BJPsych | The British Journal of Psychiatry (2022)
221, 692–700. doi: 10.1192/bjp.2022.54

Effectiveness of medical treatment for bipolar disorder regarding suicide, self-harm and psychiatric hospital admission: between- and within-individual study on Danish national data

Cecilie Fitzgerald, Rune Haubo Bojesen Christensen, Jerome Simons, Per Kragh Andersen, Michael Eriksen Benros, Merete Nordentoft, Annette Erlangsen and Keith Hawton

Background

Mood stabilisers are the main treatment for bipolar disorder. However, it is uncertain which drugs have the best outcomes.

Aims

To investigate whether rates of suicide, self-harm and psychiatric hospital admission in individuals with bipolar disorder differ between mood stabilisers.

Method

A cohort design was applied to people aged ≥15 years who were diagnosed with bipolar disorder and living in Denmark during 1995–2016. Treatment with lithium, valproate, other mood stabilisers and antipsychotics were compared in between- and within-individual analyses, and adjusted for sociodemographic characteristics and previous self-harm.

Results

A total of 33 337 individuals with bipolar disorder were included (266 900 person-years). When compared with individuals not receiving treatment, those receiving lithium had a lower rate of suicide (hazard ratio 0.40, 95% CI 0.31–0.51). When comparing treatment and non-treatment periods in the same individuals, lower rates of self-harm were found for lithium (hazard ratio 0.74, 95% CI 0.61–0.91). Lower rates of psychiatric hospital admission were found for all drug categories compared with non-treatment periods in within-individual analyses (P<0.001). The low rates of self-harm and hospital admission for lithium in within-individual analyses were supported by results of between-individual analyses.

Conclusions

Lithium was associated with lower rates of suicide, self-harm and psychiatric hospital readmission in all analyses. With respect to suicide, lithium was superior to no treatment. Although confounding by indication cannot be excluded, lithium seems to have better outcomes in the treatment of bipolar disorder than other mood stabilisers.

Keywords

Suicide; self-harm; bipolar affective disorders; epidemiology; mood stabilisers.

Bipolar disorder has an estimated lifetime prevalence of 4.4%.[1] The life expectancy of persons with bipolar disorder has been shown to be considerably reduced compared with the general population,[2] with suicide being one of the leading causes of premature death.[3,4] Further, people with bipolar disorder have been reported as having an 11-fold higher risk of suicide and an 18-fold higher risk of self-harm (intentional non-fatal self-poisoning and self-injury) compared with the general population.[5] In addition, relapse of the disorder frequently necessitates psychiatric hospital admission.[6,7]

Mood stabilisers can prevent suicidal behavior.[8] Meta-analyses of randomised controlled trials suggest that lithium might be the most effective drug for preventing relapses and suicide deaths among people with bipolar disorder.[9–11] However, the current body of evidence is restrained by exclusion of persons with suicidal ideation from clinical trials.[9] Recent studies suggest a substantial reduction in the use of lithium,[12] which could be attributed to risks of relapse and suicidal behaviour when patients discontinue treatment, and adverse effects during treatment. These effects, however, might be comparable to those of other mood stabilisers.[13–15] Also, observational studies may be biased by clinicians' preference for prescribing lithium to persons with severe bipolar disorder and high adherence to treatment. Furthermore, only a few drugs have been assessed.[16,17]

Approach

Within-individual comparison is a novel methodological approach, which compares periods on and off medication for the same individual, as a means of evaluating comparative drug effectiveness.[7] Using this technique, lithium was suggested to be more effective than selected mood stabilisers at preventing suicidal behaviour and psychiatric hospital admission.[6,14] Yet, limitations persist. First, only few drugs were assessed. Second, treatment periods were assumed to be of fixed length irrespective of the amount of prescribed medication.[6,14] Third, there is a selection bias because of the inclusion of persons without recent psychiatric hospital contacts, who would be likely to have milder symptoms than those with recent contacts.[7] The aim of the present study was to investigate whether rates of suicide, self-harm and psychiatric hospital admission among individuals with bipolar disorder differ with respect to prescribed mood stabilisers, i.e. lithium, sodium valproate, other mood stabilisers and antipsychotics. We defined dosage-specific treatment lengths and conducted between- and within-individual comparisons.

Method

A cohort design was applied to longitudinal data to study all persons aged 15 years and older who were living in Denmark at some point between 1 January 1995 and 31 December 2016 (N = 6 295 164). In Denmark, every citizen is given a unique personal identification number at birth or upon immigration.[18] Using this identification number, data from the Civil Registration System were linked to complete information on redeemed prescriptions from the National Prescription Registry, data on contacts with psychiatric

https://doi.org/10.1192/bjp.2022.54 Published online by Cambridge University Press

and somatic hospitals from the Psychiatric Central Research Register (PCRR; dating back to 1969) and the National Patient Register, respectively, and information on deaths from the Cause of Death Registry.

Study sample

Individuals recorded with a diagnosis of bipolar disorder from 1 January 1995 onward were included in the analyses on the date of first diagnosis. Psychiatric diagnoses were recorded according to the ICD-10.[19] Diagnoses of bipolar disorders (WHO ICD-10, 2019 edition, https://icd.who.int/browse10/2019/en) were identified by screening all records of admitted patients, as well as those attending emergency rooms or out-patient treatment. Individuals who had been diagnosed with schizophrenia (ICD-10 code F20) were excluded from the study on the date of first diagnosis.

