Title: Serotonin reuptake inhibitors and mortality in epilepsy: a linked primary-care cohort study

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SUMMARY

Objective: Preliminary evidence suggests that serotonin reuptake inhibitor (SRI) use may increase postictal respiratory drive and prevent death. We sought to determine whether SRIs are associated with improved all-cause and possible seizure-specific mortality in patients with epilepsy.

Methods: Patients with epilepsy and a random 10:1 sample without epilepsy were extracted from The ClinicAl Research using LInked Bespoke studies and Electronic health Records (CALIBER) resource. The hazard ratio (HR) of all-cause and possible seizure-specific mortality, treating SRI use as a time varying covariate, was determined using the date of a second SRI prescription as exposure and in discrete 6-month periods over the entire duration of follow-up. We used Cox regression and competing risk models with Firth correction to calculate the HR. We controlled for age, sex, depression, comorbidity (Charlson comorbidity index) and socioeconomic status (Index of Multiple Deprivation).

Results: We identified 2,718,952 eligible patients in CALIBER of whom 16,379 (0.60%) had epilepsy. Median age and follow-up were 44 (interquartile range [IQR] 29-61]) and 6.4 years (IQR 2.4-10.4 years) respectively and 53% were female. A total of 2178 patients (13%) had at least two SRI prescriptions. Hazard of all-cause mortality was significantly elevated following a second prescription for an SRI ([HR 1.64 95% confidence interval [95%CI] 1.44-1.86; p<0.001). The HR was similar in 163,778 age, sex, and GP practice matched controls without epilepsy. Exposure to an SRI was not associated with seizure-related death (HR 1.08, 95%CI 0.59-1.97; 0.796).

Significance: There is no evidence in this large population-based cohort that SRIs protect against all-cause mortality or seizure-specific mortality. Rather, SRI use was associated

with increased mortality, irrespective of epilepsy, which is probably due to various factors associated with the use of antidepressants. Larger studies with systematically collected clinical data are needed to shed further light on these findings.

Key words: Linked electronic medical records, cohort study, all-cause mortality, seizure-specific mortality, antidepressants, epidemiology

KEY POINTS

1) Serotonin reuptake inhibitors have been associated with increased respiratory drive in the postictal state.
2) Clinical need for a serotonin reuptake inhibitor is associated with increased all-cause mortality in patients with and without epilepsy
3) Clinical need for a serotonin reuptake inhibitor is not associated with seizure-related mortality in this large population-based cohort.
4) Presumed use of serotonin reuptake inhibitors does not appear to be acutely associated with all-cause mortality
5) RCTs of serotonin reuptake inhibitor use for mortality in epilepsy are impractical; linked electronic health data provide an alternative

INTRODUCTION

Premature mortality in epilepsy is a major concern facing general practitioners, neurologists, and epileptologists alike. The estimated standardized mortality ratio for those with epilepsy is 2.2 fold higher than that for people without epilepsy[1]. Hence, interventions designed to reduce all-cause premature mortality are of intense interest.

In addition, sudden unexpected death in epilepsy (SUDEP) is a specific cause of death and a major health concern for people with epilepsy. It is defined as a sudden, unexpected, non-traumatic, and non-drowning death of a patient with epilepsy with no post-mortem evidence of a structural or toxicological cause for death[2]. Based on this working definition, sudden unexpected death is almost 24 times more likely in selected populations with epilepsy compared to the general population (standardised mortality ratio 23.7, 95% confidence interval [95%CI] 7.7 to 55.0)[3]. Estimates of SUDEP incidence range from 0.09 to 9.3 per 1000 person-years depending on the severity of epilepsy[4].

The pathological processes leading to seizure-related deaths and, specifically to SUDEP, remain elusive. Post-ictal respiratory depression, cardiac arrhythmias, and electrocerebral suppression may contribute to the increased risk of death[4, 5]. Serotonin reuptake inhibitors (SRIs) may have particular promise as a therapeutic intervention since they increase mental vigilance, promote respiratory activity, and may prevent sudden death[6]. Reductions in ictal respiratory arrest with SRIs and increased respiratory depression with the serotonin antagonist cyproheptadine have been demonstrated

using murine models[7, 8]. Furthermore, a reduction in ictal-related oxygen desaturations in focal seizures without bilateral convulsions has been reported in patients taking SRIs admitted to seizure monitoring units[9].

