being an extremely rare outcome from electroconvulsive therapy, with one population-level study finding a 30-day mortality risk of 2·4 per 10 000 electroconvulsive therapy treatments. Comparative studies typically identified either no association or reduced risk of adverse medical events from electroconvulsive therapy. Unfortunately, all comparative studies were at high risk of bias owing to their inability to adequately account for confounding and differences between those receiving electroconvulsive therapy and those not receiving electroconvulsive therapy. Therefore, these studies were not suitable to inform clinical decision making.

Added value of this study

This study uses rigorous methods with careful attention to bias and confounding to overcome limitations of previous work. Using propensity score matching, which included more than 75 covariates including measures of cognitive impairment and depression severity, this study found that electroconvulsive therapy was not associated with a clinically significant increased risk of serious medical events such as hospitalisation or death. Suicide as a competing risk did not alter this finding. The risk of suicide death was significantly reduced among those exposed to electroconvulsive therapy.

Implications of all the available evidence

Robust evidence that can inform clinical practice suggests that electroconvulsive therapy is a medically safe intervention that does not result in a clinically significant increased risk of serious medical events among individuals with depression, and might reduce the risk of suicide death.

electroconvulsive therapy have been extensively examined,[8] adverse medical events are also of substantial concern for patients. One report found 20% of the public identified fear of death from electroconvulsive therapy as a major concern,[7] despite evidence suggesting electroconvulsive therapy is a safe procedure. Case series of individuals receiving electroconvulsive therapy have adverse medical events occurring at an incidence similar to low-risk surgical procedures, with mortality occurring in 0·2–4·8 per 10 000 procedures[9,10] and morbidity in 16·8 per 10 000 procedures.[10] However, these event incidences reflect contributions from both the electroconvulsive therapy procedure—with its haemodynamic effects and need for general anaesthesia—and underlying psychiatric disorder.[11] For patients to make fully informed decisions regarding electroconvulsive therapy, studies need to assess risk of serious medical events among those with depression who receive electroconvulsive therapy compared with those who receive standard care.

Previous comparative studies, mostly focused on all-cause mortality, have found a decreased risk of adverse medical events ranging from 18% to 46%;[12–15] however, these studies have been limited in their ability to account for confounding by indication. The ideal approach to address this bias would be a randomised clinical trial. However, with the known efficacy of electroconvulsive therapy, it would be unethical to withhold it in a clinical comparative trial. Furthermore, given the rare nature of serious medical events related to electroconvulsive therapy, the clinical trial approach is not practical due to the large numbers required to detect a difference between groups on these outcomes. Therefore, we did a population-based cohort study, designed to compare the risk of serious medical events in a sample of individuals with severe depression treated with electroconvulsive therapy with similar individuals who did not receive electroconvulsive therapy. Our hypothesis was that electroconvulsive therapy would result in a small increase in the risk of serious medical events due to the need for general anaesthesia and haemodynamic changes associated with the treatment.

Methods

Study design and data sources

We did a propensity-score matched, retrospective cohort study across all of the designated psychiatric inpatient units (around 84 separate units) in Ontario, Canada, using linked population-based administrative health-care databases at the ICES (formerly the Institute for Clinical Evaluative Sciences), an independent, non-profit research organisation evaluating provincial health-care services. The objective of this work was to make causal inferences regarding electroconvulsive therapy and serious medical events. We therefore developed a causal model using a directed acyclic graph (appendix p 24).

See Online for appendix

Patient-level records were linked across multiple administrative databases using unique encoded identifiers and analysed at ICES. Data sources are listed in the appendix (p 5). Designated psychiatric inpatient units were identified using the Ontario Mental Health Reporting System (OMHRS), which includes a range of clinical information including measures of depression severity, functional status, cognition, and sociodemographic information.

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45

of PHIPA authorises ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management, evaluation, or monitoring of the allocation of resources to, or planning for, all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from Research Ethics Board review. The use of the data in this project is authorised under section 45 and approved by ICES' Privacy and Legal Office.

Cell sizes of five or smaller and point estimates from analyses based on these small cells are suppressed due to risk of re-identification of individuals whose data are included in the study; the direction of results (ie, increased or decreased risk) as well as approximate p values are shown.

Study population

We considered for inclusion all adults (aged ≥18 years) with a discharge diagnosis of a major depressive episode during a hospital stay that lasted more than 3 days, who were initially admitted to a designated psychiatric inpatient unit (ie, a facility contributing to the OMHRS) in Ontario between April 1, 2007, and Feb 28, 2017 (appendix p 5). Admissions shorter than 3 days were excluded because these records included abbreviated assessments that were missing clinical information necessary to account for differences between individuals exposed to electroconvulsive therapy and individuals who were not exposed. Individuals with a primary psychotic illness (ie, schizophrenia or schizoaffective disorder) were excluded owing to differing indications for electroconvulsive therapy, concomitant treatments, and baseline medical morbidity in this population.