Measures

Treatment periods were determined by using data on mood stabilisers from the National Prescription Registry, which covers all prescriptions redeemed at Danish pharmacies since 1995, including information on drug name, Anatomical Therapeutic Chemical (ATC) code and Defined Daily Dose (DDD; a constant denoting the standard daily dose of each drug and provided by the World Health Organization),[20] number of pills and packages, and date of redeemed prescriptions. We distinguished between treatment with lithium (ATC code N05AN01), sodium valproate (ATC code N03AG01), other mood stabilisers (carbamazepine, ATC code N03AF01; lamotrigine, ATC code N03AX09) and antipsychotics (quetiapine, ATC code N05AH04; olanzapine, ATC code N05AH03, aripiprazole, ATC code N05AX12), all of which are commonly used for treatment of bipolar disorder in Denmark.[21,22] Individuals who had not redeemed prescriptions for any of these drugs were, for our purposes, considered as not receiving treatment. Mood stabilisers are only available by prescription in Denmark.

Drug-specific treatment periods were considered as commencing on the date of when the first prescription was redeemed. Using information on the DDD, strength of the drug, number of pills and packages, we calculated when a next prescription was due (Supplementary Fig. 1 available at https://doi.org/10.1192/bjp.2022.54). The number of available pills in each prescription (i.e. number of pills multiplied by number of packages) was multiplied by their strength and divided by 50% of the DDD, to calculate the treatment length. We opted for a conservative approximation of the DDD to account for variation in dosages. Furthermore, we allowed for accumulation of up to 21 days of pills from previous treatment periods, e.g. to cover holiday closures or vacation periods. A similar approach has previously been employed.[23] The end of treatment was defined as the date when a next prescription of the same drug was due, but had not been redeemed. Distinct treatment lengths were calculated for each drug group, hence allowing individuals to be in simultaneous treatment with multiple drugs.

Outcomes

The primary outcome was suicide, with self-harm and psychiatric hospital admission as secondary outcomes. Suicide deaths were identified in the Cause of Death Registry as an ICD-10 code of X60–X84 or where the manner of death was listed as suicide. Self-harm was defined as a record of hospital contact in the National Patient Register or the PCRR with a diagnosis indicative of self-harm (ICD-10 codes X60–X84), or if the reason of contact was listed as 'suicide attempt'. Self-harm is known to be underreported in Denmark.[24] Therefore, we applied a wider definition in a sensitivity analysis, where people with a recorded main diagnosis of a psychiatric disorder (ICD-10 codes F00-F99) and an additional diagnosis of poisoning or a lesion to the lower arm (ICD-10 codes S51, S55, S59, S61, S65, S69, T36–T50, T52–T60, T39, T40, T42, T43 and T48) were also considered as having self-harmed.[24] Psychiatric hospital admission was defined as an in-patient admission to a psychiatric hospital, as recorded in the PCRR.

Follow-up

The follow-up period covered January 1995 to 31 December 2016. Persons who fulfilled the inclusion criterion of a diagnosis of bipolar disorder but were under 15 years of age were included in the study on their 15th birthday. For persons who died or emigrated, follow-up ended on the date of this event. Time since inclusion was subdivided into distinct treatment periods, denoting whether an individual was receiving treatment or not, and periods were defined for each of the included mood stabilisers.

Statistical analyses

Cox proportional hazards models were used to estimate rate ratios. Between-individual analyses, where periods receiving treatment were compared with periods not receiving treatment between different individuals, were conducted for all outcomes (i.e. suicide, self-harm and psychiatric hospital admission). Repeat events were allowed for self-harm and hospital admission. In the within-individual analysis, treatment and non-treatment periods for the same individual were compared, hence allowing each person to act as their own control. This analysis was performed for the time to non-fatal outcomes (i.e. self-harm and psychiatric hospital admission), where an individual's clock was reset to zero after the occurrence of an event. In this model, robust standard errors were used. Each drug was examined independently in a pairwise comparison (model 1: lithium versus no treatment with any other drug, valproate versus no treatment with any other drug, etc.) and compared with other drugs (model 2: lithium, valproate, other mood stabilisers, antipsychotics and none of these). In the latter model, we used a hierarchical order, where lithium was prioritised over valproate, which was prioritised over other mood stabilisers, which was prioritised over antipsychotics, i.e. if a person was receiving treatment with both lithium and antipsychotics, this person would be considered as receiving treatment with lithium.

The hazard ratios were adjusted for a set of basic covariates: gender (male, female), calendar period (1995–2000, 2001–2005, 2006–2010, 2011–2016) and age group (15–30, 31–40, 41–50, 51–60, 61–70, ≥71 years). Additional covariates were included as a sensitivity analyses: living status (cohabiting, single-adult household), socioeconomic status (working, unemployed, disability pension, retired, student), Charlson Comorbidity Index score (0, 1, ≥2) and previous self-harm (0, ≥1). The Charlson Comorbidity Index gives a score denoting individual risk of mortality based on the number and severity of comorbid health conditions.[25] Covariates were treated as time-varying. We considered the models with basic adjustment as the primary analysis. The fully adjusted model controlled for factors that potentially could act as mediators, and were therefore a potential source of bias. Risks relative to time since initiation of treatment or end of treatment were examined by using cumulative incidence curves, taking the competing risks from all-cause mortality into account.

