Original Investigation

Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment

A UK Population-Based Electronic Health Records Study

Joseph F. Hayes, MSc, MBChB; Alexandra Pitman, PhD; Louise Marston, PhD; Kate Walters, PhD; John R. Geddes, MD; Michael King, PhD; David P. J. Osborn, PhD

IMPORTANCE Self-harm is a prominent cause of morbidity in patients with bipolar disorder and is strongly associated with suicide. There is evolving evidence that lithium use may reduce suicidal behavior, in addition to concerns that the use of anticonvulsants may increase self-harm. Information is limited about the effects of antipsychotics when used as mood stabilizer treatment. Rates of unintentional injury are poorly defined in bipolar disorder, and understanding drug associations with this outcome may shed light on mechanisms for lithium's potential antisuicidal properties through reduction in impulsive aggression.

OBJECTIVE To compare rates of self-harm, unintentional injury, and suicide in patients with bipolar disorder who were prescribed lithium, valproate sodium, olanzapine, or quetiapine fumarate.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a propensity score (PS)–adjusted and PS-matched longitudinal cohort study in a nationally representative UK sample using electronic health records data collected between January 1, 1995, and December 31, 2013. Participants included all patients diagnosed as having bipolar disorder who were prescribed lithium, valproate, olanzapine, or quetiapine as maintenance mood stabilizer treatment.

MAIN OUTCOMES AND MEASURES The primary outcome was any form of self-harm. Secondary outcomes were unintentional injury and suicide.

RESULTS Of the 14 396 individuals with a diagnosis of BPD, 6671 were included in the cohort, with 2148 prescribed lithium, 1670 prescribed valproate, 1477 prescribed olanzapine, and 1376 prescribed quetiapine as maintenance mood stabilizer treatment. Self-harm rates were lower in patients prescribed lithium (205; 95% CI, 175-241 per 10 000 person-years at risk [PYAR]) compared with those prescribed valproate (392; 95% CI, 334-460 per 10 000 PYAR), olanzapine (409; 95% CI, 345-483 per 10 000 PYAR), or quetiapine (582; 95% CI, 489-692 per 10 000 PYAR). This association was maintained after PS adjustment (hazard ratio [HR], 1.40; 95% CI, 1.12-1.74 for valproate, olanzapine, or quetiapine vs lithium) and PS matching (HR, 1.51; 95% CI, 1.21-1.88). After PS adjustment, unintentional injury rates were lower for lithium compared with valproate (HR, 1.32; 95% CI, 1.10-1.58) and quetiapine (HR, 1.34; 95% CI, 1.07-1.69) but not olanzapine. The suicide rate in the cohort was 14 (95% CI, 9-21) per 10 000 PYAR. Although this rate was lower in the lithium group than for other treatments, there were too few events to allow accurate estimates.

CONCLUSIONS AND RELEVANCE Patients taking lithium had reduced self-harm and unintentional injury rates. This finding augments limited trial and smaller observational study results. It supports the hypothesis that lithium use reduces impulsive aggression in addition to stabilizing mood.

JAMA Psychiatry. 2016;73(6):630-637. doi:10.1001/jamapsychiatry.2016.0432
Published online May 11, 2016.

Author Audio Interview at jamapsychiatry.com

Author Affiliations: Division of Psychiatry, University College London, London, England (Hayes, Pitman, King, Osborn); Department of Primary Care and Population Health, University College London, London, England (Marston, Walters); Department of Psychiatry, University of Oxford, Oxford, England (Geddes).

Corresponding Author: Joseph F. Hayes, MSc, MBChB, Division of Psychiatry, University College London, Sixth Floor, Maple House, 149 Tottenham Ct Rd, London W1T 7NF, England (joseph.hayes@ucl.ac.uk).