Exposure groups

To ensure efficient use of the data, the unit of analysis was the individual admission rather than individual patient. Individuals contributed multiple admissions to the analytic cohort provided they were in separate calendar years. When there were multiple admissions in the same calendar year, we used the first admission. For example, an individual admitted in December, 2010, and then February, 2011, would contribute two admissions to the analytic cohort, while an individual admitted in March, 2010, and December, 2010, would contribute a single admission (March, 2010). Only admissions starting April 1, 2007, were eligible for inclusion in the analytic cohort; however, a look-back period of up to 12 months was used. Admissions were selected on an annual basis to minimise the risk of overlapping outcome periods from repeat admissions, and to mitigate any carryover effects related to previous electroconvulsive therapy exposure. Selecting admissions on an annual basis reduced the risk that a serious medical event related to a previous electroconvulsive therapy procedure—which typically occur close in time to the procedure[10]—would confound the effect of a subsequent electroconvulsive therapy procedure on the outcome. Electroconvulsive therapy exposure was determined using physician billing codes for inpatient electroconvulsive therapy procedures (G478),[10] and each admission was categorised as electroconvulsive therapy-exposed or electroconvulsive therapy-unexposed (referred to throughout as exposed or unexposed for brevity). Individuals could contribute exposed and unexposed admissions to the cohort provided they were in separate calendar years.

Propensity scores

The propensity score is the probability of treatment assignment conditional on observed baseline characteristics.[16] Conditional upon the propensity score, the distribution of observed baseline covariates between exposed and unexposed patients is independent of treatment received, which allows for estimating the unbiased treatment effect.[16] Propensity scores have been used in previous register-based studies of electroconvulsive therapy to account for confounding by indication.[17,18] We used propensity score matching to match each exposed admission to an unexposed admission to estimate the average treatment effect of electroconvulsive therapy among the treated.[16] Matching rather than weighting was used to ensure an appropriate index date was available for unexposed individuals. The propensity score was estimated using a logistic regression model with covariates assessed at admission to the psychiatric unit and included more than 75 potential confounders from a range of psychiatric and functional symptoms, and sociodemographic, clinical, and health service use characteristics (table 1). All patient-level covariates measured at hospital admission were potential confounders, while variables measured after electroconvulsive therapy exposure were not adjusted for in our primary analysis. Included in the propensity score model were multiple covariates such as medication use, comorbid substance use, and medical history that would be important to the clinical decision around whether the patient was medically fit to receive anaesthetic and electroconvulsive therapy. Details regarding the propensity score regression model are available in the appendix (pp 2, 6–10), including details regarding the use of multiple imputation for missing covariates (appendix p 3).[19]

After estimating the propensity score, we initially matched each exposed admission to two unexposed admissions by (1) hard-matching admissions on the basis of sex, depression subtype, presence of psychotic symptoms, and year of admission, and (2) greedy nearest neighbour matching without replacement using a caliper width of 0·2 SD of the estimated propensity score logit.[16] Hard-matching on age was not possible owing to imbalance on multiple covariates.

The at-risk period began on the first date of electroconvulsive therapy exposure (in the exposed group) or

corresponding index date (in the unexposed group). The index date for unexposed admissions was defined so that the number of days from admission to index date was the same as their propensity-score-matched exposed pair. This date was selected, as opposed to admission date, to mitigate immortal time bias. As a result of this definition, some unexposed records had index dates occurring after death or during a medical hospital admission. These matched pairs were excluded and we then selected matched pairs with the smallest difference in propensity scores to minimise bias for a final 1:1 matching ratio. 47 matched pairs were excluded, 40 in the exposed group and seven in the unexposed group.

Outcomes

The primary outcome was serious medical events defined as either medical hospitalisation or non-suicide death within 30 days of the exposure date or corresponding index date, a commonly used time-frame for surgical procedures.[20] The rationale for selecting this outcome was owing to its specificity (allowing for superior detection of treatment effects) and owing to supporting validation studies for inpatient medical hospitalisation diagnoses and cause of death in Ontario data sources.[21,22] Specifically, medical hospitalisations were defined as any hospitalisations in which the most responsible diagnosis, defined as the diagnosis or condition considered most responsible for the patient's stay in a facility, was not psychiatric (ICD-10-CA: F04–F99) or inclusive of a diagnosis of deliberate self-injury (ICD-10-CA: X60–X84, Y87.0, Y10–Y34).[22] There were no exclusion criteria in the definition of medical hospitalisation. This definition included serious medical events occurring during an individual's psychiatric hospitalisation resulting in transfer to a medical bed at the same or different facility. Non-suicide death was death due to any non-suicide cause (ICD-10-CA suicide: X60–X84).[21]