Additional sensitivity analyses were conducted to explore deviation of the results, depending on the definition of the model. The included sample was redefined as: (a) persons who had been diagnosed with bipolar disorder at least twice (to increase the reliability of the measure); (b) persons with no psychiatric comorbidity (defined as attention-deficit hyperactivity disorder (ICD-10 codes

https://doi.org/10.1192/bjp.2022.54 Published online by Cambridge University Press

F90, F98.8), anxiety disorders (ICD-10 codes F40, F41), autism (ICD-10 codes F84.0, F84.1, F84.5), depression (ICD-10 codes F32–F33), neurotic disorders including obsessive–compulsive disorders (ICD-10 codes F40–F42), personality disorders including borderline personality disorder (ICD-10 code F60), post-traumatic stress disorder (ICD-10 code F43.1), schizophrenia spectrum disorders (ICD-10 codes F20–F25) and substance use disorders (ICD-10 codes F10–F19)), so as to reduce the influence of other disorders; (c) persons in monotherapy (to exclude drug interactions); (d) persons with either bipolar disorder type 1 or type 2 (to account for different patterns in the illness); (e) redefining drug exposure as being a fixed time slot of 90 days for each redeemed prescription; and (f) including persons diagnosed with bipolar disorder (ICD-8 codes 296, 298.19; ICD-10 codes F30–F31) before the study period. Finally, we assessed the effect of using the wider definition of self-harm described above as an outcome. To explore the risk of adverse effects after treatment with lithium and other mood stabilisers, we obtained information on poisonings or adverse effects related to antipsychotics and antiepileptics (ICD-10 codes T42, T43, Y46, Y49) and accidental, intentional or unintentional poisonings (ICD-10 codes X40–X49, X60–X69, Y10–Y19) from somatic hospital contacts in the National Patient Register and causes of death in the Cause of Death Register.

Data management and statistical analyses were conducted with SAS software, version 9.4 for Windows.[26] This study was approved by the Danish Data Protection Agency (approval number RHP-2012-021). Informed consent is neither feasible, nor required, for register-based studies.

Results

A total of 33 337 persons (59.8% female) were diagnosed with bipolar disorder (mean age 54.7 years, s.d. 16.4) between 1995 and 2016 (see Supplementary Fig. 1). These were followed over 266 779 person-years, of which individuals spent 145 899 person-years (54.7%) receiving treatment with mood stabilisers and 120 880 (45.3%) person-years not receiving treatment (see Supplementary Table 1). Allowing for multi-drug use, the largest number of individuals were treated with lithium (68 675 person-years, 25.7%), followed by antipsychotics (44 889 person-years, 16.8%), other mood stabilisers (36 055 person-years, 13.5%) and valproate (14 723 person-years, 5.5%). Mean treatment lengths ranged from 148 to 238 days (Supplementary Table 2), and mean number of treatment periods from 10 to 14.

A total of 580 suicides (mean age 51.9 years; s.d. 13.9) were observed, of which 235 (40.5%) took place when individuals were in treatment periods (see Table 1). With respect to self-harm, 2921 episodes were observed, of which 1390 (47.6%) occurred when individuals were in treatment periods. A total of 83 603 episodes of psychiatric hospital admission were observed, of which 45 761 (54.7%) occurred when individuals were in treatment periods.

We report the findings from basic adjusted models (adjusted for gender, calendar period and age group), as mediation could not be excluded in the fully adjusted models (further adjusted for living status, socioeconomic status, Charlson Comorbidity Index score and previous self-harm) (see Tables 2 and 3).

Suicide

When using a pairwise comparison of treatments (model 1) in the between-individual analysis, individuals receiving treatment with lithium were found to have a lower rate of suicide (hazard ratio 0.40, 95% CI 0.31–0.51) than those not receiving treatment (Table 2). Higher rates of suicide were found for people receiving treatment with antipsychotics (hazard ratio 1.30, 95% CI 1.04–1.62) when compared with those not receiving treatment. When compared directly with other drugs (model 2), lithium was associated with a lower risk of suicide (hazard ratio 0.40, 95% CI 0.31–0.51) than non-treatment, whereas higher rates were found for antipsychotics (hazard ratio 1.88, 95% CI 1.45–2.44) and no significant difference was found for valproate (hazard ratio 0.94, 95% CI 0.62–1.44). Treating 106 individuals with bipolar disorder with lithium was linked to the prevention of one suicide death (Supplementary Table 3).

Self-harm

Treatment with lithium was associated with a lower rate of self-harm (hazard ratio 0.74, 95% CI 0.65–0.85) when using a pairwise comparison with individuals not receiving treatment in the between-individual analysis (model 1), whereas higher rates were found in the same analyses for individuals receiving treatment with valproate (hazard ratio 1.33, 95% CI 1.07–1.66), antipsychotics (hazard ratio 1.23, 95% CI 1.07–1.40) and other mood stabilisers (hazard ratio 1.59, 95% CI 1.40–1.80). When compared with other drugs in a hierarchical manner (model 2) and using those not receiving treatment as a reference, lithium was associated with a lower rate of self-harm (hazard ratio 0.74, 95% CI 0.65–0.85), whereas antipsychotics (hazard ratio 1.17, 95% CI 1.01–1.34) and other mood stabilisers (hazard ratio 1.55, 95% CI 1.31–1.82) were associated with higher rates of self-harm.

In the within-individual comparison, where treatment and non-treatment periods for the same person were compared, lithium was associated with a lower rate of self-harm (hazard ratio 0.74, 95% CI 0.61–0.91) when using pairwise comparison, whereas no significant differences were found for any of the other drugs (Table 3). Comparing all drugs in a hierarchical manner (model 2), we found a lower rate of self-harm associated with lithium (hazard ratio 0.74, 95% CI 0.61–0.91) when using non-treatment periods as a reference, but found no significant differences for valproate (hazard ratio 0.95, 95% CI 0.69–1.30), other mood stabilisers (hazard ratio 0.95, 95% CI 0.77–1.18) or antipsychotics (hazard ratio 1.15, 95% CI 0.94–1.41).

