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Research Paper

Association of lithium use with rate of out-of-hospital cardiac arrest in patients with bipolar disorder

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ABSTRACT

Background: Lithium has been linked with induction of proarrythmic electrocardiographical changes. However, it is unclear whether lithium use is associated with an increased rate of cardiac arrest. We investigated the rate of out-of-hospital cardiac arrest associated with lithium exposure in a nationwide cohort of patients with bipolar disorder.

Methods: Data from Danish registries was used to conduct a nationwide nested case-control study assessing the rate of out-of-hospital cardiac arrest associated with lithium exposure among 47,745 bipolar disorder patients from 2001 through 2015. 284 cases with out-of-hospital cardiac arrest were matched on age, sex, and age at first diagnosis of bipolar disorder with 1,386 controls. Rate analyses were performed using Cox regression.

Results: Fewer cases than controls were exposed to lithium (24.3% vs. 34.9%, $p<.001$). In adjusted analyses, lithium monotherapy was not significantly associated with increased rate of out-of-hospital cardiac arrest compared with no mood stabilizing treatment (Hazard ratio [HR] = 0.71 [95% CI, 0.46–1.10]), atypical antipsychotic monotherapy (HR = 0.69 [95% CI, 0.41–1.15]), and anticonvulsant monotherapy (HR = 1.37 [95% confidence interval [CI], 0.65–2.88]). Combination therapy with lithium plus one or more other mood stabilizers was not associated with increased rate of out-of-hospital cardiac arrest compared with combination therapy with two or more non-lithium mood stabilizers (HR = 0.58, [95% CI, 0.31–1.08]).

Limitations: Possible residual confounding due to unmeasured variables. Lack of statistical power to detect weak associations.

Conclusions: Lithium was not associated with increased rate of out-of-hospital cardiac arrest in bipolar disorder patients compared with other guideline-recommended mood stabilizing pharmacotherapy, nor compared with no mood stabilizer treatment.

Introduction

Bipolar disorder is a severe and recurring mental illness that affects more than 1% of the world's population and often requires long-term mood stabilizing treatment to prevent recurrence of manic or depressive episodes (Grande et al., 2016). For several decades, lithium has been the most important mood stabilizing treatment for bipolar disorder and continues to be widely used, as all international guidelines recommend lithium as first line treatment (Grunze et al., 2013; Kessing, 2019; Yatham et al., 2018). Thus, adverse effects of lithium treatment including cardiac adverse effects represent a large global health concern and may deter patients' adherence to lithium treatment and discourage

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physicians from prescribing it (Karanti et al., 2016; Kessing et al., 2016; Lyall et al., 2019).

Several studies have linked lithium with proarrhythmic electrocardiographic (ECG) changes such as QT-prolongation, T-wave changes, sinus bradycardia and ventricular tachyarrythmias (Acciavatti et al., 2017; Altinbas et al., 2014; Mehta and Vannozzi, 2017). In a recommendation paper regarding risk of arrhythmias induced by psychotropic drugs, lithium was classified as a drug with propensity of inducing QT-prolongation and arrhythmias (Fanoe et al., 2014). However, this classification is based on expert consensus and low-level evidence. To our knowledge, no study has specifically investigated the risk of cardiac arrest associated with lithium.

Thus, the aim of the present study was to investigate, in a population of patients with bipolar disorder, the association between lithium use and rate of cardiac arrest compared with other guideline-recommended mood stabilizing pharmacotherapy.

Methods

Data sources

All Danish residents have a unique and personal civil registration number, which we used to crosslink information from nationwide administrative registries. Patients with out-of-hospital cardiac arrest were identified from the Danish Cardiac Arrest Registry, which contains information on all out-of-hospital cardiac arrests where resuscitative efforts were commenced in Denmark between June 1st 2001 and December 31st 2015 (Wissenberg et al., 2013). Patients with obvious late signs of death with no resuscitiation attempt were not included in the registry. Hospital diagnoses and death certificates were used to identify arrests of presumed cardiac cause, as done previously (Christensen et al., 2019; Wissenberg et al., 2013). A cardiac arrest was presumed to be of cardiac cause if the etiology was a known cardiac disease, the patient collapsed suddenly and unexpectedly, or if the cause was unknown (Perkins et al., 2015). Hospital diagnoses were obtained from the Danish National Patient Registry (Lynge et al., 2011). The Danish Central Psychiatric Registry holds information on all inpatient (since 1970) and outpatient (since 1995) psychiatric hospital contacts (Mors et al., 2011). Diagnoses from these registries were classified according to *International Classification of Diseases, 8th revision (ICD-8)* codes before 1994 and *International Classification of Diseases, 10th revision (ICD-10)* codes since 1994. Causes of death were acquired from the Danish Cause of Death Registry (Helweg-Larsen, 2011). Information on age, sex and civil status is stored in the Danish Civil Registration System (Pedersen, 2011). The National Prescription Registry holds information on all redeemed drug prescriptions, classified according to the Anatomical Therapeutic Chemical (ATC) system (Kildemoes et al., 2011). Data on income was obtained from Statistics Denmark.