Secondary outcomes were medical hospitalisation and non-suicide death as separate outcomes, and suicide death. We also considered each ICD-10 diagnostic category related to a medical hospitalisation or non-suicide death (appendix p 11). We anticipated all medical outcomes to have qualitatively similar findings (ie, small increased risk with electroconvulsive therapy), while for suicide death we anticipated a reduced risk given the established efficacy of electroconvulsive therapy for depression.[4]

Statistical analysis

We did not calculate sample size a priori. Given the expected extent of the data available (ie, 10 years and >80 000 admission records), the study was likely to be powered to detect effects that might have been too small to be considered clinically significant. As there are no established thresholds for clinical significance of adverse events associated with electroconvulsive therapy, we followed the Grading of Recommendations, Assessment, Development, and Evaluations suggestion of 25% or greater relative risk change supporting clinical significance.[23]

	Variable measured
Sociodemographic characteristics	Age, sex, marital status, education level, employment status, urban dwelling, neighbourhood income quintile, eligibility for public drug coverage
Clinical characteristics	Indication for admission, involuntary (*vs* voluntary) admission, capacity to consent to treatment, age at first psychiatric hospitalisation, body-mass index, global assessment of functioning
Medication use	Antidepressant, antipsychotic, benzodiazepine, cholinesterase inhibitor, lithium
Psychiatric comorbidities	Bipolar disorder, anxiety disorder, personality disorder, depression with psychotic features, substance use disorder, post-traumatic stress disorder or trauma-related disorder, eating disorder, cognitive disorder
Medical comorbidities	Asthma, chronic obstructive pulmonary disease, congestive heart failure, myocardial infarction, ischaemic heart disease, atrial fibrillation, cardiac arrhythmia, inflammatory bowel disease, gastrointestinal bleed, Parkinson's disease, epilepsy, stroke, hypothyroidism, diabetes, thromboembolic disease, rheumatoid arthritis, chronic kidney disease, hip fracture, osteoporosis, human immunodeficiency disease, hypertension, visual impairment, hearing impairment, falls, Charlson comorbidity index
Psychometric and functional domains	Activities of daily living, aggressive behaviour (self and others), anhedonia, cognitive status, depressive symptoms, mania symptoms, psychotic symptoms, self-care ability
Health service use	Outpatient visits to psychiatrist, visits to family physician (mental health and non-mental health), emergency department visits (mental health and non-mental health), hospitalisations (mental health and non-mental health)

Variable definition and propensity score modelling details are available in the appendix (pp 2–3, 6–10).

Table 1: **Potential confounders included in propensity score**

Baseline characteristics were used to examine balance between groups using absolute standardised differences, which describe between-group differences in units of SD and are not substantially influenced by sample size in large cohorts.[24] Differences greater than 0·10 were considered clinically meaningful.[24]

The primary analysis was a time-to-event analysis of a serious medical event up to 30 days after the index date. We used a Cox proportional hazards model to calculate the hazard ratio (HR) for exposed and unexposed groups after propensity score matching. Patients were censored at 30 days or with suicide death. Censoring on suicide death estimates cause-specific HR, which is recommended for aetiological research questions.[25] We used a robust variance estimator to account for correlation arising from individuals with multiple admissions. Applying a robust variance estimator to account for correlation arising from matched pairs resulted in inappropriately narrow CIs. We verified the proportional hazards assumption by assessing correlation between weighted Schoenfeld residuals and failure time.

In secondary analyses, we repeated this primary analysis for each of medical (ie, non-psychiatric) admission, non-suicide death, and suicide death separately. We also analysed specific medical events by grouping each event into one of the corresponding ICD10 diagnostic categories and repeating our primary analysis for any medical event