There has therefore been interest in exploring the therapeutic role of SRIs as a means of reducing premature mortality, especially for patients at high risk of SUDEP[10]. However, to date, no large-scale studies in humans have been performed to either confirm or refute this potential indication. We carried out an observational study using large, pre-existing linked primary care data in England collected during routine clinical practice to examine the association between SRI use and mortality in patients with epilepsy.

METHODS

The ClinicAl Research using LInked Bespoke studies and Electronic health Records (CALIBER) resource (https://www.ucl.ac.uk/health-informatics/caliber)[11] contains United Kingdom (UK) nationally linked structured electronic health records (EHR) data from primary care, hospital care, and a cause-specific mortality registry between January 1, 1997 and March 31, 2010. We only followed patients enrolled from January 1, 1997 to March 31, 2009 to account for an up to one-year lag in mortality reporting.

The platform contains pseudonymised health records of 2,718,952 eligible adult patients. Primary care diagnostic data are recorded using Read codes[12]. Prescription data are recorded by the general practitioner and classified according to the British

National Formulary[13, 14]. Audit nurses and professional clinical coders are employed to abstract secondary care and administrative data into the Hospital Episode Statistics database. Diagnoses and procedures coded in the affiliated databases use the International Classification of Diseases (ICD) and the Office of Population Censuses and Surveys Classification of Interventions and Procedures terminology. Cause-specific mortality data are acquired from death certificates and categorised using the ICD-9 and -10 terminologies at the UK Office for National Statistics.

Study population

We used a published epilepsy case definition designed specifically for Clinical Practice Research Datalink (CPRD) EHR platforms[15]. This definition requires a single Read code for an epilepsy syndrome or two Read codes for symptoms of epilepsy (i.e. codes for non-febrile seizures on two or more occasions) and two anti-epileptic drug codes within 4 months. The definition is 92% accurate for detecting cases of paediatric epilepsy[15] and, after review by two adult epileptologists (CBJ and SW), is expected to perform comparably well in adult populations. We ultimately compared the prevalence to that of the UK population as a means of establish face validity the epilepsy cohort[16].

All patients aged 18 years or greater at epilepsy diagnosis, registered in CPRD practices in England, with at least 1 year of up-to-standard pre-study follow-up during which the patient was not prescribed an SRI (paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram) were included in the analysis. The up-to-standard designation

is provided by CPRD following regular quality checks and practices in each GP surgery. The date the criteria are met is the up-to-standard date.

Statistical analysis

The index date was that on which the patient met the case definition for epilepsy. The index date was 1-year post up-to-standard date in those without epilepsy (who were matched on age, sex, and GP practice). Parametric and non-parametric descriptive statistics were used to compare populations of interest. We calculated mortality incidence rates for the epilepsy and control populations as a whole and stratified by SRI use.

Multiple independent analyses were used to evaluate the association between SRI use and mortality. First, we treated SRI prescriptions as time-varying covariates. To exclude trivial exposures, a patient was considered unexposed until their second SRI prescription. On this date, their status transitioned from unexposed to exposed, and they maintained this designation until the end of follow-up.

We cannot ensure an enduring exposure through this approach and therefore, to mitigate this concern, we performed a second time-varying Cox-proportional hazards regression analysis in which we stratified follow-up into discrete 6-month epochs to more firmly establish any temporal association between SRI prescription and death. In

this time-varying analysis, exposure to an SRI prescription was recorded as a dichotomous ('yes'/'no') variable during each epoch, based on the presence or absence of a prescription code during that time period. We then coded each patient as having lived ('0') or died ('1') during that same epoch.