Study design and population

The study was conducted as a nationwide nested case-control study from June 1st 2001 through December 31st 2015 based on prospectively gathered registry data. The patient selection and matching process is illustrated in Fig. 1. Only patients with a diagnosis of a single manic episode or bipolar disorder from an inpatient or outpatient hospital contact were included (*ICD-10* codes: DF30–31.9 and DF38.00; *ICD-8* codes: 29,619, 29,639, 29,629, 29,689, 29,699*)* (Kessing et al., 2015). We chose to include only patients with diagnosed bipolar disorder, as bipolar disorder per se is a risk factor for out-of-hospital cardiac arrest (Barcella et al., 2021). Patients with chronic kidney disease (CKD) *(ICD-10* codes: DN18–19.9, DN14.1, DN14.2, DN16.8, DN25.1, DN26, and DN27) were excluded from the study population, as it is a relative counterindication for lithium treatment, and the patients with CKD who do continue lithium treatment are highly selected (Kessing et al., 2017). Patients with epilepsy (*ICD-10* codes: DG40–41) were also excluded to ensure that anticonvulsant prescriptions were intended as mood stabilizing treatment. Patients without at least one redemption of a prescription for a mood stabilizer after 1994 were excluded before matching.

The matching was performed using an incidence density matching approach: Cases were defined as patients with an out-of-hospital cardiac arrest of presumed cardiac cause and matched with up to five controls on birth year, sex, year of first hospital contact for bipolar disorder, and year of out-of-hospital cardiac arrest. The control group consisted of persons who were alive and had not emigrated prior to the date of out-of-hospital cardiac arrest of their corresponding case, which was assigned as index date (Christensen et al., 2020).

Exposure definitions

The exposure window was set to 60 days prior to index date. Use of lithium, anticonvulsants (valproate or lamotrigine) or atypical antipsychotics (quetiapine, olanzapine, aripiprazole, clozapine, risperidone, or ziprasidone) were included as mood stabilizing pharmacotherapy and defined by redeemed prescriptions. These drugs were selected as they are universally recommended by international guidelines for treatment of bipolar disorder as mood stabilizers (Grunze et al., 2013; Yatham et al., 2018). Other guideline-recommended drugs were not included in the study due to a limited number of observations. Monotherapy was defined as use of a single mood stabilizing drug without use of other mood stabilizing drugs during the 60 days prior to index date. Exposure to combination therapy was defined as use of ≥2 mood stabilizing drugs during the 60 days prior to index. Daily estimated dosage of ≥900 mg per day for lithium carbonate and ≥42 mmol per day for lithium citrate were categorized as high-dose lithium exposure (Grunze et al., 2009). Daily dosage was estimated by calculating mean dosages from up to five consecutive prescriptions before the prescription of interest. Treatment duration was calculated by dividing the number of tablets in the prescription of interest by daily dosage as described previously elsewhere (Kessing et al., 2017).

Outcome

The main outcome was out-of-hospital cardiac arrest of presumed cardiac cause.

Demographic characteristics, comorbidities, and concomitant pharmacotherapy

Civil status was defined as living alone or cohabitation. Socioeconomic status was defined according to household income and categorized into tertiles. Comorbidities were defined using *ICD-10* diagnosis codes from hospital contacts within 5 years prior to start of the exposure window. Hypertension was defined as redemption within 90 days of two or more concomitant prescriptions for antihypertensive drugs up to 5 years prior to start of the exposure window. Concomitant pharmacotherapy, including QT-prolonging drugs, and diabetes were defined by redemption of prescriptions within 180 days prior to start of the exposure window (eFigure 1). QT-prolonging drugs were identified as drugs with "known risk" of QT-prolongation and torsade de pointes (TdP) ventricular tachycardia according to www.crediblemeds.org (accessed September 19th 2019) (Weeke et al., 2019; Woosley).

Statistical analysis

Statistical analyses were computed with survival methods. Time origin for all survival analyses was set at the onset of bipolar disorder or June 1st 2001, whatever came last. Patients were followed until cardiac arrest, death without outcome defined cardiac arrest, or December 31st 2015, whatever came first. Exposure to mood stabilizing drugs in the previous 60 days at any time during the follow up period was classified as lithium monotherapy, anticonvulsant monotherapy, and