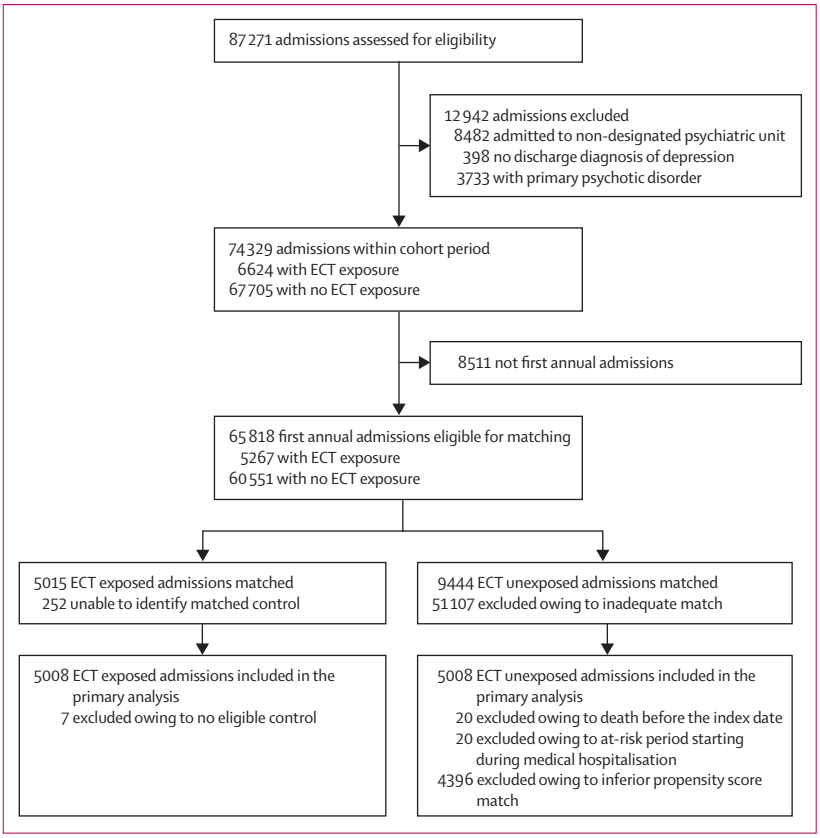

Figure 1: **Flow chart of admission record selection**
ECT=electroconvulsive therapy.

with five or more events in both exposure groups. In these analyses, we censored on suicide death as well as all serious medical events other than the outcome being analysed. Statistical tests were two-sided with $\alpha=0\cdot05$ except for tests of interaction, which used $\alpha=0\cdot20$. We did not adjust for multiple comparisons of secondary analyses due to their exploratory nature.[26]

Due to the possibility of time-varying HRs during follow-up, we calculated analyses for two additional at-risk time periods: (1) index to 10 days, and (2) index to 20 days. We examined effect modification by doing sequential tests of interaction for three prespecified subgroups: sex, presence of psychotic symptoms, and illness polarity. We report sex-stratified results independent of the presence or absence of effect modification. We did not assess effect modification for age due to being unable to hard match on this variable; however, we reported subgroup effect sizes for descriptive purposes. Models assessing effect modification included the main effect of each covariate as well an interaction term. We examined the association between the number of electroconvulsive therapy treatments and risk of serious medical events by reclassifying our exposure as a time-varying counter for number of electroconvulsive therapy treatments.

We also did several analyses to ensure the robustness of the primary analysis. First, to determine the effect of suicide as a competing risk on our primary outcome, we used the Fine and Gray proportional hazards model to calculate subdistribution HR with suicide as a competing risk.[27] Second, even with propensity score matching, subtle differences between groups related to very strong confounders could lead to residual confounding. We therefore repeated our primary analysis incorporating a fixed covariate for age and a time-varying covariate for hospitalisation status (ie, inpatient *vs* outpatient). Third, we examined the effect of including repeat admissions by randomly selecting an individual admission and used a robust variance estimator for matched pairs. Fourth, to test sensitivity of our results to the original 2:1 matching procedure, we repeated the matching procedure using initial 1:1 matching and excluded matched pairs in which the unexposed did not survive until the index date, either due to medical hospitalisation or death.

All analyses were done using SAS version 9.4 and reported according to RECORD guidelines for cohort studies.[28]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

87 271 psychiatric hospitalisation records were assessed for eligibility and 74 329 admissions met selection criteria, of which 6624 (8·9%) involved exposure to electroconvulsive therapy. After selecting the first annual admission for each individual, there were 65 818 admissions, 5267 (8·0%) of which were exposed to electroconvulsive therapy (figure 1). Before matching, these groups were imbalanced on numerous covariates (appendix pp 12–15). 5008 exposed admissions (in 3314 women and 1694 men; 95·1% of eligible exposed admissions) were matched to an unexposed admission (table 2; appendix pp 16–17), none of which showed clinically significant baseline imbalance and substantial overlap in distribution of propensity scores (appendix p 25). Of 10 016 psychiatric hospitalisation records, 6628 were women and 3388 were men, with a mean age of 56·6 years (SD 16·3); and no ethnicity data were available. Compared with exposed matched admissions, exposed unmatched admissions tended to be in older patients with more severe symptoms and functional impairment, and a higher prevalence of psychotic symptoms, antidepressant drug use, and antipsychotic drug use (appendix pp 18–21). The analytic cohort included 8512 unique individuals, of whom 1166 individuals contributed more than one admission. For the sake of brevity, for the remainder of the Article we refer to all matched exposed admissions as exposed admissions, and all matched unexposed admissions as