Psychiatric hospital admission

In between-individual analyses, higher rates of psychiatric hospital admission were found for all drug groups when compared with those not receiving treatment (model 1: lithium: hazard ratio 1.13, 95% CI 1.07–1.19; valproate: hazard ratio 1.33, 95% CI 1.22–1.45; other mood stabilisers: hazard ratio 1.19, 95% CI 1.12–1.26; antipsychotics: hazard ratio 1.40, 95% CI 1.33–1.47). When comparing all drugs in a hierarchical manner (model 2) with those not receiving treatment, higher rates of hospital admission were also found for all drug groups.

In the within-individual analyses, the rates of psychiatric hospital admission were lower during treatment periods on lithium (hazard ratio 0.87, 95% CI 0.85–0.89), valproate (hazard ratio 0.89, 95% CI 0.86–0.93) and other mood stabilisers (hazard ratio 0.96, 95% CI 0.93–0.99), when compared pairwise with non-treatment periods (model 1). When comparing all drugs in a hierarchical manner (model 2) with non-treatment periods, lower rates of hospital admission were found for both lithium (hazard ratio 0.87, 95% CI 0.85–0.89) and valproate (hazard ratio 0.91, 95% CI 0.87–0.95), whereas there were higher rates for antipsychotics (hazard ratio 1.07, 95% CI 1.03–1.10). In terms of numbers needed to treat, treatment of four to five individuals with one of the examined mood stabilisers for 1 year was linked to avoidance of one psychiatric hospital admission (Supplementary Table 3).

https://doi.org/10.1192/bjp.2022.54 Published online by Cambridge University Press

Table 1 Characteristics of the sample with respect to suicide

	Any drug		Lithium		Valproate		Other mood stabilisers		Antipsychotics		No treatment	
	n	Incidence rate per 100 000	*n*	Incidence rate per 100 000	*n*	Incidence rate per 100 000	*n*	Incidence rate per 100 000	*n*	Incidence rate per 100 000	*n*	Incidence rate per 100 000
Total	235	182.9	73	106.3	25	169.8	74	205.2	118	262.9	345	249.4
Age, years												
15–30	18	173.4	6	139.0	<3	Not applicable	6	149.5	9	230.3	18	106.1
31–40	35	205.9	13	150.6	6	348.9	9	150.0	17	286.4	65	304.7
41–50	52	202.8	18	127.3	4	141.8	17	216.4	27	303.9	81	309.7
51–60	66	208.3	22	119.9	8	216.9	19	223.3	29	273.0	80	288.9
61–70	49	190.1	11	77.4	4	131.2	19	307.3	27	297.8	58	249.1
≥71	15	83.5	3	33.3	<3	Not applicable	4	114.4	9	139.1	43	187.8
Period												
1995–2000	24	235.2	14	159.7	3	856.2	9	598.6	<3	Not applicable	80	561.2
2001–2005	57	267.2	26	168.3	6	312.9	15	395.9	19	501.8	94	372.4
2006–2010	60	191.0	13	75.1	6	150.9	20	244.0	39	351.7	71	220.6
2011–2016	94	143.5	20	73.7	10	117.9	30	132.9	59	198.6	100	150.0
Gender												
Male	125	253.3	45	161.1	10	160.5	34	273.5	60	359.0	174	322.4
Female	110	139.1	28	68.7	15	176.7	40	169.3	58	205.9	171	202.7
Living status												
Cohabiting/married	156	211.9	43	116.9	20	215.1	52	253.9	79	277.4	232	272.7
Single	79	144.2	30	94.2	5	92.2	22	141.3	39	237.7	112	211.6
Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	<3	Not applicable
Socioeconomic status												
Working	37	137.8	15	87.4	5	238.4	7	97.2	15	237.8	60	179.4
Unemployed	17	123.5	9	158.4	0	0.0	<3	Not applicable	9	152.3	24	137.1
Disability pension	96	202.2	29	117.3	13	204.2	34	241.4	46	246.4	111	292.1
Retired	40	121.6	7	40.5	3	74.2	14	201.1	25	215.2	69	185.2
Student	5	165.0	<3	Not applicable	<3	Not applicable	<3	Not applicable	3	311.9	7	160.0
Missing	40	903.5	11	444.5	3	631.4	15	1186.1	20	1400.4	74	954.8
Charlson Comorbidity Index												
No comorbidity	168	176.6	59	109.7	17	170.9	52	195.0	83	263.9	268	267.2
Index score of 1	36	199.2	10	116.6	<3	Not applicable	16	313.6	15	209.8	41	197.0
Index score of ≥2	31	203.3	4	63.2	6	240.6	6	140.0	20	317.8	36	209.1
History of self-harm												
None	189	162.4	56	90.6	16	120.5	59	179.4	102	249.4	291	228.8
Previous self-harm	46	381.9	17	248.6	9	621.1	15	474.1	16	400.8	54	484.3

Individuals are allowed to contribute to more than one drug if they redeemed prescriptions on several drugs in overlapping periods.