Self-harm is a major cause of morbidity in bipolar disorder (BPD),[1] and drug treatments that reduce suicidal and nonsuicidal self-harm could improve quality of life for individuals with BPD and their families.[2] Furthermore, individuals who self-harm have a substantially increased suicide risk.[3] Bipolar disorder is associated with an annual risk of suicidal acts that is 10 times that of the general population[4] and a lifetime risk of suicide that is almost 15 times greater.[5] Randomized clinical trials of maintenance medication show that drugs like lithium, valproate sodium, olanzapine, and quetiapine fumarate can stabilize mood.[6,7] However, balancing the relative benefits and potential risks of these medications is not straightforward, and potential drug effects on self-harm have been underexamined in this regard.

Because trials often exclude those with a history of suicidal behavior, drug effects on self-harm have been difficult to quantify due to low event rates.[8] The findings of a meta-analysis[9] of 48 trials suggested that suicide was less likely in people prescribed lithium than placebo or active comparator groups but found no difference in self-harm rates. The results of observational studies have suggested that lithium use may reduce fatal and nonfatal self-harm compared with maintenance treatment alternatives, most commonly anticonvulsant medication,[10-14] but the findings have not always been consistent.[15-17] After a warning from the US Food and Drug Administration[18] that anticonvulsant medications carry an increased risk of suicidal self-harm, a number of studies investigated this issue in BPD. A meta-analysis[19] that included only patients with BPD and several observational studies[20-22] did not replicate this finding. There are sparse data on the association between antipsychotic medication use and self-harm. Small retrospective cohorts have shown no difference in suicidal self-harm in patients taking olanzapine or quetiapine[23] and have demonstrated higher rates of suicide attempts in those prescribed second-generation antipsychotics compared with lithium or valproate.[16,24]

Risk of unintentional injury has also been understudied in BPD despite deaths from unintentional injury being approximately 6 times higher in BPD than in the general population.[25] Although unintentional injuries are often recorded in drug trials, they are rarely reported as important outcomes.[26] Observational studies of drug treatments are even more limited.[27] It has been suggested that unintentional injuries are associated with hypomanic rather than depressive morbidity,[28] in which case drugs with the strongest anti-unintentional injury properties may not be those with the strongest antisuicidal effects.

Three mechanisms for lithium's potentially superior antisuicidal effects have been proposed. The first is that lithium reduces risk through reducing depressive relapse, in which case drugs that also protect against depressive relapse should show comparable effects (eg, quetiapine).[9] The second is that there are specific serotonin-mediated effects of lithium that result in reduced aggressive behavior, risk taking, and impulsivity,[29-31] in which case one would also expect to see reductions in unintentional injury in this group. The third is that the close monitoring of patients taking lithium may provide psychosocial support that is lacking with other drug treatments, thereby mitigating suicide risk,[32] in which case one would expect to see variability in service use across treatment groups.

This study compares rates of self-harm, unintentional injury, and suicide deaths in patients prescribed lithium, valproate, olanzapine, or quetiapine using a large electronic health records (EHRs) database representative of the United Kingdom (UK) population. We hypothesized that lithium use would be associated with reduced rates of self-harm, unintentional injury, and suicide.

Key Points

Question What are rates of self-harm, unintentional injury, and suicide in people with bipolar disorder who were prescribed lithium, valproate sodium, olanzapine, or quetiapine fumarate?

Findings In this longitudinal cohort study of 6671 individuals, those prescribed lithium had lower self-harm and unintentional injury rates than those prescribed valproate, olanzapine, or quetiapine after propensity score adjustment. Suicide rates reflected those in other cohorts but were too low to make between-group comparisons.

Meaning Lithium prescribing is associated with reduced self-harm and unintentional injury rates, consistent with the hypothesis that lithium use has specific effects on impulsive aggression.

