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Research Paper

Real-world effectiveness of mood stabilizers on self-harm and suicide attempts in patients with bipolar disorder: A 2-year mirror-image study

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ABSTRACT

Background: Bipolar disorder (BD) is associated with a high incidence of intentional self-harm and suicide attempts (SH/SA), however the effectiveness of mood-stabilizers on SH/SA remains controversial. We aimed to evaluate the real-world effectiveness of mood-stabilizers (lithium, lamotrigine, valproate, olanzapine, risperidone, aripiprazole, clozapine, and quetiapine) on SH/SA in patients with BD.

Methods: A two-year mirror-image design (traditional and reverse) was applied using data from nationwide Danish healthcare registers.

Results: In the traditional mirror-image design, treatment initiation with valproate was associated with a decreased SH/SA-incidence in all patients with BD (from 18 to 11 events/1000 person years (PYs), $P = .03$). In treatment-naïve patients with BD, lithium initiation was associated with a decreased SH/SA-incidence (from 12 to 7 incidents per 1000 PYs, $P < .01$). In the reverse mirror-image design, lamotrigine discontinuation was associated with a decreased SH/SA-incidence for all patients (from 27 to 14 incidents per 1000 PYs, $P = .03$). In a secondary analysis, not restricted to patients with BD, lithium initiation was associated with a decreased SH/SA-incidence (from 16 to 11 events/1000 PYs, $P < .01$) and lithium discontinuation with an increased SH/SA-incidence in males (from 6 to 10 incidents per 1000 PYs, $P = .03$).

Limitations: Time-variant confounders may influence the results and may yield false positive (mimicking either a harmful or a protective effect) or false negative findings (no effect).

Conclusion: The present findings suggest that lithium and valproate may protect against self-harm and suicide attempts in bipolar disorder.

Abbreviations

AED	antiepileptic drug
BD	bipolar disorder
SA	suicide attempt
SH	self-harm

1. Introduction

Bipolar disorder (BD) is a severe, chronic mental illness characterised by recurrent episodes of depression, mania, hypomania, and mixed episodes, with a lifetime prevalence of ~2% (Merikangas et al., 2011; Pini et al., 2005). Patients suffering from BD are at increased risk of suicide and self-harm (SH/SA) compared to the general population, emphasising the importance of optimizing long-term treatment to reduce morbidity and mortality (Chesney et al., 2014; Crump et al., 2013; Hayes et al., 2015; Nordentoft, Mortensen and Pedersen, 2011; Singhal et al., 2014). Long-term mood-stabilizing pharmacotherapy is the recommended treatment. Lithium, antiepileptic drugs (AEDs), and antipsychotics all effectively reduce mood relapses and recurrences in randomised controlled trials (RCTs) with patients with BD (Miura et al., 2014; Smith et al., 2007). However, it has been difficult to estimate their effects on SH/SA from RCTs due to exclusion criteria (i.e. patient history of suicide attempts), short follow-up, and low event rates (Perlis, 2011). A meta-analysis of 48 lithium RCTs suggested that lithium was more effective than placebo in reducing the number of suicides (odds ratio (OR): 0.38, confidence interval (CI): 0.03–0.66), but found no clear effect on intentional self-harm rates (OR: 0.60, CI: 0.27–1.32)(Cipriani et al., 2013a). Observational studies have demonstrated that long-term lithium

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treatment is associated with reduced SH/SA, but whether this effect is shared by other mood stabilizers is still unclear (Ahearn et al., 2013; Baldessarini et al., 2006; Gibbons et al., 2009; Hayes et al., 2016; Smith et al., 2009; Song et al., 2017; Søndergård et al., 2008). On the contrary, in 2008, the U.S. Food and Drug Administration (FDA) issued a warning that AEDs (i.e. valproate and lamotrigine) might carry an increased risk of suicide (US Food and Drug Administration, 2008). Subsequent studies were unable to replicate this finding, and found no effect, or even a protective effect of AEDs on suicidality in BD patients (Ahearn et al., 2013; Arana et al., 2010; Gibbons et al., 2009; Leon et al., 2012; Smith et al., 2009; Song et al., 2017; Søndergård et al., 2008). The effect of antipsychotics (i.e. olanzapine, quetiapine, risperidone, aripiprazole, and clozapine) on SH/SA in BD is sparsely investigated. In two retrospective studies, prescription of antipsychotics was associated with a greater risk of suicide attempts in BD (Ahearn et al., 2013; Yerevanian et al., 2007). Another study found quetiapine and olanzapine to be associated with a higher self-harm risk compared to lithium after propensity score adjustment (Hayes et al., 2016). In contrast, several observational studies have found evidence that antipsychotics reduce the risk of suicide in schizophrenia, with clozapine showing the largest effect (Ma et al., 2018; Ringbäck Weitoft et al., 2014; Taipale et al., 2020). Encouragingly, Nielsen et al. (2012) also found clozapine treatment for BD to be associated with a significant reduction in self-harm in a register-based 2 year mirror-image study (Nielsen et al., 2012). In summary, evidence on the effects of mood stabilizers on SH/SA is currently sparse, and causal inference is limited by the observational nature of the previous study designs.