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Table 2 Between individual analyses for the outcomes of suicide, self-harm and psychiatric hospitalisation, model 1[a] and model 2[b] (reference group: persons not receiving treatment with any of the examined drugs)

	n	Person-years	Unadjusted hazard ratio (95% CI)	Basic adjusted hazard ratio (95% CI)[c]	Fully adjusted hazard ratio (95% CI)[d]
Suicide					
Model 1					
Lithium	73	68 675	0.46 (0.36–0.59)***	0.40 (0.31–0.51)***	0.42 (0.33–0.55)***
No treatment	345	145 899	1	1	1
Valproate	25	14 723	0.76 (0.50–1.14)	0.78 (0.51–1.17)	0.77 (0.51–1.16)
No treatment	345	145 899	1	1	1
Other mood stabilisers	74	36 056	0.86 (0.67–1.11)	0.96 (0.75–1.25)	0.99 (0.77–1.28)
No treatment	345	145 899	1	1	1
Antipsychotics	118	44 889	1.10 (0.89–1.36)	1.30 (1.04–1.62)*	1.29 (1.03–1.61)*
No treatment	345	145 899	1	1	1
Model 2					
Lithium	73	68 675	0.46 (0.36–0.59)***	0.40 (0.31–0.51)***	0.42 (0.33–0.55)***
Valproate	24	12 145	0.86 (0.57–1.30)	0.94 (0.62–1.44)	0.94 (0.62–1.44)
Other mood stabilisers	63	27 759	0.93 (0.71–1.21)	1.12 (0.85–1.47)	1.15 (0.87–1.52)
Antipsychotics	75	19 875	1.50 (1.16–1.92)**	1.88 (1.45–2.44)***	1.84 (1.41–2.40)***
None of these	345	138 325	1	1	1
Self-harm					
Model 1					
Lithium	499	68 675	0.77 (0.68–0.87)***	0.74 (0.65–0.85)***	0.77 (0.67–0.87)***
No treatment	1531	145 899	1	1	1
Valproate	176	14 723	1.33 (1.07–1.65)*	1.33 (1.07–1.66)*	1.15 (0.93–1.42)
No treatment	1531	145 899	1	1	1
Other mood stabilisers	472	36 056	1.30 (1.14–1.47) ***	1.23 (1.07–1.40)**	1.15 (1.01–1.32)*
No treatment	1531	145 899	1	1	1
Antipsychotics	705	44 889	1.53 (1.35–1.74)***	1.59 (1.40–1.80)***	1.42 (1.26–1.59)***
No treatment	1531	145 899	1	1	1
Model 2					
Lithium	499	68 675	0.77 (0.68–0.87)***	0.74 (0.65–0.85)***	0.77 (0.67–0.87)***
Valproate	153	12 145	1.34 (1.06–1.69)*	1.39 (1.10–1.76)**	1.21 (0.96–1.52)
Other mood stabilisers	373	27 759	1.27 (1.10–1.46)***	1.24 (1.07–1.43)**	1.17 (1.01–1.34)*
Antipsychotics	365	19 875	1.62 (1.36–1.93)***	1.75 (1.47–2.07)***	1.55 (1.31–1.82)***
None of these	1531	138 325	1	1	1
Psychiatric hospital admission					
Model 1					
Lithium	22 455	68 675	1.15 (1.10–1.22)***	1.13 (1.07–1.19)***	1.12 (1.06–1.18)***
No treatment	37 842	145 899	1	1	1
Valproate	6885	14 723	1.32 (1.21–1.45)***	1.33 (1.22–1.45)***	1.22 (1.12–1.33)***
No treatment	37 842	145 899	1	1	1
Other mood stabilisers	12 153	36 056	1.16 (1.09–1.23)***	1.19 (1.12–1.26)***	1.14 (1.07–1.20)***
No treatment	37 842	145 899	1	1	1
Antipsychotics	22 046	44 889	1.34 (1.27–1.40)***	1.40 (1.33–1.47)***	1.32 (1.25–1.38)***
No treatment	37 842	145 899	1	1	1
Model 2					
Lithium	22 455	68 675	1.15 (1.14–1.17)***	1.13 (1.07–1.19)***	1.12 (1.06–1.17)***
Valproate	5437	12 145	1.29 (1.25–1.33)***	1.30 (1.17–1.44)***	1.19 (1.08–1.32)***
Other mood stabilisers	8460	27 759	1.06 (1.04–1.09)***	1.10 (1.05–1.16)***	1.06 (1.01–1.11)*
Antipsychotics	9409	19 875	1.28 (1.25–1.31)***	1.31 (1.25–1.38)***	1.25 (1.19–1.32)***
None of these	37 842	138 325	1	1	1

a. Model 1: Each model consisted of three subgroups: group 1, persons using the examined drug (e.g. lithium); group 2, persons using other study drugs; and group 3, persons not currently receiving treatment. Only estimates for groups 1 and 3 were reported in the table.
b. Model 2: We constructed a hierarchical variable where lithium was prioritised over valproate, which was prioritised over other mood stabilisers (carbamazepine, lamotrigine), which was prioritised over antipsychotics (quetiapine, olanzapine, aripiprazole). For instance, if a person was receiving treatment with both lithium and antipsychotics, this person would be considered as receiving treatment with lithium.
c. Adjusted for gender, calendar period and age group.
d. Adjusted for gender, calendar period, age group, living status, socioeconomic status and Charlson Comorbidity Index score. This model served as a sensitivity analysis, as described in the Method section.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 3 Within-individual analyses for the outcomes of self-harm and psychiatric hospitalisation, model 1[a] and model 2[b] (reference group: persons not receiving treatment with any of the examined drugs)