The primary outcome was all-cause mortality. The secondary outcome was possible seizure-related death (under which SUDEP would fall) as defined by selected ICD-10 codes from epilepsy/seizures/convulsions, unknown/unspecified death, and sudden death diagnostic categories (Appendix 1). In addition to time-varying SRI status, we also controlled for baseline age, sex, past or current depression (using an electronic health records phenotype defined in a prior CALIBER study[17]), comorbidity using the Charlson comorbidity index (CCI) and for socioeconomic status with the Index of Multiple Deprivation (IMD), a measure of relative deprivation in 32,844 localised regions of England (1 being the most deprived and 32,844 being the least deprived)[18]. In a separate analysis, we also included an interaction term between sex and second SRI prescription exposure to investigate any putative sex-specific effect. In each analysis, patients were censored at the end of the follow-up if no outcome occurred or they were lost to follow-up.

We considered a p-value of ≤0.05 to be statistically significant. We used cause-specific Cox regression and the Fine and Gray competing risks models[19] that used a Firth

penalised likelihood method[20] to account for the rarity of seizure-related deaths in this sample.

Sensitivity analyses

We randomly identified exact age, sex, and general practitioner (GP) practice matched control patients without epilepsy in a 10:1 ratio using MySQL 5.7[21]. The algorithm identifies potential matches and orders them randomly by assigning a random seed. Checks are then instituted to ensure minimum follow-up, concordant observation periods, and up-to-standard data. All aforementioned analyses were replicated in this control cohort to determine if the association between SRI use and mortality is unique to patients with epilepsy or common to the general population.

Finally, we performed a sensitivity analysis in which we evaluated the risk of all-cause death and possible seizure-related death, using the analysis plan described above, following a second prescription for bupropion. This is a unique antidepressant that does not modulate the serotonin system. Thus, we aimed to determine whether any putative association between prescription coding and death was serotonin-specific or related to antidepressant use in general.

Software

All analyses were conducted using Stata version 13.1[22], R[23], and SAS® software[24].

Approvals and governance

CALIBER is registered with the University College London Data Protection Office (Z6364106/2009/2/26). Scientific Approval for this study was obtained through the Independent Scientific Advisory Committee (ISAC) Evaluation of Protocols For Research Involving CPRD Data process (protocol number 15_215R2).

RESULTS

We identified 2,718,952 patients in CALIBER of whom 16,379 (0.60%) met the case definition for epilepsy. Median age was 44 years (interquartile range [IQR] 29-61) and 8610 (53%) were female. Median follow-up was 6.4 years (IQR 2.4-10.4 years). For basic descriptive statistics, we considered exposure to two or more SRIs prescriptions as meaningful. According to this definition, 2178 patients with epilepsy (13%) received an SRI. Patients receiving two SRI prescriptions differed from those receiving one or no prescription on a number of demographic indices in directions anticipated from clinical experience (Table 1).

SRI exposure and all-cause mortality

The unadjusted incidence rate of all-cause mortality was approximately two-fold higher for those with epilepsy (n=16,379; incidence rate = 0.024 [2524 deaths/105644.1 person-years]) compared to those without (n=163, 778; incidence rate = 0.012 [14523 deaths/1196841 person-years]). Exposure to a second SRI prescription was associated with an increased mortality rate in both those with epilepsy (0.035 [337

deaths/9766.809 person-years] *versus* 0.023 [2187 deaths/95877.27 person-years] in those unexposed; incidence rate ratio [IRR] = 1.51) and in the general population (0.021 [1587 deaths/77243.51 person-years *versus* 0.012 [12936 deaths/1119597 person-years] in those unexposed; IRR = 1.79).

Exposure to a second SRI prescription was associated with an increased hazard of death (hazard ratio (HR) 1.64, 95%CI 1.44-1.86; p<0.001) in those with epilepsy. Additional associations with all cause death were noted for age (HR 1.06 for each increment in age, 95%CI 1.06-1.07), female sex (HR 0.78, 95%CI 0.72-0.85; p<0.001), and IMD score (HR 1.01, 95%CI 1.01-1.01; p<0.001; Table 2, Figure 1). There was no sex-specific effect of a second SRI prescription on premature mortality when an interaction term was included in the regression model (sex by SRI prescription HR = 0.87, 95%CI 0.69-1.10; p=0.252).