One of the major limitations in these observational, pharmacoepidemiologic studies is confounding by indication; when the choice of drug may be influenced by certain patient characteristics (such as illness severity or polarity, depressive vs. manic), which may themselves be associated with the outcome of interest (here increased risk of SH/SA). If these characteristics are not properly adjusted for, some drugs may falsely appear to carry an higher or lower risk of SH/SA. This limitation may be partially overcome by applying a 'mirror-image' (and a 'reverse-mirror image') design, in which each patient acts as his/her own control (Gault et al., 2017; Nielsen et al., 2012). In this design, the event rate of an outcome is compared before vs. after initiation (or discontinuation) of the treatment, on an individual level. This design protects against time-invariant confounding. By using nationwide health registries, the incidence of an outcome of interest can be compared for patients in a naturalistic setting, to evaluate the real-world effectiveness of pharmacotherapies (Rohde et al., 2020, 2019). Accordingly, we used Danish register data to evaluate the real-world effectiveness of the most commonly used mood stabilizers for bipolar disorders on SH/SA.

2. Methods

2.1. Registers

The Danish Civil Registration System (DCRS) contains information on all individuals with legal residence in Denmark from 1969 and onwards (Pedersen, 2011). The DCRS includes information on date of birth, birthplace, vital status, as well as a unique 10-digit personal identifier, which enables linkage of information – at the level of the individual – across other national Danish registers. The Danish Psychiatric Central Research Register (DPCRR) contains information on all contacts to Danish psychiatric hospitals, including admissions, and psychiatric diagnoses, and (since 1995) outpatient contacts and emergency room visits (Mors et al., 2011). The Danish National Prescription Register (DNPreR) contains information on all redemptions of prescribed medicine since 1995 (Wallach Kildemoes et al., 2011). The Danish National Patient Register (DNPatR) contains information on all contacts to the healthcare system in Denmark since 1977 (Lynge et al., 2011).

2.2. Study population

We used the DCRS, DPCRR, and DNPreR to identify all Danish residents who received a diagnosis of bipolar affective disorder (ICD-8: 296.19, 296.39, 298.19. ICD-10: F30-F31) in relation to inpatient, outpatient, or emergency room assessment/treatment at a Danish psychiatric hospital in the period from January 1st 1996 to January 1st 2011. Treatment naïve BD patients were defined as patients who did not receive any mood stabilizing medicine (lithium, AEDs or antipsychotics) during the pre-treatment period. As a secondary analysis, data on all individuals who redeemed a prescription of lithium were analysed, regardless of diagnoses.

2.3. Exposure and outcome

The exposure was defined as the first redemption of a prescription for each of the following drugs used in the treatment of bipolar disorder, including lithium, valproate, lamotrigine, olanzapine, quetiapine, risperidone, aripiprazole, and clozapine (Anatomical Therapeutic Chemical (ATC) classification system codes: N05AN01, N03AG01, N03AX09, N05AH03, N05AH04, N05AX08, N05AX12, N05AH02). Outcomes included intentional self-harm or suicide attempts (ICD-10 codes: X60–84) identified through the DPCRR and DNPatR. Completed suicides were not counted in the post-mirror period since completed suicides could only occur in the post-mirror period and never pre-mirror; an imbalance that would inflate the SH/SA rate in the post-mirror period (survival bias).

2.4. Statistical analyses

First, a traditional two-year mirror-image model was applied to assess whether intentional SH/SA were changed after treatment initiation (Gault et al., 2017; Rohde et al., 2018, 2019). This was done by comparing the pre-mirror period (the two years prior to the first redemption of a drug prescription), to the post-mirror period (from the first redemption of a drug prescription and two years forward). If the patient died or stopped redeeming prescriptions for the drug, the post-mirror period was stopped at the date of death or one month after the last drug redemption, respectively, and the pre-mirror period was shortened accordingly. After defining the mirror periods, the incidence of SH/SA attempts were compared between the mirror periods using a paired *t*-test (assumptions for the paired t-tests were checked with Bland-Altman- and QQ-plots). After this, a reverse mirror-image model was applied to assess whether incidents of SH/SA were changed after the treatment discontinuation. In this model, the post-mirror period started one month after the last redeemed prescription and ended two years forward. The pre-mirror period stretched from one month after the last prescription and two years back. Again, the periods were shortened equally if the patient died in the post-mirror period or if the patients had not received a drug for the full two-year pre-mirror period. First, the analyses were done for all patients with BD. Afterwards it was repeated for treatment-naïve patients with BD. As a secondary analysis, we performed a (similar) traditional and reverse mirror-image analysis on the number of SH/SA incidents in all patients receiving lithium (not restricted to patients with BD).