Methods

Study Design

We completed a cohort study using primary care EHRs data collected between January 1, 1995, and December 31, 2013, by The Health Improvement Network (THIN) system. The study was approved by the Cegedim Strategic Data Medical Research UK Scientific Review Committee in March 2015. The scheme for THIN to provide anonymized patient data to researchers was approved in 2003 by the National Health Service (NHS) South-East Multicenter Research Ethics Committee.[33]

Setting

The UK THIN database contains primary care EHRs for a representative sample of the population, with unique identifiers (eg, name, address, and NHS number) removed.[34-36] The database began in 1998 and by 2013 contained the longitudinal health records of more than 11 million people, covering 5.7% of the UK population.[33] THIN records are based on Read codes, a hierarchical coding system that includes diagnoses (which map onto *International Statistical Classification of Diseases, Tenth Revision* codes), medication prescriptions, symptoms, examination findings, referrals, test results, and hospital attendance information.[37,38] Within the NHS, primary care physicians are responsible for issuing prescriptions for ongoing medication use, so this information is well defined in the cohort.[39] They also provide most long-term care to people with BPD, although the diagnosis is made in secondary care by a psychiatrist.[40] The validity of severe mental illness diagnoses (including BPD) in primary care records has been

established.[41,42] The incidence rate of BPD is similar to that of other European cohorts.[43]

Participants

All individuals 16 years or older with a diagnosis of BPD were considered for inclusion in the cohort. They were included if they received 2 or more consecutive prescriptions for treatment lasting 28 days or longer of lithium, valproate, olanzapine, or quetiapine prescribed after December 31, 1994, or after the date at which the medical records met recognized quality assurance criteria for mortality recording and computer use.[44,45] These drugs were selected because they are suggested maintenance treatments in several guidelines internationally.[40,46-48] They are the most commonly used in the UK,[49] reflecting the recommendation for first-line treatment by the National Institute for Health and Care Excellence during most of the study period.[50] The minimum duration of treatment was chosen, in line with hypotheses about lithium's early effect on suicidal thoughts and behavior.[51]

To remove patients with multiple drug exposures, individuals were excluded if they were prescribed more than 1 study drug at the start of follow-up or in the 28 days preceding this date. Individuals receiving a diagnosis of schizophrenia or schizoaffective disorder after their BPD diagnosis were excluded, but individuals could receive a later diagnosis of depression. All records for selected individuals were included.

Exposure

The start of the exposure period was defined as the date of first prescription. The end of the exposure period was calculated from the number of days of medication prescribed. Individuals were considered to have a period of continuous prescribing if another prescription for the same drug was issued within 3 months of the calculated end date. To account for the potential destabilizing effects of stopping the study drug, 3 months was then added to the end of each calculated drug exposure period, during which an outcome event was still considered to be associated with the drug treatment.[52] Individuals could not reenter the cohort once they had left and could not contribute to more than 1 study drug (permitting the outcome to be assigned to a specific drug). Patients were censored if they left the primary care practice, died of nonsuicide causes, or reached the end of follow-up (December 31, 2013).

Outcomes

The primary outcome of interest was emergency department or primary care attendance for self-harm during the period of drug exposure and the 3 months afterward. This outcome included Read codes for intentional poisoning, intentional self-injurious behavior, and self-harm acts of uncertain intent. The positive predictive value of this outcome in THIN has been shown to be 97%.[20] It was not possible to separate nonsuicidal self-harm from self-harm with suicidal intent or to grade the event's severity. However, our unitary categorization of nonsuicidal and suicidal self-harm is consistent with UK research norms.[53] Secondary outcomes were unintentional injury (eg, falls or motor vehicle crashes) seen in primary or secondary care and a record of the patient's suicide during this period, defined in line with previous research.[20]