	Exposed (n=5008)	Unexposed (n=5008)	Absolute standardised difference
Sociodemographic characteristics			
Age, years	56·4 (16·4)	56·7 (16·2)	0·02
Sex*			
Men	1694 (33·8%)	1694 (33·8%)	0
Women	3314 (66·2%)	3314 (66·2%)	0
Marital status			
Never married	1183 (23·6%)	1165 (23·3%)	0·01
Widowed, separated, or divorced	1368 (27·3%)	1335 (26·7%)	0·01
Married or partnered	2457 (49·1%)	2508 (50·1%)	0·02
Education			
Less than high school	918 (18·3%)	879 (17·6%)	0·02
High school	1211 (24·2%)	1221 (24·4%)	0
Any post-secondary	2306 (46·0%)	2351 (46·9%)	0·02
Unknown	573 (11·4%)	557 (11·1%)	0·01
Employment			
Employed	917 (18·3%)	925 (18·5%)	0
Unemployed, seeking employment	211 (4·2%)	191 (3·8%)	0·02
Unemployed, not seeking employment	2238 (44·7%)	2275 (45·4%)	0·01
Other	1544 (30·8%)	1528 (30·5%)	0·01
Unknown	98 (2·0%)	89 (1·8%)	0·01
Rural living dwelling	490 (9·8%)	485 (9·7%)	0
Neighbourhood income quintile†			
1	1125 (22·5%)	1088 (21·7%)	0·02
2	1043 (20·8%)	1088 (21·7%)	0·02
3	981 (19·6%)	996 (19·9%)	0·01
4	940 (18·8%)	933 (18·6%)	0
5	919 (18·4%)	903 (18·0%)	0·01
Clinical characteristics			
Depression type			
Unipolar	4061 (81·1%)	4061 (81·1%)	0
Bipolar	753 (15·0%)	753 (15·0%)	0
Unspecified	194 (3·9%)	194 (3·9%)	0
Reason for admission			
Problem with addiction	352 (7·0%)	327 (6·5%)	0·02
Forensic, justice, or other	232 (4·6%)	226 (4·5%)	0·01
Specific psychiatric symptoms	4142 (82·7%)	4113 (82·1%)	0·02
Risk to others	210 (4·2%)	221 (4·4%)	0·01
Risk to self	2517 (50·3%)	2625 (52·4%)	0·04
Inability to care for self due to illness	1981 (39·6%)	1998 (39·9%)	0·01
Involuntary admission	1845 (36·8%)	1882 (37·6%)	0·02
Incapable to consent to treatment	355 (7·1%)	328 (6·5%)	0·02
Age of first psychiatric hospitalisation, years			
0–14	87 (1·7%)	75 (1·5%)	0·02
15–24	680 (13·6%)	633 (12·6%)	0·03
25–44	1833 (36·6%)	1752 (35·0%)	0·03
45–64	1542 (30·8%)	1661 (33·2%)	0·05
≥65	866 (17·3%)	887 (17·7%)	0·01
Body-mass index, kg/m²	27·35 (6·34)	27·28 (6·28)	0·01
Psychiatric comorbidities			
Anxiety disorder	1041 (20·8%)	1124 (22·4%)	0·04
Psychotic symptoms	959 (19·1%)	959 (19·1%)	0
Personality disorder	794 (15·9%)	819 (16·4%)	0·01
Substance use disorder	341 (6·8%)	308 (6·2%)	0·03
Trauma-related disorder	163 (3·3%)	177 (3·5%)	0·02
Eating disorder	66 (1·3%)	60 (1·2%)	0·01
Cognitive disorder	342 (6·8%)	363 (7·2%)	0·02
Medications‡			
Any medication	2969 (65·1%)	2954 (64·8%)	0·01
Anticonvulsant	488 (10·7%)	441 (9·7%)	0·03
Antidepressant	2409 (52·8%)	2424 (53·2%)	0·01
Antipsychotic	1947 (42·7%)	1920 (42·1%)	0·01
Benzodiazepine	1692 (37·1%)	1644 (36·1%)	0·02
Cholinesterase inhibitor	120 (2·6%)	118 (2·6%)	0
Lithium	338 (7·4%)	277 (6·1%)	0·05

Data are mean (SD) or n (%). Baseline medical comorbidities, psychiatric and functional scales, and health service use are listed in the appendix (pp 16–17).
*Due to limitations of the administrative health datasets, only biological sex as reported on the individual's provincial health registration file is available and gender identity or expression are not collected. There is no current opportunity to identify gender diverse individuals in the administrative health datasets and gender diverse individuals are therefore likely to be represented by their assigned sex at birth. †Income quintiles from lowest (1) to highest (5). ‡Prescriptions in the 120 days before admission and only for patients aged 65 years and older or patients younger than 65 years and on social assistance.

Table 2: **Baseline admission characteristics after matching**

unexposed admissions. There were nine covariates with missing information, and the proportion of missingness ranged from 1·4% to 14·0%. The mean number of electroconvulsive therapy procedures in the exposed group was 8 (SD 4). Median length of hospital stay in the exposed group was 40 days (IQR 24–62) compared with 17 days (10–31) for the unexposed group (p<0·0001).