3. Results

3.1. Patient characteristics

Demographics and patient characteristics for mood stabilizer-treated BD patients are presented in Table 1, with all characteristics representing the patients at the time of treatment initiation. As each patient may have received more than one treatment over the course of the follow-up time, each patient may be counted more than once in Table 1. The most commonly prescribed drugs amongst all BD patients were olanzapine, quetiapine, lithium, and lamotrigine (see Table 1). For treatment naïve

Table 1
Demographics and characteristics for all bipolar disorder patients, at the time of treatment initiation. During the follow-up time, one patient may have received more than one treatment and will then be indexed once for each treatment. Data are therefore not mutually exclusive.

Characteristic	Lithium	Lamotrigine	Valproate	Olanzapine	Risperidone	Aripiprazole	Clozapine	Quetiapine
n	6,436	5,468	3,886	7,362	4,537	1,927	489	6,558
Gender, male, n (%)	2,714 (42%)	1,917 (35%)	1,583 (41%)	3,031 (41%)	1,627 (36%)	708 (37%)	209 (43%)	2,439 (37%)
Age of onset of bipolar disorder, years, mean (SD)	44.72 (0.19)	42.02 (0.20)	44.24 (0.26)	44.83 (0.19)	45.41 (0.26)	37.38 (0.31)	35.92 (0.64)	42.44 (0.19)
Age at treatment initiation, years, mean (SD)	48.29 (0.19)	48.14 (0.21)	52.21 (0.26)	52.84 (0.19)	54.14 (0.26)	45.74 (0.33)	47.81 (0.65)	49.85 (0.20)
Charlson cormorbidity index (n)								
0	1,306	843	586	1,252	722	302	77	985
1	4,055	3,409	2,312	4,344	2,645	1,237	312	3,985
2	1,075	1,216	988	1,766	1,170	388	100	1,588
Hospitalizations (mean) (within one year prior to treatment initiation)								
Somatic	1.23	1.76	2.34	1.84	1.78	1.56	1.82	2.19
Psychiatric	1.14	0.90	1.31	1.12	1.08	1.06	0.81	1.03
Education, highest acheived (n)								
Primary school	2,767	2,394	1,864	3,461	2,282	936	310	3,006
Secondary school	1,644	1,262	958	1,709	973	454	95	1,588
Higher education	1,649	1,618	843	1,762	890	494	68	1,732
Marital status (n)								
Living with partner	2,565	1,943	1,322	2,472	1,402	531	117	2,179
Not living with partner	3,803	3,492	2,537	4,845	3,113	1,392	372	4,337
Job (n)								
Working	2,248	1,517	817	1,663	796	341	33	1,445
Jobless	178	100	50	105	52	21	0	84
Not in the labour force	3,903	3,776	2,912	5,388	3,534	1,543	447	4,906

Table 2
Traditional mirror-image design for patients with bipolar disorder (BD) and all patients receiving lithium.

PATIENTS WITH BD			SELF-HARM INCIDENTS AND SUICIDE ATTEMPTS BEFORE		SELF-HARM INCIDENTS AND SUICIDE ATTEMPTS AFTER		
Mood stabilizer	n	Person years	Events	Rate per 1000 person years	Events	Rate per 1000 person years	Paired *t*-test (p-value)
Lithium	6436	9624	149	15	113	12	.08
Females	3720	5559	103	19	73	13	.09
Males	2714	4063	46	11	40	10	.59
Lamotrigine	5468	7738	156	20	142	18	.49
Females	3551	5038	116	23	90	18	.13
Males	1917	2700	40	15	52	19	.29
Valproate	3886	5011	90	18	56	11	.03
Females	2303	2980	73	24	35	12	< 0.01
Males	1583	2030	17	8	21	10	.59
Olanzapine	7362	8303	130	16	135	16	.83
Females	4329	4935	70	14	94	19	.23
Males	3031	3367	60	18	41	12	.11
Risperidone	4537	4866	68	14	62	13	.72
Females	2908	3177	52	16	50	16	.90
Males	1627	1688	16	9	12	7	.49
Aripiprazole	1927	2099	39	19	39	19	1.00
Females	1219	1318	33	25	30	23	.78
Males	708	782	6	8	9	12	.49
Clozapine	489	711	15	21	8	11	.31
Females	280	390	–	–	–	–	–
Males	209	321	–	–	–	–	–
Quetiapine	6558	8788	205	23	171	19	.16
Females	4119	5601	137	24	123	22	.51
Males	2439	3188	68	21	48	15	.08
ALL PATIENTS							
Lithium	16,515	20,121	325	16	217	11	< 0.01
Females	9928	12,093	229	19	159	13	< 0.01
Males	6554	8019	96	12	58	7	.02