Propensity Score Estimation

We developed a propensity score (PS) model based on factors decided a priori and according to existing research and clinical experience that were likely to affect the physician's prescribing choice.[40,54,55] This approach attempts to limit confounding and aims to replicate a randomized experiment as closely as possible by obtaining treatment groups with similar distributions of known covariates.[56,57] Included variables were sex, age at the start of treatment with the study drug, year of entry to the cohort, race/ethnicity (grouped as white, black, Asian, mixed, or other, with missing values coded as white),[37] cardiovascular disease diagnosis before baseline, hypertension, chronic kidney disease at baseline, history of hypothyroidism or hyperthyroidism, history of liver disease, type 2 diabetes mellitus, epilepsy, alcohol use (grouped as none or low, moderate or heavy, or dependence), history of illicit drug use, smoking status (grouped as never smoker, exsmoker, or current smoker), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) (grouped as healthy weight, overweight [BMI 25-30], or obese [BMI >30]), anxiety symptoms or diagnosis before baseline, depressive symptoms or diagnosis before baseline, sleep disturbance before baseline, treatment with the study drug at or before baseline, and history of previous self-harm. For demographic and health-related covariates, the entire medical record before baseline was reviewed (potentially including records preceding 1988, when paper records were transposed to EHRs). For BMI, alcohol use, and smoking status, the most proximate data in the 5 years before baseline were used.

Statistical Analysis

Cox proportional hazards regression analyses were conducted comparing rates of self-harm, unintentional injury, and suicide in the 4 treatment groups. Time to adverse outcome was summarized by Kaplan-Meier curves. Analysis of Schoenfeld residuals was completed to test the assumption of proportional hazards.[58] The PS was calculated by multinomial logistic regression using the covariates described as independent variables and drug treatment as the dependent variable. The PS was used as a linear term in a Cox proportional hazards regression analysis. A 1:1 PS-matched analysis was also completed, with each patient in the valproate, olanzapine, or quetiapine group matched to a lithium group patient with a 0.01 caliper, dropping all other patients from the analysis. These 2 approaches to PS analysis have different strengths: the adjusted analysis may be more generalizable and is a more efficient use of the data (because no patients are dropped), while the matched analysis may provide a more valid estimate of treatment effect because only patients with similar observed characteristics are included.[59,60] Both adjusted and matched PS models were also adjusted for time-updated variables (age and calendar year) and clustering of patients by primary care practice. All analyses were completed using statistical software (Stata, version 14; StataCorp LP).[61]

Results

Clinical and Demographic Features

Of the 14 396 individuals with a diagnosis of BPD, 6671 were included in the cohort, with 2148 prescribed lithium, 1670 prescribed valproate, 1477 prescribed olanzapine, and 1376 prescribed quetiapine (**Figure 1**). The characteristics of these patients are summarized in **Table 1**. Drug exposure ranged from 28 days to 17 years 11 days. People prescribed lithium tended to be older than those taking other study drugs, with more years of follow-up data. These individuals were less likely to have records of depression, anxiety, or self-harm before entry into the cohort. Individuals prescribed lithium had no more contacts with primary care services during follow-up than individuals prescribed other drugs.

Self-harm

The rate of self-harm reported to primary care physicians in individuals prescribed maintenance mood stabilizer medication for BPD was 340 (95% CI, 313-370) per 10 000 person-years at risk (PYAR). In unadjusted analysis, self-harm rates were reduced in people taking lithium compared with those taking valproate, olanzapine, or quetiapine (**Table 2** and **Figure 2**). This finding was also the case after adjustment for PS, age, calendar year, and primary care practice (hazard ratio [HR], 1.40; 95% CI, 1.12-1.74 for valproate, olanzapine, or quetiapine vs lithium). After 1:1 PS matching with lithium, rates of self-harm remained higher in individuals prescribed valproate (n = 1186) (HR, 1.31; 95% CI, 1.01-1.70), olanzapine (n = 1100) (HR, 1.33; 95% CI, 1.01-1.75), and quetiapine (n = 790) (HR, 1.36; 95% CI, 1.00-1.87). One-to-one matching of individuals taking lithium with those taking any other study drug showed higher self-harm rates in the nonlithium group (n = 1501) (HR, 1.51; 95% CI, 1.21-1.88).