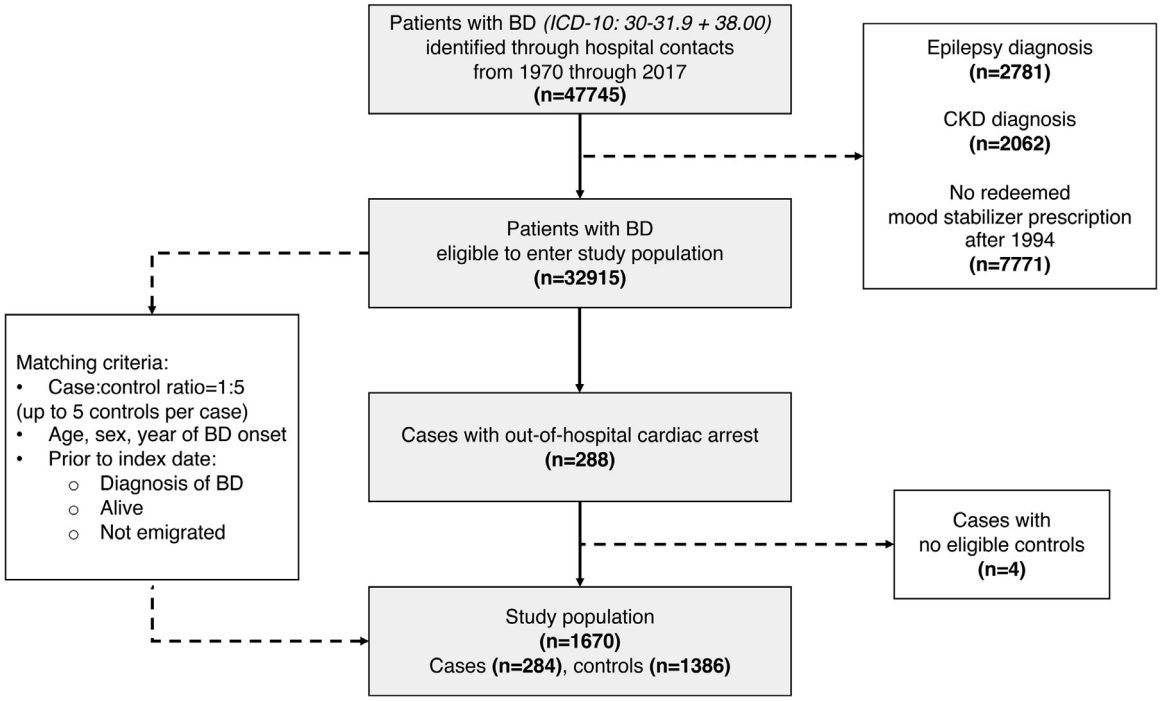

Fig. 1. Flowchart of patient selection and matching. *Abbreviations: BD, bipolar disorder; ICD-10, international classification of diseases, 10th revision; CKD, chronic kidney disease.*

antipsychotic monotherapy, and combination therapy (eFigure 1). No treatment was defined as no exposure to mood stabilizing drugs during the exposure window. Time-varying Cox regression was used to associate the differences in mood stabilizer exposure with the hazard rate of cardiac arrest. The Cox regression models were fitted using a nested-case control design with up to five controls matched on sex, year of first bipolar disorder diagnosis, and birth year (Borgan et al., 1995). We adjusted for co-medication and comorbidities up to the start of the exposure window. Reported were hazard ratios for the varying exposure references.

We conducted the following analyses to fully evaluate the rate of cardiac arrest associated with lithium:

- Lithium monotherapy overall as well as stratified by high- and low-dose was compared to anticonvulsant monotherapy, antipsychotic monotherapy, and no mood stabilizer treatment.
- Lithium monotherapy was compared with each individual mood stabilizing drug in monotherapy (valproate, lamotrigine, quetiapine, olanzapine, ziprasidone, risperidone, clozapine, and aripiprazole).
- Any combination mood stabilizing therapy including lithium was compared with any combination mood stabilizing therapy not including lithium.

All analyses were adjusted for socioeconomic status, civil status, comorbidities, and co-medication listed in Table 1. eTable 1 shows all ICD-10 and ATC codes used to define comorbidities and co-medication. Differences of baseline characteristics among cases and controls were examined using Chi-squared test for categorical variables and Mann-Whitney test for continuous variables. The level of statistical significance was set at 5%. Data management and statistical analyses were performed with the use of SAS version 9.4 (SAS Institute Inc.) and R version 3.6.1 (R Development Core Team) (R Core Team, 2018).

Ethics

The study was approved by the Danish Data Protection Agency (Ref.no. 2007–58–0015, local ref.no. GEH-2014–017, I-Suite.nr. 02,735). For register-based studies based on anonymous data in Denmark ethical approval is not required, however to ensure patient anonymity, categories with three or less observations were required to be reported as *"<3"*. Danish healthcare registry data are not shared publicly.

Results

Patient characteristics

We identified 284 cases with bipolar disorder suffering from out-of-hospital cardiac arrest and 1386 controls with bipolar disorder without out-of-hospital cardiac arrest, Table 1. Median age of cases and controls was 69 years (Interquartile range [IQR]: 62–77). Amongst cases, 43.0% were male versus 41.9% of controls. A lower proportion of cases were exposed to lithium compared with controls (24.3% cases vs. 34.9% controls, $p<.001$). A similar proportion of cases (39.1% antipsychotics, 15.8% anticonvulsants) and controls (34.0% antipsychotics, 17.0% anticonvulsants) were exposed to atypical antipsychotics ($p=.12$) as well as anticonvulsants ($p=.71$). A higher proportion of cases compared to controls were not exposed to any mood stabilizing drug (41.2% vs. 34.5%, $p=.04$). Exposure to antidepressants among cases and controls was similar, whereas a higher proportion of cases were co-medicated with other QT-prolonging drugs (33.1% vs 24.8%, $p=.004$). Cases had a generally higher burden of comorbidities compared with controls and were more frequently exposed to other drugs.