	n	Person-years	Unadjusted hazard ratio (95% CI)	Basic adjusted hazard ratio (95% CI)[c]	Fully adjusted hazard ratio (95% CI)[d]
Self-harm					
Model 1					
Lithium	499	68 675	0.76 (0.62–0.93)**	0.74 (0.61–0.91)**	0.74 (0.60–0.91)**
No treatment	1531	145 899	1	1	1
Valproate	176	14 723	0.70 (0.52–0.93)*	0.79 (0.59–1.07)	0.79 (0.59–1.07)
No treatment	1531	145 899	1	1	1
Other mood stabilisers	472	36 056	0.87 (0.71–1.07)	0.93 (0.76–1.15)	0.94 (0.76–1.16)
No treatment	1531	145 899	1	1	1
Antipsychotics	705	44 889	0.84 (0.71–0.99)*	0.99 (0.83–1.18)	0.99 (0.84–1.18)
No treatment	1531	145 899	1	1	1
Model 2					
Lithium	499	68 675	0.75 (0.62–0.92)**	0.74 (0.60–0.91)**	0.73 (0.60–0.90)**
Valproate	153	12 145	0.81 (0.59–1.10)	0.95 (0.69–1.30)	0.94 (0.69–1.30)
Other mood stabilisers	373	27 759	0.90 (0.72–1.11)	0.95 (0.77–1.18)	0.96 (0.77–1.20)
Antipsychotics	365	19 875	1.00 (0.82–1.21)	1.15 (0.94–1.41)	1.14 (0.93–1.40)
None of these	1531	138 325	1	1	1
Psychiatric hospital admission					
Model 1					
Lithium	22 455	68 675	0.87 (0.85–0.89)***	0.87 (0.85–0.89)***	0.87 (0.85–0.89)***
No treatment	37 842	145 899	1	1	1
Valproate	6885	14 723	0.89 (0.86–0.93)***	0.89 (0.86–0.93)***	0.89 (0.86–0.93)***
No treatment	37 842	145 899	1	1	1
Other mood stabilisers	12 153	36 056	0.96 (0.93–0.99)**	0.96 (0.93–0.99)**	0.96 (0.93–0.99)*
No treatment	37 842	145 899	1	1	1
Antipsychotics	22 046	44 889	1.02 (0.99–1.04)	1.03 (1.00–1.06)*	1.03 (1.01–1.06)*
No treatment	37 842	145 899	1	1	1
Model 2					
Lithium	22 455	68 675	0.86 (0.84–0.89)***	0.87 (0.84–0.89)***	0.87 (0.84–0.89)***
Valproate	5437	12 145	0.90 (0.87–0.94)***	0.91 (0.87–0.95)***	0.91 (0.87–0.95)***
Other mood stabilisers	8460	27 759	0.99 (0.95–1.02)	0.99 (0.96–1.02)	0.99 (0.96–1.03)
Antipsychotics	9409	19 875	1.06 (1.03–1.09)***	1.07 (1.03–1.10)***	1.07 (1.03–1.10)***
None of these	37 842	138 325	1	1	1

a. Model 1: Each model consisted of three subgroups: group 1, persons using the examined drug (e.g. lithium); group 2, persons using other study drugs; and group 3, persons not currently receiving treatment. Only estimates for groups 1 and 3 were reported in the table.
b. Model 2: We constructed a hierarchical variable where lithium was prioritised over valproate, which was prioritised over other mood stabilisers (carbamazepine, lamotrigine), which was prioritised over antipsychotics (quetiapine, olanzapine, aripiprazole). For instance, if a person was receiving treatment with both lithium and antipsychotics, these persons would be considered as receiving treatment with lithium.
c. Adjusted for gender, calendar period and age group.
d. Adjusted for gender, calendar period, age group, living status, socioeconomic status, and Charlson Comorbidity Index score. This model served as a sensitivity analysis. as described in the Method section.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Sensitivity analyses

Minor differences were noted between the basic adjusted analyses and the model adjusted for additional covariates, which was conducted as a sensitivity analysis. Restricting the study sample to persons who had been diagnosed with bipolar disorder twice, a hazard ratio of 0.36 (95% CI 0.28–0.48) for suicide was found for those receiving lithium (see Supplementary Tables 2A and 2B). A lower rate of suicide for those receiving lithium was also found when excluding persons with comorbid disorders, restricting the sample to those on monotherapy and using a fixed period for drug exposure (see Supplementary Tables 1A and 1B). Higher suicide rate ratios were observed for other mood stabilisers and antipsychotics in several of the sensitivity analyses. Lithium was associated with lower rates of self-harm in most models, whereas valproate was associated with lower rates of self-harm in two restricted samples.

Cumulative incidences of suicide and self-harm during the first 5 months after treatment initiation were assessed, accounting for competing risks. Lower risks were found among those receiving lithium compared with those receiving other drugs (Fig. 1). With regard to psychiatric hospital admission, lower rates were found for lithium and valproate. Risks of suicide after end of treatment were comparable between all drug groups, whereas risks of suicide attempt were lowest among former users of lithium. Those receiving antipsychotics had lower risks of hospital admission than those receiving other treatments.

Based on information on contacts with somatic hospitals and causes of death, it was evaluated that adverse poisoning events might have occurred in 0.08–0.12% of treated individuals (Supplementary Table 4).

Discussion

Using different analytic strategies, precise measures for treatment lengths and extensive sensitivity analyses, we found that treatment with lithium was associated with lower rates of suicide, self-harm and psychiatric hospital admission compared with no treatment. The majority of examined drugs were associated with lower rates of psychiatric hospital admission compared with no treatment. The favourable results for lithium for all three outcomes found in the between-individual analyses were confirmed in the within-individual analyses. Across drug types, comparable patterns of risks were observed after treatment was discontinued.