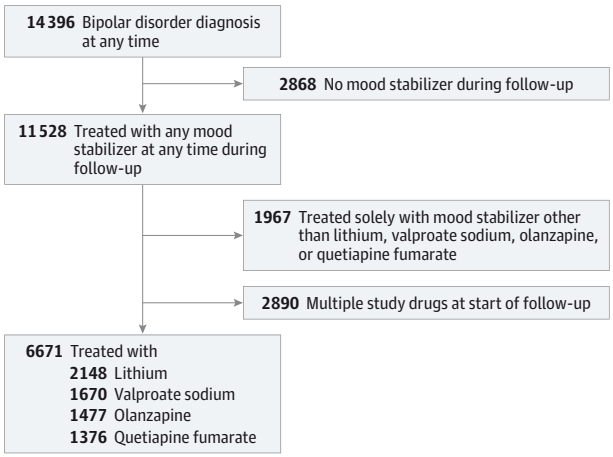
Unintentional Injury

The rate of unintentional injury was 616 (95% CI, 579-656) per 10 000 PYAR. Rates of unintentional injury were lower in people taking lithium compared with those taking valproate or quetiapine but not olanzapine in unadjusted, PS-adjusted, and PS-matched analyses (Table 2). Individuals prescribed lithium had lower unintentional injury rates compared with those taking other study mood stabilizers, whether after adjustment for PS, calendar year, age, and primary care practice (HR, 1.26; 95% CI, 1.07-1.47) or after 1:1 PS matching with people taking valproate, olanzapine, or quetiapine (HR, 1.19; 95% CI, 1.01-1.41).

Suicide

The rate of suicide deaths in the cohort was 14 (95% CI, 9-21) per 10 000 PYAR. The number of suicides was too low to show differences by individual drugs. The HR point estimate for suicide was elevated for all other study drugs compared with lithium, but 95% CIs overlapped unity, indicating no effect (unadjusted HR, 2.60; 95% CI, 0.96-7.03 and PS-adjusted HR, 2.86; 95% CI, 0.88-9.26) (Table 2).

Figure 1. Flow Diagram of Patient Selection



Mood stabilizer is defined as antipsychotic or anticonvulsant medication.

Discussion

To our knowledge, this investigation is the largest naturalistic longitudinal study of fatal and nonfatal self-harm rates in individuals with BPD treated with lithium, valproate, olanzapine, or quetiapine. We found increased rates of self-harm in individuals prescribed valproate, olanzapine, or quetiapine compared with those prescribed lithium. We did not find differences in rates among valproate, olanzapine, and quetiapine. This association remained after PS adjustment and PS matching. We also found reduced rates of unintentional injury in those prescribed lithium, an important association that has not been widely investigated or found previously. We did not find differences in rates of suicide because of the small number of suicides in the cohort. However, the point estimates for rates of suicide among individuals taking lithium or valproate matched those found in the US retrospective cohort study by Goodwin et al[10] (7 per 10 000 PYAR and 17 per 10 000 PYAR, respectively) and are similar to other findings.[11]

The lower rates of self-harm in those prescribed lithium may be due either to improved mood stabilization compared with other treatments or specific effects on impulsive aggression and risk taking. The similarity of the negative association between lithium use and unintentional injury and that between lithium use and self-harm supports the latter hypothesis because there is little reason to expect that lower rates of depressive symptoms would reduce unintentional injury.[28] Also, there is scant evidence that lithium is superior to quetiapine in preventing depressive episode relapse.[7]

Our study had notable strengths and limitations. This study uses a large, nationally representative sample to examine rates of fatal and nonfatal self-harm and unintentional injury. The use of EHRs to capture those episodes of self-harm managed entirely in primary care, as well as those admitted to secondary care, captures the true burden of self-harm morbidity both in the community and hospital presentation. Therefore, rates of recorded self-harm in our study were slightly higher than