patients, antipsychotics (combined) were the most commonly prescribed drugs, followed by lithium (see Table 3). As seen in Table 2, 3 and 4, the raw SH/SA rates were higher for female compared to male BD patients and varied between treatment groups, however no between-individual comparisons were conducted in the present study. In the secondary analyses, amongst the lithium-treated patients without a BD-diagnosis, we identified patients with the following diagnoses: F2x schizophrenia-related disorders (n = 2426), F32–39 other affective disorders than mania/BD (n = 9097), F4x anxiety and somatoform disorders (n = 562), F6x personality disorders (n = 180).

3.2. Mirror-image model

In the traditional mirror-image model (Table 2), the mean follow-up time was between 1.07 and 1.50 years for all BD patients, and between 0.92 and 1.44 for treatment naïve BD patients. In BD patients, lithium

Table 3
Traditional mirror-image design for treatment naïve patients with bipolar disorder (BD).

TREATMENT NAÏVE PATIENTS WITH BD			SELF-HARM INCIDENTS AND SUICIDE ATTEMPTS BEFORE		SELF-HARM INCIDENTS AND SUICIDE ATTEMPTS AFTER		
Mood stabilizer	n	Person years	Events	Rate per 1000 person years	Events	Rate per 1000 person years	Paired *t*-test (p-value)
Lithium	3842	5543	69	12	37	7	< 0.01
Females	2197	3160	44	14	21	9	.01
Males	1643	2381	25	11	16	7	.24
Lamotrigine	2060	2557	38	15	46	18	.47
Females	1360	1692	31	18	28	12	.75
Males	700	865	7	8	18	21	.08
Valproate	1249	1234	21	17	16	13	.48
Females	723	730	–	–	–	–	.51
Males	526	504	–	–	–	–	.78
Olanzapine	3330	3308	59	18	70	21	.53
Females	1920	1928	25	13	50	26	.10
Males	1409	1380	34	25	20	14	.11
Risperidone	2134	1972	16	8	25	13	.32
Females	1409	1325	–	–	–	–	.35
Males	724	647	–	–	–	–	.74
Aripiprazole	412		–	–	–	–	–
Females	257		–	–	–		–
Males	155		–	–	–	–	–
Quetiapine	2169	2409	62	26	51	21	.36
Females	1357	1505	34	23	33	22	.92
Males	812	904	28	36	18	24	.13

Table 4
Reverse mirror-image design for all patients with bipolar disorder (BD) and all patients receiving lithium, showing the number and incidence rates per 1000 person years of self-harm incidents and suicide attempts, before and after treatment discontinuation. Significant differences (P-value < 0.05) between the number of incidents before vs. after treatment discontinuation are marked in bold.

PATIENTS WITH BD			SELF-HARM INCIDENTS AND SUICIDE ATTEMPTS BEFORE		SELF-HARM INCIDENTS AND SUICIDE ATTEMPTS AFTER		
Mood stabilizer	n	Person years	Events	Rate per 1000 person years	Events	Rate per 1000 person years	Paired *t*-test (p-value)
Lithium	6749	6859	68	10	75	11	.57
Females	4097	4244	44	10	52	12	.45
Males	2651	2614	24	9	23	9	.88
Lamotrigine	2996	2559	69	27	37	14	.03
Females	1901	1594	45	22	18	11	< 0.01
Males	1094	966	24	25	19	20	.66
Valproate	2434	1832	31	17	36	20	.61
Females	1470	1130	22	19	23	20	.91
Males	963	702	9	13	13	19	.41
Olanzapine	5360	4040	95	24	79	20	.33
Females	3134	2383	63	26	50	21	.31
Males	2225	1658	32	19	29	17	.77
Risperidone	3788	2787	59	21	49	18	.38
Females	2428	1821	46	25	36	20	.32
Males	1358	965	13	13	13	13	.00
Aripiprazole	1441	910	33	36	21	23	.22
Females	913	578	27	47	12	21	.08
Males	528	331	6	18	9	27	.49
Quetiapine	3282	2275	50	22	35	15	.25
Females	1970	1400	33	17	22	9	.33
Males	1312	876	17	57	13	39	.53
ALL PATIENTS							
Lithium	16,234	13,581	129	9	148	11	.33
Females	9950	8469	99	12	96	11	.86
Males	6248	5104	30	6	52	10	.02

treatment initiation was weakly (non-significantly) associated with a decreased SH/SA rate in females, but not in males. In the secondary analysis (not restricted to patients with BD), lithium treatment initiation was associated with a significant decrease in SH/SA rates in both females and males. Focusing on treatment naïve BD patients (Table 3), lithium treatment initiation was associated with a highly significant decrease in the SH/SA rate in females (and both sexes combined), but showed only a non-significant decrease in males. Lamotrigine treatment initiation was not associated with any significant changes in SH/SA rates in BD patients. Valproate treatment initiation was associated with a significant decrease in the SH/SA rate in females, but not in males. In treatment-naïve BD patients, this association was attenuated and non-significant. Valproate thus appeared to modestly decrease the risk of SH and SA in females. None of the investigated antipsychotics were as-

sociated with any significant changes in SH/SA rates upon treatment initiation.