Exposure to a single SRI prescription was associated with a statistically significant increased hazard of death within 6-months (hazard ratio [HR] 1.04, 95%CI 1.00-1.09, p=0.04; Table 3) when controlling for age, sex, CCI, IMD, and depression in those with epilepsy. In addition, the hazard of death was elevated for each one-year increment in age (HR 1.06, 95%CI 1.06-1.07; p<0.001), and each incremental one-rank increase in social deprivation (HR 1.01, 1.01-1.01; p<0.001). Female sex was protective (HR 0.76, 95%CI 0.70-0.83; p<0.001; Table 3).

The hazard ratio of all-cause death was similarly elevated for 163,778 age, sex, and GP practice matched controls without epilepsy. Those exposed to a second SRI prescription had an increased risk of all-cause death (HR 2.07, 95%CI 1.95-2.20; p<0.001; Table e-1) when controlling for age, sex, depression, CCI, and IMD. Increasing age (HR 1.10 for each incremental year, 95%CI 1.09-1.10; p<0.001) and increasing social deprivation (HR 1.01, 95%CI 1.01-1.01; p<0.001) were also independently associated with all-cause mortality whilst female sex was associated with a significantly decreased risk (HR 0.69, 95%CI 0.67-0.72; p<0.001). When evaluated in 6-month epochs, the hazard of death in the general population without epilepsy was not significantly elevated for those taking an SRI compared to the unexposed (HR 1.00, 95%CI 0.98-1.02; p=0.74) when controlling for age, sex, CCI, depression, and IMD (Table e-2).

SRI exposure and possible seizure-related mortality

The unadjusted incidence rate of possible seizure-specific mortality was roughly equivalent for those with epilepsy exposed to two or more SRI prescriptions (incidence rate = 0.0013 [13 deaths/9766.8 person-years]) compared to those exposed to one or no SRI prescriptions (incidence rate = 0.0014 [138 deaths/95877.3 person-years]).

Using a cause-specific Cox regression model, there was no significant difference in possible seizure-related mortality according to time-varying SRI exposure (HR 1.08, 95%CI 0.59-1.98; p=0.80) in the epilepsy population though female sex was protective

(HR 0.70, 95%CI 0.50-0.96; p=0.03; Table 4). The estimate was imprecise due to few outcomes. Likewise, using a competing risks model with a Firth correction, the hazard of a possible seizure-related death within 6-months of prescription was not significantly elevated (HR 1.04, 95%CI 0.91-1.20; p=0.51). Each 1-year increment increase in age was associated with an elevated risk of possible seizure-related death, as was each one-point increase in CCI and with worsening IMD. Female sex was, again, protective (Table e-3)

Bupropion exposure and mortality

We identified 15 (0.10%) patients exposed to two or more prescriptions for bupropion in the epilepsy cohort. The hazard of all-cause death was not significantly higher if exposed (HR 1.91, 95%CI 0.61-5.93; p=0.26) though the overall estimate was imprecise due to the low number of outcomes (5 deaths over 74.8 person-years in the bupropion group compared to 2517 deaths over 105,569.3 person-years in the unexposed group). Insufficient numbers were available to evaluate the hazard of possible seizure-related mortality (0 possible seizure-related deaths over 74.8 person-years in those exposed to two or more bupropion prescriptions compared to 151 possible seizure-related deaths over 105,569.3 person-years in those exposed to one or no bupropion prescription).

We identified 685 of 163,778 (0.42%), who received two bupropion prescriptions in the age, sex, and GP practice matched general population without epilepsy. Of those receiving two bupropion prescriptions, 296 (43%) had a code for current or past depression. Interestingly, unlike the SRI analysis, the unadjusted mortality rate for those

exposed to two or more bupropion prescriptions (incidence rate of all-cause death = 0.012 [43 deaths/3599 person-years]) did not appear to differ substantially from those exposed to one or no prescription (incidence rate = 0.012 [14480 deaths/1,193,242 person-years). However, bupropion is not approved for depression or anxiety in the UK (only for smoking cessation) and therefore we were concerned that there may be an age discrepancy between the two groups. Those unexposed to two or more bupropion prescriptions were significantly older (median age 42; range 17-88) than those exposed (median age 40, range 18-69; p = 0.02) thus indicating a potential confounding protective effect. Indeed, when adjusting for age, the HR of death was twice that for the exposed compared to unexposed (HR 2.06, 95%CI 1.52-2.81; p <0.001)