Table 1. Cohort Characteristics by Mood Stabilizer Treatment

Variable	Lithium (n = 2148)	Valproate Sodium (n = 1670)	Olanzapine (n = 1477)	Quetiapine Fumarate (n = 1376)
Female sex, No. (%)	1287 (59.9)	911 (54.6)	791 (53.6)	959 (69.7)
Age, median (IQR), y	46.28 (35.70-60.67)	42.31 (31.95-54.80)	41.01 (32.03-53.08)	38.08 (29.30-48.71)
Duration of drug exposure, median (IQR), y	2.03 (0.77-4.86)	1.48 (0.65-3.35)	1.28 (0.59-3.29)	1.06 (0.56-2.26)
Nonwhite racial/ethnic background, No. (%)	55 (2.6)	85 (5.1)	78 (5.3)	43 (3.1)
Primary care contacts per year, median (IQR)	11.14 (7.36-19.92)	12.51 (7.36-19.95)	11.94 (7.08-19.55)	14.61 (9.21-22.55)
Physical health characteristics at baseline, No. (%)				
Cardiovascular disease history	124 (5.8)	121 (7.2)	68 (4.6)	53 (3.9)
Thyroid disease	234 (10.9)	130 (7.8)	92 (6.2)	87 (6.3)
Liver disease	33 (1.5)	40 (2.4)	36 (2.4)	19 (1.4)
Type 2 diabetes mellitus	108 (5.0)	140 (8.4)	45 (3.0)	86 (6.3)
Obesity[a]	896 (41.7)	716 (42.9)	509 (34.5)	609 (44.3)
Hypertension	184 (8.6)	173 (10.4)	103 (7.0)	130 (9.4)
Epilepsy	43 (2.0)	132 (7.9)	50 (3.4)	49 (3.6)
Moderate to heavy alcohol use	1189 (55.4)	899 (53.8)	791 (53.6)	708 (51.5)
Current smoker	711 (33.1)	652 (39.0)	632 (42.8)	567 (41.2)
Illicit drug use history	93 (4.3)	148 (8.9)	179 (12.1)	160 (11.6)
Mental health characteristics at baseline, No. (%)				
Previous suicidal or nonsuicidal self-harm	468 (21.8)	424 (25.4)	349 (23.6)	473 (34.4)
Sleep problems	200 (9.3)	197 (11.8)	191 (12.9)	230 (16.7)
Depression symptoms or diagnosis	1238 (57.6)	990 (59.3)	915 (61.9)	1015 (73.8)
Anxiety symptoms or diagnosis	144 (6.7)	150 (9.0)	137 (9.3)	201 (14.6)
Previous exposure to drug	1731 (80.6)	1157 (69.3)	886 (60.0)	847 (61.6)

Abbreviation: IQR, interquartile range.

[a] Obesity is defined as body mass index exceeding 30, calculated as weight in kilograms divided by height in meters squared.

Table 2. Rates of Self-harm, Unintentional Injury, and Suicide by Mood Stabilizer Treatment[a]