Suicide rates were approximately 60% lower among those receiving lithium when compared with persons not receiving treatment, whereas self-harm rates were 26% lower. The lower rates of suicide and self-harm associated with lithium compared with valproate is similar to those of less elaborate studies.[6,7,14] However, the lack of difference between treatment and no treatment for valproate could be related to the low prescription rate for this drug. The elevated rates of suicidal behaviour related to treatment with antipsychotics in the between-individual analyses could be a result of an overrepresentation of persons with more severe illness (who might not have responded to standard treatment). The outcome of psychiatric hospital admission, which was included as a proxy for worsening of the disorder, gave results with opposite interpretations for the between-individual and within-individual analyses. It is likely that the between-individual analyses compare people who have a greater tendency to relapse (and are therefore more likely to be on medication) with less vulnerable individuals (who are therefore less likely to be on medication), and that despite treatment, the first group of individuals are more likely to relapse. The within-individual analyses, on the other hand, are likely to reflect the fact that among people whose disorder and therefore need for treatment varies over time, periods with worsening illness associated with higher rates of hospital admission are more likely to occur during non-treatment periods than treatment periods.

Discontinuation of lithium treatment has previously been linked to increased risk of suicide among persons with bipolar disorder.[27] However, our findings suggest that cumulative risks of suicidal behaviour among former lithium users are comparable to those of other drug groups.

Our finding that lithium is associated with better outcomes for persons with bipolar disorder than other drug therapies is in accordance with previous findings.[7,14] Yet, the use of lithium is declining in some high-income countries.[28,29] This might be because lithium has been linked to adverse outcomes after ending treatment,[13] which could lead practitioners to use alternatives. In this study, we did not find differences in this respect when compared with other treatments, which is supported by other investigations.[15] Another reason for the limited use of lithium is probably that it is not a patented drug and, consequently, not actively promoted commercially. The findings of this study suggest that limited or reduced use of lithium in patients with bipolar disorder could adversely affect their risks of both suicidal behaviour and relapse.

Strengths and limitations

Strengths of this study include the use of nationwide and longitudinal data with complete coverage of all hospital-related events, which have previously been evaluated as reliable. Prescription data with exact dates and number of dispersed pills allowed definition of precise exposure times. All persons with a hospital-based diagnosis were studied over the long term, with no loss to follow-up, unless because of death or emigration. By including all persons with a diagnosis after 1995, accurate estimates were achieved. The within-individual comparison minimised confounding by inherently adjusting for unmeasured, time-constant risk factors. This includes the within-individual factors relating to whether a person is willing to initiate and adhere to treatment. Nevertheless, unmeasured, time-varying confounding cannot be excluded.

One limitation concerns registration of self-harm. Although registration of suicides in Denmark is regarded as being reliable,[30] self-harm episodes may be underreported by up to 30%.[24] However, the rate of underreporting is not expected to vary throughout the population and, therefore, underreporting might only attenuate the relative effect measures. Also, a wider definition of self-harm was applied to compensate for this.[24] Individuals who were exclusively treated in private practice would not have been identified in this study, but these people are likely to have milder symptoms and therefore be at lower risk of adverse outcomes. Information on drugs prescribed during hospital stays and whether drugs were actually consumed was not available. However, if collected pills were not consumed, this would bias our results in a conservative direction. Indication bias cannot be excluded in the within- and between-individual analysis. For example, prescription with lithium requires close follow-up, implying that individuals prescribed this treatment might be more adherent to treatment and have received more personal attention than those prescribed other drugs. Lithium may, therefore, to a larger extent than other mood stabilisers, have been prescribed to persons with a lower than average risk of adversities or by more experienced clinicians who were more confident in the use of the drug, and therefore possibly provided better treatment.

The study findings were evaluated with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) classification framework and were classified as high, as estimates are not likely to change with additional research (Supplementary Table 5).

https://doi.org/10.1192/bjp.2022.54 Published online by Cambridge University Press