Similar to the SRI analyses, the adjusted hazard of all-cause mortality (when controlling for age, sex, depression, CCI, and IMD) was significantly higher for those exposed to two or more bupropion prescriptions (HR 1.95, 95%CI 1.44-2.66; p<0.001). Increasing age (HR 1.10 for each incremental year, 95%CI 1.09-1.10; p<0.001), current or past depression (HR 1.19, 95%CI 1.15-1.24; p<0.001), and increasing social deprivation (HR 1.01, 95%CI 1.01-1.01; p<0.001) were all independently associated with all-cause mortality. Female sex conversely was associated with a significant protective effect (HR 0.70, 95%CI 0.67-0.73; p<0.001).

DISCUSSION

This study using large, linked data collected during the course of routine care has paradoxically demonstrated that, contrary to evidence yielded from animal models, SRI use in patients with active epilepsy is associated with an elevated, rather than a decreased, risk of mortality. However, the risk appears generalisable to the overall population as similar results were seen in age, sex, and GP practice-matched patients without epilepsy. This association appears common to antidepressants as a class since consistent results were also obtained when substituting SRI use with bupropion, a non-serotonergic antidepressant. Furthermore, the risk associated with antidepressant use appears to result from a chronic, delayed process, rather than from an acute reaction, as the effect size is attenuated when evaluating SRI exposure and all-cause mortality during discrete 6-month epochs. Exposure to an SRI did not appear to significantly affect possible seizure-related death though the analyses were limited by few outcomes.

Likely, the elevated risk of all-cause mortality related to SRI use is secondary to unmeasured clinical factors inherently associated with antidepressant use rather than through a direct drug effect. The sub-analysis evaluating the risk over immediate 6-month intervals following drug prescription demonstrated an attenuated, rather than enhanced, risk and the overall effect failed to reach significance in the general population. This is contrary to what would be expected if antidepressants were mechanistically responsible for premature death. Interestingly, these results are consistent with a prior large prospective study that linked antidepressant use with an

increased risk of sudden cardiac death over and above that conferred by depression alone[25]. Likewise, the protective effect of female sex was anticipated prior to the study[26].

The large statistical power conferred by CALIBER is one of the benefits of this platform. A randomised controlled trial of SRI use in epilepsy is impractical due to the attendant sample size. Assuming a risk of sudden death of 0.1% in an epilepsy population, with an $\alpha = 0.05$ and a $\beta = 0.2$, one would require over 100,000 patients for a well-powered RCT. Thus, small trials will inevitably lead to imprecise estimates that are of minimal clinical utility. Hence, large linked data such as these are useful for addressing potentially small, but clinically meaningful, associations. An additional strength is the use of a previously published electronic health records case definition for epilepsy that is 92% accurate for paediatric epilepsy[15]. This definition is anticipated to perform equally well in adult populations; an assertion that is corroborated by the fact that the proportion of patients meeting our case definition for epilepsy appears similar to that in the general UK population (0.6%) thus providing face validity[27]. Comparing the consistency between observed and expected incidence rates and prevalence proportions is a common means of validating cases derived from electronic health records[16]. Requiring two codes for an SRI or bupropion on separate days enhanced the chances of an enduring prescription. It is not uncommon for antidepressants to be discontinued after a single prescription, often due to adverse effects, and therefore we imposed a stricter, more conservative, definition of exposure. However, irrespective of adherence, our results indicate that the

very need for two SRI prescriptions is associated with an elevated risk of all-cause mortality in both those with and those without epilepsy. We treated exposure to an SRI or bupropion as a time varying covariate in the primary analysis in order to minimise the risk of immortal time bias[28]. Finally, the secondary analysis (in which we stratified follow-up into discrete 6-month epochs) allowed us to further explore the immediate relationship between antidepressant exposure and mortality.