Rate of out-of-hospital cardiac arrest

Exposure to lithium monotherapy was not significantly associated with increased rate of out-of-hospital cardiac arrest compared with anticonvulsant monotherapy (Hazard ratio [HR] = 1.37 [95% confidence interval [CI], 0.65–2.88]), atypical antipsychotic monotherapy (HR = 0.69 [95% CI, 0.41–1.15]), and no mood stabilizing treatment (HR = 0.71 [95% CI, 0.46–1.10]), Fig. 2.

High-dose lithium monotherapy was not significantly associated with increased rate of out-of-hospital cardiac arrest compared with

Table 1
Characteristics of cases and controls.

Characteristics	Cases (n = 284)	Controls (n = 1386)	P-value
Median age, y [IQR]	69 [62, 77]	69 [62, 77]	.76
Male, n (%)	122 (43.0)	581 (41.9)	.80
Median years since first BD diagnosis [IQR]	7.3 [3.1–12.4]	7.4 [3.1–12.4]	.95
Civil status, living alone, n (%)	180 (63.4)	850 (61.4)	.75
SES tertiles (low, medium, high), n (%)			
Low	105 (37.0)	450 (32.5)	
Medium	114 (40.1)	442 (32.0)	
High	65 (22.9)	493 (35.6)	<0.001
Exposure to mood stabilizers			
Lithium (total), n (%)	69 (24.3)	484 (34.9)	<0.001
Any anticonvulsant, n (%)	45 (15.8)	235 (17.0)	.71
Any atypical antipsychotic, n (%)	111 (39.1)	471 (34.0)	.12
No treatment, n (%)	117 (41.2)	478 (34.5)	.04
Combination therapy *with* lithium, n (%)	28 (9.9)	173 (12.5)	.26
Combination therapy *without* lithium, n (%)	38 (13.4)	131 (9.5)	.06
Valproate, n (%)	16 (5.6)	93 (6.7)	.59
Lamotrigine, n (%)	31 (10.9)	147 (10.6)	.96
Quetiapine, n (%)	32 (11.3)	168 (12.1)	.76
Olanzapine, n (%)	46 (16.2)	207 (14.9)	.76
Aripiprazole, n (%)	8 (2.8)	26 (1.9)	.43
Risperidone, n (%)	29 (10.2)	86 (6.2)	.02
Ziprasidone, n (%)	< 3	5 (0.4)	.75
Clozapine, n (%)	5 (1.8)	12 (0.9)	.30
Characteristics (continued)	Cases (n = 284) (continued)	Controls (n = 1386) (continued)	P-value (continued)
Comorbidities			
Diabetes, n (%)	53 (18.7)	126 (9.1)	<0.001
Hypertension, n (%)	49 (17.3)	153 (11.0)	.002
Heart failure, n (%)	49 (17.3)	43 (3.1)	<0.001
Cerebrovascular disease, n (%)	34 (12.0)	92 (6.6)	.004
Ischemic heart disease, n (%)	58 (20.4)	141 (10.2)	<0.001
Chronic obstructive pulmonary disease, n (%)	67 (23.6)	80 (5.8)	<0.001
Cancer, n (%)	15 (5.3)	87 (6.3)	.68
Substance abuse, n (%)	62 (21.8)	129 (9.3)	<0.001
Concomitant pharmacotherapy			
Beta blockers, n (%)	49 (17.3)	159 (11.5)	<0.001
Antiarrythmics, n (%)	49 (14.1)	117 (8.4)	<0.001
Calcium channel blockers, n (%)	51 (18.0)	160 (11.5)	<0.001
Diuretics, n (%)	124 (43.6)	412 (29.7)	<0.001
NSAIDs, n (%)	49 (17.3)	203 (14.7)	.73
Other QT-prolonging drugs, n (%)	117 (41.2)	420 (30.3)	.004
Any antidepressant, n (%)	168 (59.2)	783 (56.5)	.34

Footnotes: Abbreviations: IQR, interquartile range; BD, bipolar disorder; SES, socioeconomic status; NSAID, non-steroidal anti-inflammatory drug.

Table 2
Adjusted HRs for out-of-hospital cardiac arrest among BD patients for lithium monotherapy compared with lamotrigine, valproate, quetiapine, olanzapine, ziprasidone, aripiprazole, or risperidone monotherapy.