3.3. Reverse mirror-image model

In the reverse mirror-image model, the mean follow-up time for BD patients was between 0.63 and 1.02 years (Table 4). Lithium treatment discontinuation was associated with a significant increase in the SH/SA rate in males but not in females (not restricted to BD) providing modest support for a protective effect of lithium. In BD patients specifically, lithium discontinuation was not associated with any significant changes in SH/SA rates. Lamotrigine treatment discontinuation was associated with a highly significant increase in the SH/SA rate in females, with no significant change in males with BD. Valproate treatment discontinuation was not associated with any significant changes in SH/SA rates. None of the investigated antipsychotics was significantly associated with any changes in the SH/SA rate in BD patients upon treatment discontinuation.

4. Discussion

The present study was designed to evaluate the real-world effectiveness of mood stabilizers on self-harm and suicide attempts in BD patients. Our findings support a protective effect of lithium and valproate. We found no evidence for neither protective nor harmful effects of antipsychotics.

Our findings regarding lithium are consistent with a large body of literature supporting a protective effect against SH and SAs in BD, from both observational and experimental designs (Ahearn et al., 2013; Baldessarini et al., 2006; Cipriani et al., 2013a; Gibbons et al., 2009; Hayes et al., 2016; Smith et al., 2009; Song et al., 2017; Søndergård et al., 2008). While our results for lithium on all patients with BD were non-significant, a secondary analysis of all patients redeeming lithium, regardless of diagnosis, revealed a significant difference compatible with a protective effect. The implications of these findings are discussed below.

Whereas our results are supportive of a protective effect of valproate, previous studies have provided somewhat inconsistent results (Ahearn et al., 2013; Cipriani et al., 2013b; Gibbons et al., 2009; Goodwin et al., 2003; Hayes et al., 2016; Smith et al., 2014; Song et al., 2017; Yerevanian et al., 2003, 2007). Gibbons et al. conducted a within-individual analysis of BD patients and found that treatment with valproate was associated with a significantly decreased SH/SA rate, compared to the pre-treatment period, in congruence with our findings (Gibbons et al., 2009). Similarly, Yerevanian et al. (2007) performed a retrospective study of 405 veterans with BD (90% male) and found significantly higher rates of suicidal behaviour after valproate discontinuation than during valproate treatment, also indicating a protective effect. Conversely, another within-individual analysis of BD patients, by Song et al., found no protective effect of valproate on suicide-related events (Song et al., 2017). Although these findings are discrepant (protective effect vs. no effect) they nevertheless oppose a harmful effect of valproate on the risk of SH/SAs in patients with BD.

The effect of lamotrigine on SH/SA in BD patients is sparsely studied. Two previous studies conducted within-individual analyses of BD patients, comparing SH/SA rates in periods on with periods off medication, however their results are inconsistent. Gibbons et al. found evidence supportive of a protective effect of lamotrigine against SH/SA, while Song et al. found no effect of lamotrigine on suicidal behaviour in within-individual analysis, where periods with vs. without medication were compared (Gibbons et al., 2009; Song et al., 2017). Our results are suggestive of a harmful effect in the reverse-mirror image model, however this finding should be interpreted with caution given the observational design and requires further investigation. The decrease in SH/SA associated with lamotrigine discontinuation could be due to, for example, concurrent initiation of other (more effective) medications, or if the lamotrigine discontinuation was indicated by a recent (and lasting) decrease in SH/SA.

Several studies have found antipsychotic treatment to be associated with a higher risk of SH/SA compared to other mood stabilizers in between-individual analyses, however these results may also be due to confounding by indication (Ahearn et al., 2013; Koek et al., 2012; Yerevanian et al., 2007). A within-individual-analysis Song et al. found a higher risk of suicide-related events in BD patients during periods with antipsychotic treatments, compared to periods without treatment (reported in their supplementary material), compatible with a harmful effect of antipsychotics. The present study did not find any effect of antipsychotics on SH/SA. Direct comparison between these discrepant findings is difficult, as Song et al. only reported a combined result for all antipsychotics, and due to the different study designs. In patients with schizophrenia, treatment with antipsychotics is associated with a lower risk of suicidality in between-individual analyses (Ma et al., 2018; Ringbäck Weitoft et al., 2014; Taipale et al., 2020). However no study has employed within-individual analysis to investigate the effect of antipsychotics on the risk of suicide-related events in schizophrenia. The only antipsychotic drug approved for treatment of suicidality in schizophrenia is clozapine, based on the results of the InterSePT trial, which found less suicidal behaviour in patients randomized to clozapine vs. olanzapine (Meltzer et al., 2003). Clozapine treatment initiation was also associated with a reduction the incidence of self-harm or overdoses in BD patients in a mirror-image study by Nielsen et al., who used the same data sources as the present study (Nielsen et al., 2012). Overdoses (ICD-10: T39–42) were not investigated in the present study, which may explain why clozapine treatment initiation was only associated with a non-significant reduction in SH/SA rates (from 21 to 11/1000 person years; $P = .31$) in the present study.