Among exposed admissions, 105 had a serious medical event within 30 days, an incidence of 0·25 per

	ECT-exposed		ECT-unexposed (reference)		Cause-specific HR (95% CI)
	Number of events/at risk	Incidence per person-year	Number of events/at risk	Incidence per person-year	
Primary analysis					
Adverse medical events	105/5008	0·25	135/5008	0·33	0·78 (0·60–1·00)
Additional analyses					
Timing					
Index to 10 days	41/5008	0·29	54/5008	0·38	0·76 (0·51–1·14)
Index to 20 days	68/5008	0·24	93/5008	0·33	0·73 (0·53–1·00)
Subgroups					
Age <65 years	31/2526	0·15	37/2526	0·18	0·84 (0·52–1·36)
Age ≥65 years	34/811	0·52	46/811	0·70	0·74 (0·47–1·14)
Psychotic depression	17/959	0·21	20/959	0·25	0·85 (0·44–1·65)
Non-psychotic depression	88/4049	0·26	115/4049	0·35	0·76 (0·58–1·01)
Unipolar depression	82/4061	0·24	104/4061	0·31	0·79 (0·59–1·05)
Bipolar depression	9/753	0·14	21/753	0·34	0·42 (0·20–0·92)
Female	62/3314	0·23	80/3314	0·29	0·77 (0·55–1·08)
Male	43/1694	0·31	55/1694	0·40	0·78 (0·52–1·16)

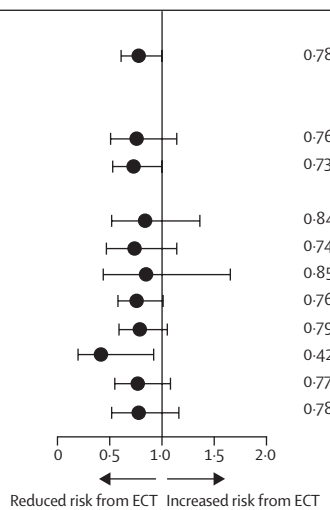

Figure 2: **Forest plot of the cause-specific HRs for the primary and additional analyses in the matched cohort**
Outcome period is from index date to 30 days unless otherwise specified. ECT=electroconvulsive therapy. HR=hazard ratio.

person-year. Of the unexposed admissions, 135 had a serious medical event within 30 days, an incidence of 0·33 per person-year. This corresponded to a cause-specific HR of 0·78 (95% CI 0·60–1·00) for exposed versus unexposed admissions (figure 2). The proportional hazards assumption was met with a non-significant correlation between weighted Schoenfeld residuals and failure time (p=0·72).

Similar HRs to the main analysis were found for serious medical events in days 0–10 in exposed versus unexposed admissions (cause-specific HR 0·76 [95% CI 0·51–1·14]; incidence 0·29 per person-year *vs* 0·38 per person-year) and for days 0–20 (cause-specific HR 0·73 [0·53–1·00]; incidence 0·24 per person-year *vs* 0·33 per person-year). The risk of serious medical events in exposed versus unexposed admissions among men (cause-specific HR 0·78 [0·52–1·16]; incidence 0·40 per person-year *vs* 0·31 per person-year) and women (cause-specific HR 0·77 [0·55–1·08]; incidence 0·29 *vs* 0·23 per person-year) was similar, with the test of interaction being non-significant (p=0·97). Tests of interaction for psychotic symptoms were also non-significant (p=0·77; figure 2). The interaction term for depression polarity was statistically significant (p=0·15), with electroconvulsive therapy associated with a greater risk reduction of serious medical events in bipolar depression versus unipolar depression (figure 2). The risk of serious medical events did not increase with an increased number of electroconvulsive therapy treatments (cause-specific HR 1·00 [0·96–1·04]).

For medical admissions, results were similar to the main analysis, but risk of medical admission between 0 and 20 days was significantly lower in the exposed group than in the unexposed group (cause-specific HR 0·71 [95% CI 0·52–0·99]; figure 3). We did not find differences between groups in the risk of specific medical events (figure 3). The absolute number of non-suicide deaths was low in both groups, with 11 (0·2%) of 5008 admissions in the exposed group and 12 (0·2%) of 5008 admissions in the unexposed group (cause-specific HR 0·92 [0·40–2·08]).

Accounting for suicide death as a competing risk had little effect on the primary outcome (subdistribution HR 0·78 [95% CI 0·60–1·00]). Suicide deaths were rare in both groups, but significantly lower in the exposed group (≤5 of 5008 admissions) versus the unexposed group (11 [0·2%] of 5008 admissions; p<0·03). Accounting for age and hospitalisation status yielded similar results to the primary analysis (cause-specific HR 0·80 [0·60–1·07]). The results of a randomly selected single admission from each individual (6674 individuals) yielded similar results, although CIs widened and overlapped the null effect considerably (appendix p 23). The use of a 1:1 matching procedure resulted in qualitatively similar findings (appendix p 23).