Despite this, the results are subject to certain limitations. Misclassification bias may exist from the case definition for epilepsy. Although it is 92% accurate[15], it was not designed for adults and we cannot exclude false positive diagnoses of epilepsy. This bias is expected to be non-differential in nature, though, thus diluting the magnitude of the overall estimate. Furthermore, there may be incomplete adjusting for depression status. Psychiatric symptoms and disorders are known to be under-ascertained in large population-based records such as administrative data[29] and we were unable to control for conditions other than depression (e.g. bipolar disorder, schizophrenia). However, we were able to use a previously published case definition of depression designed for the CALIBER database[17], and it was reassuring to note that 72% of the active seizure group and 74% of the control group who were exposed to two or more SRI prescriptions had a corresponding code for past or current depression. Further reassurance is provided by the fact that the demographic differences between those exposed and unexposed to SRIs (Table 1) differed in directions anticipated by clinical experience (e.g. higher rates of depression, comorbidities, and lower socioecomonic status).

Unmeasured confounders are always an issue in non-randomised studies. For instance, worse IMD was an independent risk factor for death. This could partially relate to medication non-adherence[30] while lower socioeconomic status has been linked to both depression and early mortality[31]. There is minimal chance of misclassification of all-cause mortality. However, the fidelity of coding for cause-specific death may not entirely be accurate. In particular, seizure-related death may be inaccurately or simply under-coded[32]. In order to compensate for this, we expanded our definition of possible seizure-related death to include unknown/unspecified death and sudden death. Although this may increase the number of false positive seizure deaths, and could have diluted the effect size, the overall number of outcomes (n=151) was still low leading to an imprecise result. Hence, even in this large cohort, the potential effect of SRI use on seizure-specific mortality may be obscured by random error. Finally, we were unable to precisely determine whether there was a differential effect between antidepressant classes on possible seizure-related mortality in patients with epilepsy due to the low numbers exposed to bupropion. This almost certainly relates to the reluctance to use this medication in those with epilepsy due to its propensity to lower the seizure threshold[33].

Ultimately, analyses such as these are hypothesis generating and help inform future endeavours. This study cannot be used to establish a cause-effect relationship due to the intrinsic study design and source of data. Prospective studies are required to establish temporality. Furthermore, we cannot ensure adherence to SRIs or bupropion,

cannot ensure the prescriptions were filled, and cannot determine the daily dose for each patient. Thus, it is not possible to comment on a biological gradient. Additional studies replicating these results would also be required to meet causal criteria. Finally, although intriguing, it is hard to argue for biological plausibility of direct death related to antidepressant use. Rather, it is more credible that antidepressants function as a marker for an underlying biological process that is not controlled for even when adjusting for age, sex, CCI attribution of comorbidities, and social deprivation according to the IMD.

This study provides important data that are directly applicable to both clinical practice and future research. Our results indicate that patients requiring multiple antidepressant prescriptions, even those without epilepsy, need to be followed closely as they represent a vulnerable population at increased risk of premature death. Vigilance may be required even for those who are seizure-free since it could potentially have a beneficial effect on all-cause mortality. Significantly, SRI was not related to seizure-related mortality, thus further alleviating fears that SRI use may be detrimental for seizures. However, the low number of possible seizure-specific outcomes and the attendant wide confidence intervals necessarily tempers any conclusion about a protective effect. Future research designed to further elaborate on this association is crucial. Finally, an RCT of SRIs for the prevention of seizure-related death in patients with epilepsy appears impractical. Using increasingly large, linked electronic health record datasets, or systematically collected clinical data from multicentre cohorts can offer a valuable solution to further our understanding of SRIs, mortality and prevention

of seizure-related deaths. By quadrupling the sample size, we can halve the 95% confidence intervals around the effect estimate. Hence, in order to obtain more precise measures of the overall effect of SRI use on possible seizure-related mortality, any future large, linked electronic and administrative health record datasets would require at least 65,000 patients with epilepsy. Therefore, concerted, multicentre efforts are required to address this critical issue.