The present findings indicate potential gender differences in the effects of mood-stabilizers on SH/SA in patients with BD. Female patients with BD had higher rates of SH/SA than males, replicating findings from prior studies (Clements et al., 2015; Hawton et al., 2003). Prior studies have found no effect of sex on the association between mood-stabilizing treatment and suicide (Søndergård et al., 2008) or clinical response (Viguera et al., 2000) and the topic remains sparsely investigated.

The findings of the present study are of high clinical relevance and suggest, in consonance with the previous literature, that lithium and valproate may be more effective in preventing SH/SA in patients with BD compared to antipsychotics. The use of lithium for BD has decreased significantly during the past decades in several countries, a potentially unfortunate trend in light of the present results (Bjørklund et al., 2016; Carlborg et al., 2015; Köhler-Forsberg et al., 2020; Rhee et al., 2020).

The mirror-image design of the present study protects it from all time-invariant covariates, limiting the risk of confounding by indication, a sore point in many previous observational studies. When certain medications are often prescribed for patients with a high risk SH/SA, those medications will appear to be associated with SH/SA. However, by comparing the SH/SA-incidence before vs. after treatment initiation/discontinuation, the mirror-image design attempts to avoid this confounding effect. Furthermore, the dual mirror image designs (traditional and reverse) provide mutual support for one another. The nationwide and naturalistic design of our study provides high generalizability to clinical settings in similar populations.

The present study has several limitations. First, the validity and reliability of the register-based SH/SA-statistics applied here is questionable. The incidence of SH/SAs is most likely under-recorded (Nordentoft, 2007) which could potentially bias the present results. Second, the study lacked information on time-variant factors that could accompany treatment initiation or discontinuation, such as initiation/discontinuation of other treatments – pharmacological or psychosocial – as well as other events. For example, if two drugs, “A” and “B” are commonly prescribed together, where “A” reduces SH/SA events and “B” has no effect, then “B” could be associated with a decrease in

SH/SA events, despite having no protective effect. Third, some events (i.e. wish to get pregnant) could guide pharmacological choices (i.e. avoiding valproate due to teratogenicity), and concurrently be associated with increasing/decreasing SH/SA risk (i.e. lowered suicide risk during pregnancy and post-partum)(Lindahl et al., 2005). Both of these limitations could bias our results in either direction, yielding both false positive and false negative results. Fourth, SH or SAs may lead to the identification and diagnosis of BD, which could inflate the rate of SH/SA events observed prior to treatment and thus give the false appearance of a protective effect of the treatment. Fifth, increased surveillance during treatment may lead to a better (higher) reporting of SH/SA events, compared to before treatment (where underreporting is likely), thus giving the false appearance of a harmful effect of treatments. The use of the reverse mirror-image design (in addition to the traditional mirror-image design) should strengthen the present study against some of these time-variant confounders, however residual (time-variant) confounding may still bias the results. For example, in the reverse mirror-image design, discontinuation of a treatment may be motivated by illness remission, where the patient no longer needs the medication, or illness exacerbation, where treatment may be intensified and medications changed or added. Both of these examples could lead to fewer incidents of SH/SA in the post-mirror window and mimic the appearance of a harmful effect of the discontinued treatment. Another factor not considered in the present data are the possible derived effect of therapeutic drug monitoring (TDM) applied in lithium treatment. Hypothetically, frequent blood samples could facilitate closer patient-physician contact, leading to better patient outcomes. However, in Denmark routine blood sampling for TDM is performed at large laboratories, limiting this putative effect.

In this nationwide, register-based, mirror-image study (traditional and reverse), we found further evidence supporting a protective effect of lithium and valproate on the risk of SH/SAs in BD patients, and no indications of a harmful effect of antipsychotics. Our findings call for further investigations into the effects of lamotrigine on SH/SAs in patients with BD.

Author statement Contributors

OHJ interpreted the results, drafted and revised the manuscript. SDO and JN interpreted the results and revised the manuscript. CR analysed the data, interpreted the results and revised the manuscript.