Discussion

In this population-based study of more than 5000 admissions involving electroconvulsive therapy for inpatients with depression, the rate of serious medical events within 30 days was very low among those exposed to electroconvulsive therapy and a closely matched unexposed group (0·25 events per person-year *vs* 0·33 events per person-year), with those who received electroconvulsive therapy having a numerically lower risk of medical complications. Although our findings

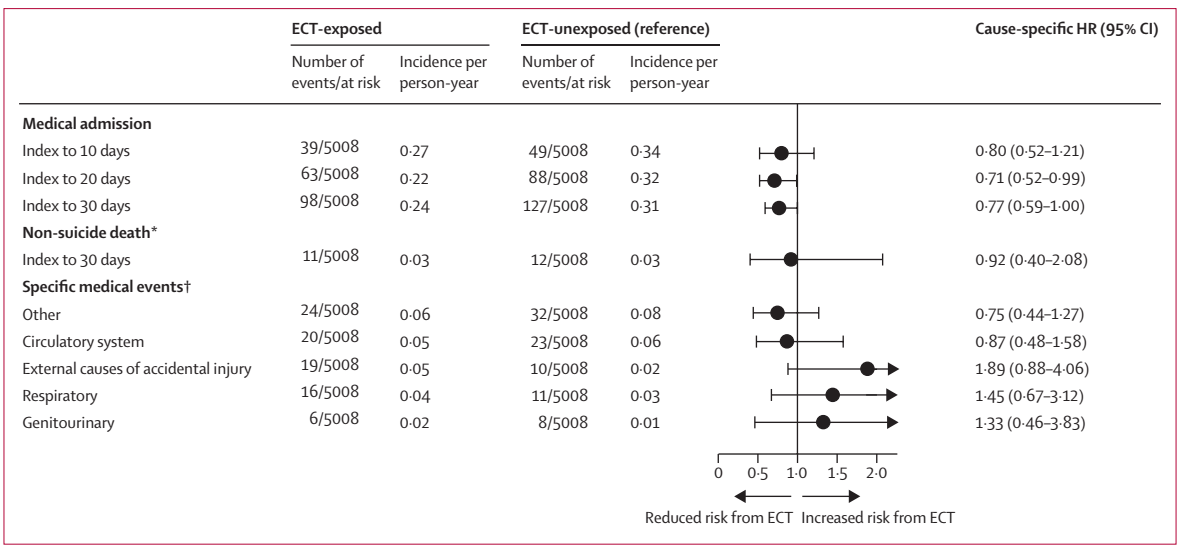

Figure 3: **Forest plot of the cause-specific HRs for the secondary outcomes in the matched cohort**
Outcome period is index date to 30 days unless otherwise specified. Hospitalisation and death do not total the composite outcome because some patients had both events. ECT=electroconvulsive therapy. HR=hazard ratio. *Non-suicide death from index to 10 days and index to 20 days was not reported due to small cell sizes. †Specific adverse medical outcomes that were excluded due to small cell size included endocrine, eye or ear, gastrointestinal, genitourinary, infectious and parasitic, neoplasms, neurological, haematological, musculoskeletal, and obstetric.

cannot exclude the possibility of a null or non-clinically significant risk, our results suggest that electroconvulsive therapy does not result in a clinically significant increased risk of serious medical events. This finding was consistent in analyses that additionally accounted for hospitalisation status, number of electroconvulsive therapy treatments, age, sex, and type of psychiatric diagnosis, and was robust to additional analysis considering suicide as a competing risk. When considering a single hospital admission for each individual, CIs overlapped considerably with the null effect. In secondary analysis among individuals with bipolar depression, electroconvulsive therapy was associated with a significantly lower risk for serious medical events. There also seemed to be a protective effect of electroconvulsive therapy on suicide risk within 30 days, and although this was a secondary outcome and should be interpreted accordingly, it supports the known efficacy of this treatment with respect to suicidality.[5] The clinical implication of this study is that electroconvulsive therapy is likely to be safe with respect to medical risks; considering its established efficacy in depression, the benefits of electroconvulsive therapy might outweigh its risk in this severely ill population.

The primary result of this study is that electroconvulsive therapy exposure does not seem to result in a clinically significant increased risk of serious medical events among individuals hospitalised for depression. However, it should be noted that our results could not rule out a small increased risk of serious medical events, which is unlikely to be of clinical significance. In contrast with previous work, we did not identify statistically significant evidence of a protective effect from electroconvulsive therapy.[12–14] The most likely explanation for this discrepancy is that confounding was inadequately addressed in previous studies given the limited number of covariates included in these previous analyses (eg, 5–10).[12–14] Given the differences across numerous domains between individuals who received electroconvulsive therapy and those who did not receive electroconvulsive therapy in clinical practice,[6] there is probably significant residual confounding with these limited adjustments. This confounding might result in bias because exposed individuals might be systematically healthier than unexposed individuals owing to physician reluctance to prescribe electroconvulsive therapy for medically unwell individuals. By contrast, our results are consistent with a study examining stroke risk following electroconvulsive therapy using propensity score matching and did not find an increased stroke risk with electroconvulsive therapy.[18] Although our results identified that bipolar (*vs* unipolar) depression could be associated with a greater reduction in the risk of serious medical events, this result should be interpreted cautiously given its exploratory nature and relaxed statistical threshold used for tests of interaction. A speculative explanation of this finding is that modifiable medical comorbidities, which are highly prevalent in patients with bipolar disorder,[29] are identified during pre-electroconvulsive therapy assessment and treated.