	Cases, n/N (%)	**Controls, n/N (%)**	**Hazard ratio (95% CI)**
Lithium	41/284 (14.4)	311/1386 (22.4)	
Lithium vs lamotrigine	11/284 (4.3)	60/1386 (3.9)	0.83 (0.37–1.88)
Lithium vs valproate	<3/284 (<1.0)	39/1386 (2.8)	3.66 (0.82–16.45)
Lithium vs quetiapine	14/284 (4.9)	65/1386 (4.7)	0.74 (0.36–1.55)
Lithium vs olanzapine	21/284 (7.4)	91/1386 (6.6)	0.65 (0.34–1.26)
Lithium vs risperidone	15/284 (5.3)	41/1386 (3.0)	0.53 (0.24–1.14)
Lithium vs ziprasidone	<3/284 (<0.4)	4/1386 (0.4)	0.93 (0.09–10.00)
Lithium vs aripiprazole	<3/284 (<0.9)	12/1386 (0.9)	2.62 (0.20–35.19)
Lithium vs clozapine	0/284 (0.0)	6/1386 (0.4)	NA

Footnotes: Abbreviations: HR, hazard ratio; BD, bipolar disorder; CI, confidence interval; vs, versus; NA, not applicable.

low-dose lithium, anticonvulsant, and antipsychotic monotherapy, nor was low-dose lithium monotherapy when compared with anticonvulsant monotherapy or antipsychotic monotherapy, Fig. 2.

As shown in Table 2 , lithium monotherapy was not associated with an increased rate of out-of-hospital cardiac arrest when compared with monotherapy with each individual mood stabilizing drug (clozapine could not be evaluated as reference, as there was no exposure among cases).

Combination therapy with lithium and one or more other mood stabilizers (9.9% cases vs 12.5% controls) was not associated with increased rate of out-of-hospital cardiac arrest compared with combination therapy with two or more non-lithium mood stabilizers (13.4% cases vs 9.5% controls), HR = 0.58, (95% CI, 0.31–1.08).

DISCUSSION

This study investigated the association between out-of-hospital cardiac arrest of presumed cardiac cause with lithium therapy within 60 days in a matched population of patients with bipolar disorder. In patients with bipolar disorder, lithium treatment was not associated with

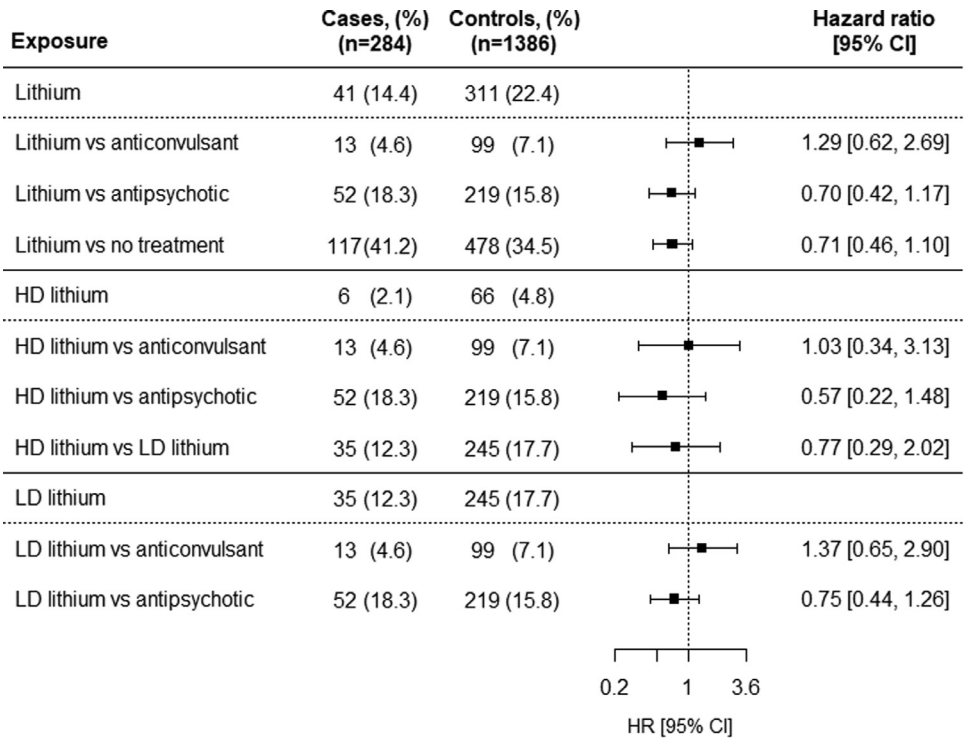

Fig. 2. Adjusted hazard ratios for out-of-hospital cardiac arrest among BD patients for lithium monotherapy overall, high-dose lithium monotherapy, and low-dose lithium monotherapy compared with atypical antipsychotic monotherapy, anticonvulsant monotherapy, and no mood stabilizer treatment. *Abbreviations: HD, high-dose; LD, low-dose; CI, confidence interval; BD, bipolar disorder.*

a significantly increased rate of cardiac arrest compared to any other guideline-recommended mood stabilizing drug treatment, neither in monotherapy, combination therapy, nor in a dose dependent manner. Furthermore, lithium was not associated with a significantly increased rate of cardiac arrest when compared with no mood stabilizing drug treatment. To our knowledge, this is the first nationwide population-based study to investigate the association of lithium use with cardiac arrest.