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TABLES

Table 1. Demographic comparison between those exposed to an SRI medication (two prescription codes) *versus* unexposed (one or no prescription codes).

	SRI exposed	**SRI unexposed**	**P value**
n (%)	2178 (13%)	14,201 (87%)	N/A
Age (years; IQR)	43 (31-59)	44 (29-61)	0.19
Female sex (n; %)	1333 (61%)	7277 (51%)	<0.001
Charlson comorbidity index (median; IQR)	4 (0-13)	0 (0-11)	<0.001
Depression (n; %)	1564 (72%)	3318 (23%)	<0.001
Past or current smoker (n; %)	1204 (59%)	5880 (46%)	<0.001
Diabetes mellitus (n; %)	259 (12%)	1003 (7%)	<0.001
Hypertension (n; %)	615 (28%)	2827 (20%)	<0.001
IMD (median; IQR)	19 (11-33)	17 (10-30)	<0.001

Table 2. Hazard ratio for all-cause mortality according to receipt of a second serotonin reuptake inhibitor (SRI) prescription code in 16,379 patients with epilepsy. Use of SRI was treated as a time-varying covariate.

	Hazard ratio	95%CI	p-value
SRI exposure	1.64	1.44-1.86	<0.001
Age	1.06	1.06-1.07	<0.001
Female sex	0.78	0.72-0.85	<0.001
Depression	0.98	0.89-1.07	0.641
CCI	0.99	0.99-1.00	0.420
IMD	1.01	1.01-1.01	<0.001

Depression is past or current depression

Abbreviations: 95%CI = 95% confidence interval; CCI = Charlson comorbidity index; IMD = Index of Multiple Deprivation

Table 3. Hazard ratio for all-cause mortality according to receipt of a serotonin reuptake inhibitor (SRI) prescription code in 16,379 patients with epilepsy during discrete 6-month epochs of follow-up.

	6-month epochs		
	Hazard ratio	**95%CI**	**p-value**
SRI exposure	1.04	1.00-1.09	0.044
Age	1.06	1.06-1.07	<0.001
Female sex	0.76	0.70-0.83	<0.001
Depression	1.06	0.96-1.16	0.208
CCI	1.00	0.99-1.00	0.838
IMD	1.01	1.01-1.01	<0.001

Depression is past or current depression

Abbreviations: 95%CI = 95% confidence interval; CCI = Charlson comorbidity index; IMD = Index of Multiple Deprivation

Table 4. Hazard ratio for possible seizure-specific mortality according to receipt of a second serotonin reuptake inhibitor (SRI) prescription code in 16,379 patients with epilepsy using a cause specific Cox proportional hazards regression model. Use of SRI was treated as a time-varying covariate.

	Hazard ratio	95%CI	p-value
SRI exposure	1.08	0.59-1.97	0.796
Age	1.01	1.00-1.02	0.005
Female sex	0.70	0.50-0.96	0.028
Depression	0.81	0.55-1.20	0.300
CCI	0.97	0.94-0.99	0.035
IMD	1.01	0.99-1.02	0.145

Depression is past or current depression

Abbreviations: 95%CI = 95% confidence interval; CCI = Charlson comorbidity index; IMD = Index of Multiple Deprivation

FIGURE LEGEND

Figure 1. Nelson-Aalen cumulative hazard estimates curve for all-cause death in patients with active epilepsy stratified according to time-varying SRI status (patients were considered exposed after their second code for an SRI prescription).

DECLARATIONS AND CONFLICTS OF INTEREST

Declarations/Acknowledgements:
- CBJ has nothing to declare
- AG-I has nothing to declare
- SD has nothing to declare
- NKF has nothing to declare
- TTS has nothing to declare
- JDTE has nothing to declare
- SP has nothing to declare
- NJ is the holder of a Canada Research Chair in Neurological Health Services Research and is an Associate Editor of Epilepsia.
- SW is the holder of the Hopewell Professorship for Clinical Neurosciences Research at the Hotchkiss Brain Institute, University of Calgary

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Epilepsia Ethics Guidelines: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.