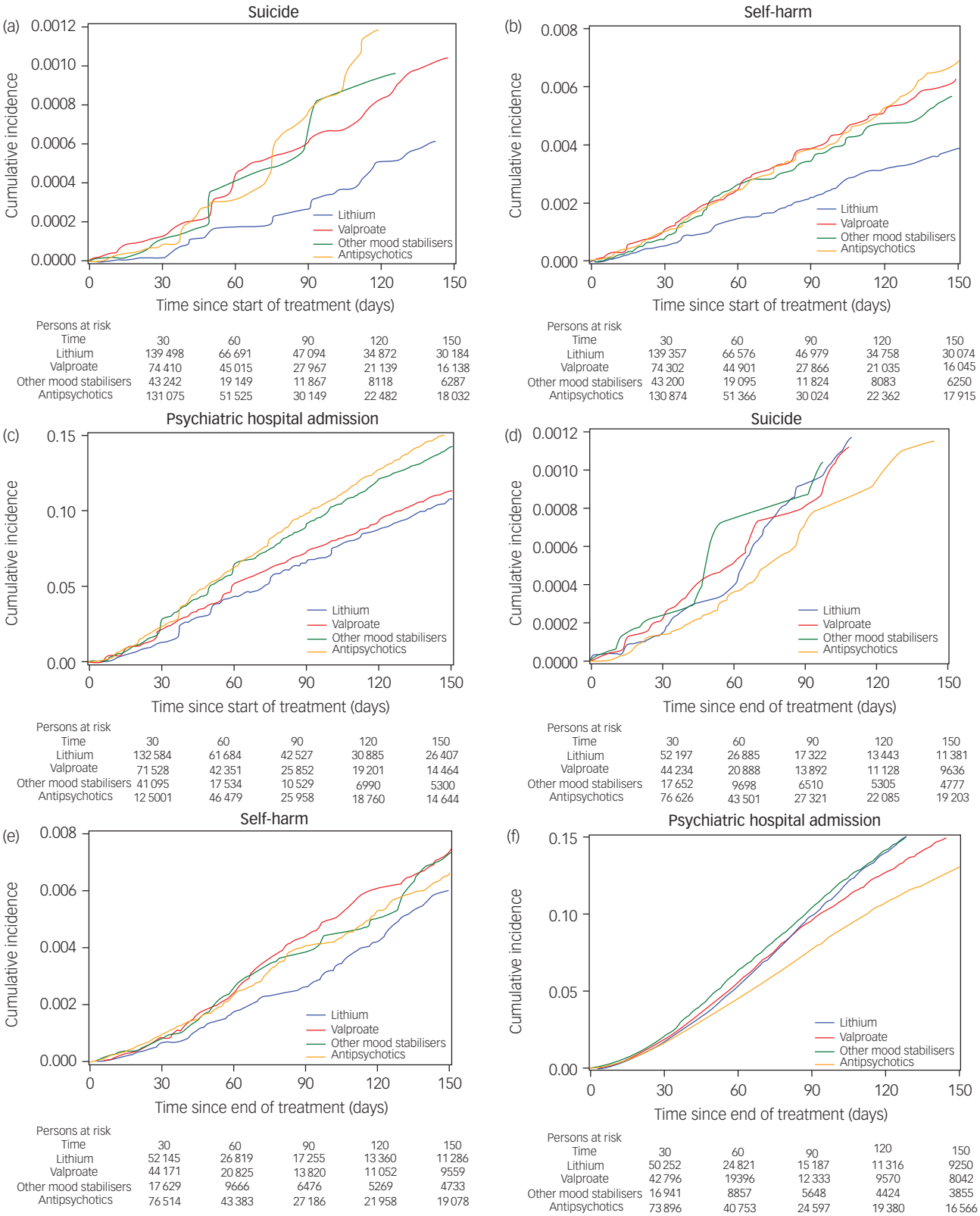

Fig. 1 (a)–(c) Cumulative incidence curves showing (a) death by suicide, (b) self-harm and (c) psychiatric hospital admission in the days after start of treatment. Participants were censored when they ended treatment or migrated. (d)–(f) Cumulative incidence curves showing (d) death by suicide, (e) self-harm and (f) psychiatric hospital admission in the days after end of treatment. Participants were censored when they initiated a new treatment with the same drug or migrated.

In summary, comprehensive analyses showed that treatment with lithium was associated with lower rates of suicide, self-harm and psychiatric hospital admission in persons with bipolar disorder. In addition to lithium, other types of mood stabilisers were linked to lower rates of psychiatric hospital admission. Also, risks after ending treatment differed little between the examined drugs with

https://doi.org/10.1192/bjp.2022.54 Published online by Cambridge University Press

respect to suicidal behaviour. The findings of this study support the preference for lithium as the treatment of choice for people with bipolar disorder.

Cecilie Fitzgerald, Danish Research Institute for Suicide Prevention, Mental Health Centre Copenhagen, Denmark; and Copenhagen Research Center for Mental Health, Mental Health Centre Copenhagen, Denmark; **Rune Haubo Bojesen Christensen**, Copenhagen Research Center for Mental Health, Mental Health Centre Copenhagen, Denmark; **Jerome Simons**, Department of Economics, University of Oxford, UK; **Per Kragh Andersen**, Section of Biostatistics, University of Copenhagen, Denmark; **Michael Eriksen Benros**, Copenhagen Research Center for Mental Health, Mental Health Centre Copenhagen, Denmark; **Merete Nordentoft**, Danish Research Institute for Suicide Prevention, Mental Health Centre Copenhagen, Denmark; Copenhagen Research Center for Mental Health, Mental Health Centre Copenhagen, Denmark; and Institute of Clinical Medicine, University of Copenhagen, Denmark; **Annette Erlangsen**, Danish Research Institute for Suicide Prevention, Mental Health Centre Copenhagen, Denmark; Copenhagen Research Center for Mental Health, Mental Health Centre Copenhagen, Denmark; Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, USA; and Center of Mental Health Research, Australian National University, Australia; **Keith Hawton**, Centre for Suicide Research, University of Oxford, UK; and, Oxford Health NHS Foundation Trust, UK

Correspondence: Cecilie Fitzgerald. Email: Cecilie.aalling.husballe.01@regionh.dk

First received 13 Nov 2021, final revision 3 Mar 2022, accepted 15 Mar 2022

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1192/bjp.2022.54

Data availability

The data that support the findings of this study are available on request from the corresponding author, C.F. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Author contributions

K.H., J.S., M.E.B. and A.E. were responsible for study concept and design. C.F., R.H.B.C., M.E.B., A.E. and K.H. were responsible for acquisition, analysis or interpretation of data. C.F. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. C.F., P.K.A., R.H.B.C., J.S. and A.E. performed statistical analysis. A.E. and M.N. obtained funding. M.N. provided study support. M.E.B., K.H. and M.N. supervised the study.

Funding

The study was supported by a research trainee grant from the Danish Lundbeck Foundation. The research of M.E.B. and R.H.B.C. is supported by grants from the Lundbeck Foundation (grant number R277-2018-1411).

Declaration of interest

K.H. is a member of the Department of Health and Social Care's National Suicide Prevention Strategy for England Advisory Group.

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