In a recommendation paper regarding clinical management of arrhythmia risk and psychotropic medication, lithium is classified as a drug with risk of inducing cardiac arrhythmia (Fanoe et al., 2014). These recommandations on lithium are based on small studies or case reports, which have linked lithium to proarrhythmic ECG-changes e.g. QT-prolongation which may lead to potentially fatal arrhythmias such as TdP (Altinbas et al., 2014; Mehta and Vannozzi, 2017). However, lithium has not been subjected to a 'thourough QT study', as is gold standard practice since 2005 for all new drugs with potential proarrythmic and cardiac effects (Fanoe et al., 2014). Concerns regarding the cardiac safety of lithium may have played a role in the decreasing adherence to international guidelines in regard to the prescription patterns of mood stabilizers (Karanti et al., 2016; Kessing et al., 2016; Lyall et al., 2019). Our study suggests that lithium is not associated with increased rate of out-of-hospital cardiac arrest; thus, the potential risk of cardiac arrest should be considered in context with the evidence regarding the clinical efficacy of lithium in bipolar disorder (Grunze et al., 2013; Yatham et al., 2018).

Overall, significantly less cases than controls were exposed to lithium and, in the fully adjusted analyses, we did not observe differences in the rate of cardiac arrest when comparing patients treated with lithium with those receiving other mood stabilizers and even those not exposed to mood stabilizing drug therapy. However, it must be emphasized that our findings may be influenced by surveillance bias, as patients in lithium therapy likely have increased ECG monitoring and clinical monitoring. Further, physicians may be prone to discontinue lithium or switch to a different drug if ECG changes are observed. Although lithium was not associated with cardiac arrest, we cannot derive from the present study that lithium does not cause arrhythmia.

The recommendation paper by Fanoe et al. classified anticonvulsants as a drug class with no risk of cardiac arrhythmia, while previous studies have found atypical antipsychotics to be associated with cardiac arrest (Fanoe et al., 2014; Ray et al., 2009; Weeke et al., 2014). Even though there was no significant association in the present study, we observed a somewhat lower hazard ratio of cardiac arrest for lithium compared with atypical antipsychotics and an slightly higher hazard ratio compared with anticonvulsants. This should be interpreted very cautiously due to the wide confidence intervals of the estimates, but is in line with the current understanding of the arrhythmic risk profiles of these drugs (Polcwiartek et al., 2016).

Our findings are consistent with previous studies, which found no significant difference in the risk of cardiovascular disease in patients taking the most commonly prescribed mood stabilizers (Hayes et al., 2016; Lahteenvuo et al., 2018). The study by Hayes et al. defined cardiovascular disease as a composite outcome consisting of ischemic heart disease, myocardial infarction, and cerebrovascular events using diagnoses from primary and hospital care. The nationwide Finnish study used cardiovascular hospitalizations as a proxy for cardiovascular disease (Lahteenvuo et al., 2018). However, studies using in-hospital data to define cardiac events may underestimate the burden of sudden cardiac arrest, as patients suffering from a fatal cardiac outcome in an outpatient setting would not likely make it to the hospital (Weeke et al., 2012). Using out-of-hospital cardiac arrest as outcome allowed us to extend the current literature on the topic identifying patients who collapsed suddenly and unexpectedly, i.e. patients in whom cardiac arrest may represent the debut of cardiovascular disease.

Strengths and limitations

The major advantages of this study was its nationwide setting, which limited the risk of selection bias. Some of the main sources of bias in observational studies of treatment effects were addressed in our design: Confounding by indication may occur if an unobserved variable (e.g., bipolar disorder) is a risk factor for the studied outcome (cardiac arrest) and at the same time is an indication for the drug of interest. Bias may

also occur if subjects who are prescribed mood stabilizing drugs are more likely to suffer from cardiac arrest than those who are not.

We addressed these issues by using an active comparator design (Lund et al., 2015), comparing different treatments with similar indications. We analyzed our clinical question using time-varying Cox regression models fitted by a nested case-control design. This is not the most well-known method compared to, e.g., a cohort design, but it is a computationally efficient alternative, that has been used previously for pharmacoepidemiologic research when studying large, nationwide datasets (Kessing et al., 2020a, 2020b).

The main limitation of the study is its observational nature, which does not allow us to draw conclusions on the causality of the findings. Moreover, although we did adjust for potential confounders, we cannot rule out unmeasured confounding due to e.g. body mass index, renal function, blood pressure, and smoking status, which could affect our results. Additionally, we did not have access to ECG data, which could clarify if cardiac arrest was preceded by ECG changes.

Another limitation was the lack of statistical power: despite the nationwide setting and almost 15 years of follow-up, only 284 cases of patients with out-of-hospital cardiac arrest and bipolar disorder were observed and eligible for the study. This limited the possibility of conducting additional sensitivity analyses and stratified analyses. Additionally, the lack of evidence for an association cannot be interpreted as evidence of no association.

We did not have data on serum-lithium measurements. In fact, lithium treatment may lead to cardiac arrest through acute lithium-toxicity rather than therapeutic lithium levels directly affecting the myocardium. However, we did not find any dose-dependent difference in the rate of cardiac arrest with lithium treatment.

Conclusion

In this nationwide nested case-control study, lithium was not associated with increased rate of out-of-hospital cardiac arrest in patients with bipolar disorder. However, further studies are needed to corroborate our findings.