A limitation of any observational study is the possibility of residual confounding. Although this possibility cannot be eliminated, we believe it is unlikely to account for our study's findings for two reasons. First, our analytic cohort showed balance on a wide range of

clinically important covariates, suggesting that our sample was well matched. Second, given the broad range of covariates, although unobserved confounding could account for our results, propensity scores can mitigate unobserved confounding to the extent that observed covariates correlate with unobserved covariates.[30] Because this was a retrospective study using routinely collected administrative health data, several important characteristics and covariates were unavailable. Patient characteristics not available in the datasets included information on gender identity or expression as well as race or ethnicity. With respect to electroconvulsive therapy exposure, we did not have information on anaesthetic doses, which could be associated with risk of serious medical events.[11] A particularly serious outcome that we did not have information on was so-called anaesthesia awareness—when an individual awakens under general anaesthesia—that in some cases leads to trauma-related symptoms.[31] We also had no data on electrode placement (ie, unilateral, bitemporal, or bifrontal) that might affect efficacy and cognitive outcomes.[4] However, electrode placement is unlikely to affect the risk of serious medical events given that anaesthetic use and haemodynamic consequences are similar regardless of electrode placement. Another limitation of this study is that we only included serious medical events and excluded minor medical complications addressed in the emergency department, outpatient unit, or psychiatric inpatient unit settings. Although this study identified a protective effect of electroconvulsive therapy for risk of suicide death at the group level, due to the rare occurrence of suicide death we were unable to examine effect modifiers to determine which individuals could most benefit from electroconvulsive therapy. This study also did not consider the presence of any potential mediators in the relationship between electroconvulsive therapy exposure and serious medical events, such as time spent in hospital. Last, this study also only included inpatients with depression in a high-income country with universal health insurance. Although this might affect external validity, given that most electroconvulsive therapy in Ontario is provided to inpatients (>80%),[10] the comprehensive clinical information available for inpatients outweighed this limitation and has no affect on this study's internal validity. However, settings without universal health insurance or less well resourced settings will be an important area for study.

Contributors

All authors conceived and designed the study. TSK, SNV, DMB, RS, and TG acquired, analysed, or interpreted the data. TSK, SNV, DMB, RS, and DNW drafted the manuscript. All authors critically revised the manuscript for important intellectual content. TSK, SNV, TG, and RS did the statistical analysis. TSK, SNV, and DMB provided administrative, technical, or material support. SNV and DMB supervised the study. TSK and SNV accessed and verified the data. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

TSK is supported by the Canadian Institute for Health Research Fellowship Award. DMB is supported by the Canadian Institutes of Health Research, the US National Institutes of Health, Weston Brain Institute, Brain Canada, and the Temerty Family through the Centre for Addiction and Mental Health Foundation and the Campbell Research Institute. DMB also received research support and in-kind equipment support for an investigator-initiated study from Brainsway, is the site principal investigator for three sponsor-initiated studies for Brainsway, received in-kind equipment support from Magventure for an investigator-initiated study, received medication supplies for an investigator-initiated trial from Indivior, and has participated in an advisory board for Janssen. TG is supported by a Canada Research Chair in Drug Policy Research and Evaluation and has received grant support for a research programme outside of the present manuscript from the Ontario Ministry of Health. DNW is supported by a New Investigator Award from the Canadian Institutes of Health Research, an Excellence in Research Award from the Department of Anesthesia at the University of Toronto, and the Endowed Chair in Translational Anesthesiology Research at St Michael's Hospital and University of Toronto. SNV is supported by Women's College Hospital, the University of Toronto Department of Psychiatry, and by a New Investigator Award from the Canadian Institutes for Health Research. SNV also reports royalties from UpToDate for authorship of materials related to antidepressants and pregnancy. RS declares no competing interests.

Data sharing

The data set from this study is held securely in coded form at ICES. Although data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs might rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Acknowledgments

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). This work was also supported by the University of Toronto Department of Psychiatry Clinician Scientist Program Norris Scholar Award and a Canadian Institutes for Health Research Fellowship Award. Parts of this material are based on data and information compiled and provided by MOHLTC, Canadian Institute for Health Information (CIHI), Ontario Registrar General (ORG), ServiceOntario, and IQVIA Solutions Canada. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended nor should be inferred. Parts of this material are based on data or information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed in the material are those of the authors, and not necessarily those of CIHI. Parts of this report are based on ORG information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the authors and do not necessarily reflect those of ORG or Ministry of Government Services. We thank IQVIA Solutions Canada for use of their drug information file. We thank MOHLTC for their data as well as Kinwah Fung for her assistance in this work.

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