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References

Ahearn, E.P., Chen, P., Hertzberg, M., Cornette, M., Suvalsky, L., Cooley-Olson, D., Swanlund, J., Eickhoff, J., Becker, T., Krahn, D., 2013. Suicide attempts in veterans with bipolar disorder during treatment with lithium, divalproex, and atypical antipsychotics. J. Affect. Disord. 145, 77–82.

Arana, A., Wentworth, C.E., Ayuso-Mateos, J.L., Arellano, F.M., 2010. Suicide-related events in patients treated with antiepileptic drugs. N. Engl. J. Med. 363, 542–551.

Baldessarini, R.J., Tondo, L., Davis, P., Pompili, M., Goodwin, F.K., Hennen, J., 2006. Decreased risk of suicides and attempts during long-term lithium treatment: a meta–analytic review. Bipolar Disord. 8, 625–639.

Bjørklund, L., Horsdal, H.T., Mors, O., Østergaard, S.D., Gasse, C., 2016. Trends in the psychopharmacological treatment of bipolar disorder: a nationwide register-based study. Acta Neuropsychiatr. 28, 75–84.

Carlborg, A., Ferntoft, L., Thuresson, M., Bodegard, J., 2015. Population study of disease burden, management, and treatment of bipolar disorder in S weden: a retrospective observational registry study. Bipolar Disord. 17, 76–85.

Chesney, E., Goodwin, G.M., Fazel, S., 2014. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 13, 153–160.

Cipriani, A., Hawton, K., Stockton, S., Geddes, J.R., 2013a. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ 346, f3646.

Cipriani, A., Reid, K., Young, A.H., Macritchie, K., Geddes, J., 2013b. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Systemat. Rev. 10.

Clements, C., Jones, S., Morriss, R., Peters, S., Cooper, J., While, D., Kapur, N., 2015. Self-harm in bipolar disorder: findings from a prospective clinical database. J. Affect. Disord. 173, 113–119.

Crump, C., Sundquist, K., Winkleby, M.A., Sundquist, J., 2013. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 70, 931–939.

Gault, N., Castañeda-Sanabria, J., De Rycke, Y., Guillo, S., Foulon, S., Tubach, F., 2017. Self-controlled designs in pharmacoepidemiology involving electronic healthcare databases: a systematic review. BMC Med. Res. Method. 17, 25.

Gibbons, R.D., Hur, K., Brown, C.H., Mann, J.J., 2009. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. Arch. Gen. Psychiatry 66, 1354–1360.

Goodwin, F.K., Fireman, B., Simon, G.E., Hunkeler, E.M., Lee, J., Revicki, D., 2003. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 290, 1467–1473.

Hawton, K., Harriss, L., Hall, S., Simkin, S., Bale, E., Bond, A., 2003. Deliberate self-harm in Oxford, 1990-2000: a time of change in patient characteristics. Psychol. Med. 33, 987.

Hayes, J., Miles, J., Walters, K., King, M., Osborn, D., 2015. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr. Scand. 131, 417–425.

Hayes, J.F., Pitman, A., Marston, L., Walters, K., Geddes, J.R., King, M., Osborn, D.P., 2016. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: a UK population-based electronic health records study. JAMA Psychiatry 73, 630–637.

Koek, R.J., Yerevanian, B.I., Mintz, J., 2012. Subtypes of antipsychotics and suicidal behavior in bipolar disorder. J. Affect. Disord. 143, 27–33.

Köhler-Forsberg, O., Gasse, C., Hieronymus, F., Petersen, L., Christensen, R.H., Nierenberg, A.A., Østergaard, S.D., 2020. Pre-diagnostic and post-diagnostic psychopharmacological treatment of 16 288 patients with bipolar disorder. Bipolar Disord..

Leon, A.C., Solomon, D.A., Li, C., Fiedorowicz, J.G., Coryell, W.H., Endicott, J., Keller, M.B., 2012. Antiepileptic drugs for bipolar disorder and the risk of suicidal behavior: a 30-year observational study. Am. J. Psychiatry 169, 285–291.

Lindahl, V., Pearson, J.L., Colpe, L., 2005. Prevalence of suicidality during pregnancy and the postpartum. Arch. Women's Mental Health 8, 77–87.

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

Ma, C.H., Chang, S.S., Tsai, H.J., Gau, S.F., Chen, I.M., Liao, S.C., Chien, Y.L., Hsieh, M., Wu, C.S., 2018. Comparative effect of antipsychotics on risk of self-harm among patients with schizophrenia. Acta Psychiatr. Scand. 137, 296–305.

Meltzer, H.Y., Alphs, L., Green, A.I., Altamura, A.C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M.Z., Kane, J., 2003. Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). Arch. Gen. Psychiatry 60, 82–91.