Author contributions

Design and conception: DMC, GHM, LVK, CAB. Acquisition, analysis, and interpretation of data: All authors. Drafting of the manuscript: DMC, GHM, CAB. Critical revision of the manuscript drafts: All authors. Statistical analyses: DMC, GHM, TAG, CAB. Supervision: LVK, GG, CTP. All authors have contributed substantially to the study and approved the final version of the manuscript.

Declaration of Competing Interest

LVK received consultancy honoraria from Lundbeck within the previous three years outside of the submitted work. CP received speaker fees from Lundbeck Pharma A/S and grants from The Danish Heart Foundation and Eva and Henry Frænkels Memorial Foundation outside of the submitted work. All other others had to conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2021.100164.

References

Acciavatti, T., Martinotti, G., Corbo, M., Cinosi, E., Lupi, M., Ricci, F., Di Scala, R., D'Ugo, E., De Francesco, V., De Caterina, R., di Giannantonio, M., 2017. Psychotropic drugs and ventricular repolarisation: the effects on QT interval, T-peak to T-end interval and QT dispersion. J. Psychopharmacol. 31, 453–460.

Altinbas, K., Guloksuz, S., Caglar, I.M., Caglar, F.N., Kurt, E., Oral, E.T., 2014. Electrocardiography changes in bipolar patients during long-term lithium monotherapy. Gen. Hosp. Psychiatry 36, 694–697.

Barcella, C.A., Mohr, G., Kragholm, K., Christensen, D., Gerds, T.A., Polcwiartek, C., Wissenberg, M., Bang, C., Folke, F., Torp-Pedersen, C., Kessing, L.V., Gislason, G.H., Bach Søndergaard, K., 2021. Risk of out-of-hospital cardiac arrest in patients with bipolar disorder or schizophrenia. Heart heartjnl-2020-318078.

Borgan, O., Goldstein, L., Langholz, B., 1995. Methods for the analysis of sampled cohort data in the cox proportional hazards model. Ann. Statistics 23, 1749–1778.

Christensen, D.M., Gerds, T., Gislason, G., Torp-Pedersen, C., 2020. Protective association of angiotensin blockade with influenza: a result of immortal time bias? Eur. Heart J. Cardiovasc. Pharmacother..

Christensen, D.M., Rajan, S., Kragholm, K., Sondergaard, K.B., Hansen, O.M., Gerds, T.A., Torp-Pedersen, C., Gislason, G.H., Lippert, F.K., Barcella, C.A., 2019. Bystander cardiopulmonary resuscitation and survival in patients with out-of-hospital cardiac arrest of non-cardiac origin. Resuscitation 140, 98–105.

Fanoe, S., Kristensen, D., Fink-Jensen, A., Jensen, H.K., Toft, E., Nielsen, J., Videbech, P., Pehrson, S., Bundgaard, H., 2014. Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management. Eur. Heart J. 35, 1306–1315.

Grande, I., Berk, M., Birmaher, B., Vieta, E., 2016. Bipolar disorder. Lancet 387, 1561–1572.

Grunze, H., Vieta, E., Goodwin, G.M., Bowden, C., Licht, R.W., Moller, H.J., Kasper, S., 2009. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J. Biol. Psychiatry 10, 85–116.

Grunze, H., Vieta, E., Goodwin, G.M., Bowden, C., Licht, R.W., Moller, H.J., Kasper, S.WFSBP Task Force on Treatment Guidelines for Bipolar Disorders, 2013. The world federation of societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J. Biol. Psychiatry 14, 154–219.

Hayes, J.F., Marston, L., Walters, K., Geddes, J.R., King, M., Osborn, D.P., 2016. Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based cohort study. PLoS Med. 13, e1002058.

Helweg-Larsen, K., 2011. The Danish register of causes of death. Scand. J. Public Health 39, 26–29.

Karanti, A., Kardell, M., Lundberg, U., Landen, M., 2016. Changes in mood stabilizer prescription patterns in bipolar disorder. J. Affect. Disord. 195, 50–56.

Kessing, L.V., 2019. Lithium as the drug of choice for maintenance treatment in bipolar disorder. Acta Psychiatr. Scand. 140, 91–93.

Kessing, L.V., Feldt-Rasmussen, B., Andersen, P.K., Gerds, T.A., Licht, R.W., 2017. Continuation of lithium after a diagnosis of chronic kidney disease. Acta Psychiatr. Scand. 136, 615–622.

Kessing, L.V., Gerds, T.A., Feldt-Rasmussen, B., Andersen, P.K., Licht, R.W., 2015. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. JAMA Psychiatry 72, 1182–1191.

Kessing, L.V., Rytgaard, H.C., Ekstrøm, C.T., Knop, F.K., Berk, M., Gerds, T.A., 2020a. Antidiabetes agents and incident depression: a nationwide population-based study. Diabetes Care 43, 3050–3060.

Kessing, L.V., Rytgaard, H.C., Ekstrøm, C.T., Torp-Pedersen, C., Berk, M., Gerds, T.A., 2020b. Antihypertensive drugs and risk of depression. Hypertension 76, 1263–1279.

Kessing, L.V., Vradi, E., Andersen, P.K., 2016. Nationwide and population-based prescription patterns in bipolar disorder. Bipolar Disord. 18, 174–182.

Kildemoes, H.W., Sorensen, H.T., Hallas, J., 2011. The Danish National Prescription Registry. Scand. J. Public Health 39, 38–41.

Lahteenvuo, M., Tanskanen, A., Taipale, H., Hoti, F., Vattulainen, P., Vieta, E., Tiihonen, J., 2018. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry 75, 347–355.

Lund, J.L., Richardson, D.B., Sturmer, T., 2015. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr. Epidemiol Rep. 2, 221–228.

Lyall, L.M., Penades, N., Smith, D.J., 2019. Changes in prescribing for bipolar disorder between 2009 and 2016: national-level data linkage study in Scotland. Br. J. Psychiatry 215, 415–421.

Lynge, E., Sandegaard, J.L., Rebolj, M., 2011. The Danish national patient register. Scand. J. Public Health 39, 30–33.

Mehta, N., Vannozzi, R., 2017. Lithium-induced electrocardiographic changes: a complete review. Clin. Cardiol. 40, 1363–1367.

Mors, O., Perto, G.P., Mortensen, P.B., 2011. The Danish psychiatric central research register. Scand. J. Public Health 39, 54–57.

Pedersen, C.B., 2011. The Danish civil registration system. Scand. J. Public Health 39, 22–25.

Perkins, G.D., Jacobs, I.G., Nadkarni, V.M., Berg, R.A., Bhanji, F., Biarent, D., Bossaert, L.L., Brett, S.J., Chamberlain, D., de Caen, A.R., Deakin, C.D., Finn, J.C., Grasner, J.T., Hazinski, M.F., Iwami, T., Koster, R.W., Lim, S.H., Huei-Ming Ma, M., McNally, B.F., Morley, P.T., Morrison, L.J., Monsieurs, K.G., Montgomery, W., Nichol, G., Okada, K., Eng Hock Ong, M., Travers, A.H., Nolan, J.P., Utstein, C., 2015. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European resuscitation Council, Australian and New Zealand council on resuscitation, heart and stroke foundation of Canada, InterAmerican Heart Foundation, Resuscitation council of Southern Africa, Resuscitation Council of Asia); and the American heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation 132, 1286–1300.

Polcwiartek, C., Kragholm, K., Schjerning, O., Graff, C., Nielsen, J., 2016. Cardiovascular safety of antipsychotics: a clinical overview. Expert Opin. Drug Saf. 15, 679–688.

R Core Team, 2018. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Ray, W.A., Chung, C.P., Murray, K.T., Hall, K., Stein, C.M., 2009. Atypical antipsychotic drugs and the risk of sudden cardiac death. New Eng. J. Med. 225–235.

Weeke, P., Jensen, A., Folke, F., Gislason, G.H., Olesen, J.B., Andersson, C., Fosbol, E.L., Larsen, J.K., Lippert, F.K., Nielsen, S.L., Gerds, T., Andersen, P.K., Kanters, J.K., Poulsen, H.E., Pehrson, S., Kober, L., Torp-Pedersen, C., 2012. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. Clin. Pharmacol. Ther. 92, 72–79.

Weeke, P., Jensen, A., Folke, F., Gislason, G.H., Olesen, J.B., Fosbol, E.L., Wissenberg, M., Lippert, F.K., Christensen, E.F., Nielsen, S.L., Holm, E., Kanters, J.K., Poulsen, H.E., Kober, L., Torp-Pedersen, C., 2014. Antipsychotics and associated risk of out-of-hospital cardiac arrest. Clin. Pharmacol. Ther. 96, 490–497.

Weeke, P.E., Kellemann, J.S., Jespersen, C.B., Theilade, J., Kanters, J.K., Hansen, M.S., Christiansen, M., Marstrand, P., Gislason, G.H., Torp-Pedersen, C., Bundgaard, H., Jensen, H.K., Tfelt-Hansen, J., 2019. Long-term proarrhythmic pharmacotherapy among patients with congenital long QT syndrome and risk of arrhythmia and mortality. Eur. Heart J..

Wissenberg, M., Lippert, F.K., Folke, F., Weeke, P., Hansen, C.M., Christensen, E.F., Jans, H., Hansen, P.A., Lang-Jensen, T., Olesen, J.B., Lindhardsen, J., Fosbol, E.L., Nielsen, S.L., Gislason, G.H., Kober, L., Torp-Pedersen, C., 2013. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA 310, 1377–1384.

Yatham, L.N., Kennedy, S.H., Parikh, S.V., Schaffer, A., Bond, D.J., Frey, B.N., Sharma, V., Goldstein, B.I., Rej, S., Beaulieu, S., Alda, M., MacQueen, G., Milev, R.V., Ravindran, A., O'Donovan, C., McIntosh, D., Lam, R.W., Vazquez, G., Kapczinski, F., McIntyre, R.S., Kozicky, J., Kanba, S., Lafer, B., Suppes, T., Calabrese, J.R., Vieta, E., Malhi, G., Post, R.M., Berk, M., 2018. Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 20, 97–170.