Merikangas, K.R., Jin, R., He, J.-.P., Kessler, R.C., Lee, S., Sampson, N.A., Viana, M.C., Andrade, L.H., Hu, C., Karam, E.G., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch. Gen. Psychiatry 68, 241–251.

Miura, T., Noma, H., Furukawa, T.A., Mitsuyasu, H., Tanaka, S., Stockton, S., Salanti, G., Motomura, K., Shimano-Katsuki, S., Leucht, S., 2014. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatr. 1, 351–359.

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

Nielsen, J., Kane, J.M., Correll, C.U., 2012. Real-world effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. Bipolar Disord. 14, 863–869.

Nordentoft, M., 2007. Prevention of suicide and attempted suicide in Denmark. Dan. Med. Bull. 54, 306–369.

Nordentoft, M., Mortensen, P.B., Pedersen, C.B., 2011. Absolute risk of suicide after first hospital contact in mental disorder. Arch. Gen. Psychiatry 68, 1058–1064.

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

Perlis, R.H., 2011. Hard outcomes: clinical trials to reduce suicide. Am. Psychiatr. Assoc. 168 (10), 1009–1011.

Pini, S., de Queiroz, V., Pagnin, D., Pezawas, L., Angst, J., Cassano, G.B., Wittchen, H.-.U., 2005. Prevalence and burden of bipolar disorders in European countries. Eur. Neuropsychopharmacol. 15, 425–434.

Rhee, T.G., Olfson, M., Nierenberg, A.A., Wilkinson, S.T., 2020. 20-year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. Am. J. Psychiatry appi. ajp. 2020.19091000.

Ringbäck Weitoft, G., Berglund, M., Lindström, E.A., Nilsson, M., Salmi, P., Rosén, M., 2014. Mortality, attempted suicide, re-hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden—A register-based study. Pharmacoepidemiol Drug Saf. 23, 290–298.

Rohde, C., Brink, P., Østergaard, S.D., Nielsen, J., 2020. The use of stimulants in depression: results from a self-controlled register study. Austr. New Zealand J. Psychiatr., 0004867420924076.

Rohde, C., Hilker, R., Siskind, D., Nielsen, J. , 2018. Real-world effectiveness of clozapine for intellectual disability: results from a mirror-image and a reverse-mirror-image study. J. Psychopharmacol. 32, 1197–1203.

Rohde, C., Siskind, D., de Leon, J., Nielsen, J., 2019. Antipsychotic Medication Exposure, Clozapine, and Pneumonia: results from a Self-controlled Study. Acta Psychiatr. Scand..

Singhal, A., Ross, J., Seminog, O., Hawton, K., Goldacre, M.J., 2014. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. J. R. Soc. Med. 107, 194–204.

Smith, E.G., Austin, K.L., Kim, H.M., Miller, D.R., Eisen, S.V., Christiansen, C.L., Kilbourne, A.M., Sauer, B.C., McCarthy, J.F., Valenstein, M., 2014. Suicide risk in Veterans Health Administration patients with mental health diagnoses initiating lithium or valproate: a historical prospective cohort study. BMC Psychiatry 14, 357.

Smith, E.G., Søndergård, L., Lopez, A.G., Andersen, P.K., Kessing, L.V., 2009. Association between consistent purchase of anticonvulsants or lithium and suicide risk: a longitudinal cohort study from Denmark, 1995–2001. J. Affect. Disord. 117, 162–167.

Smith, L.A., Cornelius, V., Warnock, A., Bell, A., Young, A.H., 2007. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. Bipolar Disord. 9, 394–412.

Song, J., Sjölander, A., Joas, E., Bergen, S.E., Runeson, B., Larsson, H., Landén, M., Lichtenstein, P., 2017. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. Am. J. Psychiatry 174, 795–802.

Søndergård, L., Lopez, A.G., Andersen, P.K., Kessing, L.V., 2008. Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. Bipolar Disord. 10, 87–94.

Taipale, H., Tanskanen, A., Mehtälä, J., Vattulainen, P., Correll, C.U., Tiihonen, J., 2020. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatr. 19, 61–68.

US Food and Drug Administration. Antiepileptic drugs and suicidality. 2008. Available at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf.

Viguera, A.C., Tondo, L., Baldessarini, R.J., 2000. Sex differences in response to lithium treatment. Am. J. Psychiatry 157, 1509–1511.

Wallach Kildemoes, H., Toft Sørensen, H., Hallas, J., 2011. The Danish national prescription registry. Scand. J. Public Health 39, 38–41.

Yerevanian, B.I., Koek, R.J., Mintz, J., 2003. Lithium, anticonvulsants and suicidal behavior in bipolar disorder. J. Affect. Disord. 73, 223–228.

Yerevanian, B.I., Koek, R.J., Mintz, J., 2007. Bipolar pharmacotherapy and suicidal behavior: part 3: impact of antipsychotics. J. Affect. Disord. 103, 23–28.