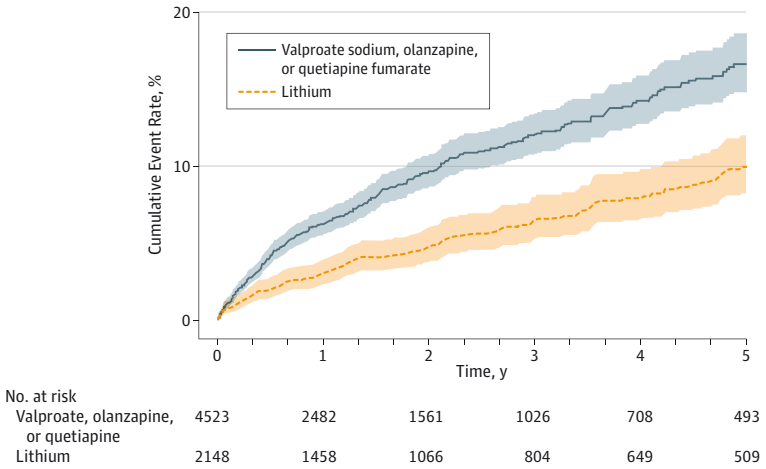
Variable	Lithium	Valproate Sodium	Olanzapine	Quetiapine Fumarate	Valproate, Olanzapine, or Quetiapine
Self-harm					
Events, No.	146	152	137	128	417
PYAR	7106	3876	3353	2200	9430
Rate per 10 000 PYAR (95% CI)	205 (175-241)	392 (334-460)	409 (345-483)	582 (489-692)	442 (402-487)
Unadjusted HR (95% CI)	1 [Reference]	1.68 (1.34-2.12)	1.76 (1.39-2.23)	2.21 (1.74-2.82)	1.84 (1.52-2.23)
Model 1 HR (95% CI)	1 [Reference]	1.39 (1.08-1.78)	1.39 (1.07-1.79)	1.52 (1.15-2.01)	1.40 (1.12-1.74)
Model 2 HR (95% CI)	1 [Reference]	1.31 (1.01-1.70)	1.33 (1.01-1.75)	1.36 (1.00-1.87)	1.51 (1.21-1.88)
Unintentional Injury					
Events, No.	388	255	190	154	599
PYAR	6615	3801	3366	2179	93.46
Rate per 10 000 PYAR (95% CI)	583 (528-644)	669 (592-757)	569 (494-655)	705 (602-825)	641 (592-694)
Unadjusted HR (95% CI)	1 [Reference]	1.18 (1.01-1.39)	1.00 (0.84-1.19)	1.29 (1.06-1.56)	1.13 (1.00-1.29)
Model 1 HR (95% CI)	1 [Reference]	1.32 (1.10-1.58)	1.14 (0.95-1.37)	1.34 (1.07-1.69)	1.26 (1.07-1.47)
Model 2 HR (95% CI)	1 [Reference]	1.34 (1.09-1.65)	1.17 (0.94-1.47)	1.44 (1.09-1.91)	1.19 (1.01-1.41)
Suicide[b]					
Events, No.	5	7	7	5	19
PYAR	7301	4043	3496	2308	9840
Rate per 10 000 PYAR (95% CI)	7 (3-16)	17 (8-36)	20 (9-42)	22 (9-52)	19 (12-32)
Unadjusted HR (95% CI)	1 [Reference]	2.35 (0.74-7.46)	2.73 (0.86-8.64)	2.85 (0.81-10.06)	2.60 (0.96-7.03)
Model 1 HR (95% CI)	1 [Reference]	2.71 (0.75-9.80)	3.18 (0.86-11.73)	3.01 (0.68-13.38)	2.86 (0.88-9.26)

Abbreviations: HR, hazard ratio; PYAR, person-years at risk.

[a] Model 1 is adjusted for propensity score, clustering by primary care practice, age, and calendar year. Model 2 is propensity score–matched (pairwise matching with lithium) and adjusted for clustering by primary care practice, age, and calendar year.

[b] Too few events for propensity score–matched analysis.

Figure 2. Cumulative Self-harm Rate in Patients Prescribed Lithium vs Valproate, Olanzapine, or Quetiapine



No. at risk

Valproate, olanzapine, or quetiapine	4523	2482	1561	1026	708	493
Lithium	2148	1458	1066	804	649	509

Shown are unadjusted Kaplan-Meier estimates of cumulative self-harm, with shaded areas showing 95% CIs.

those in previous cohort studies.[10,62] As in any analysis of health records, this study would have missed episodes of untreated and unreported self-harm: only population survey methods could capture these episodes, and estimates generated in this manner are prone to response biases. The number of suicides was low, so we were unable to examine differences in rates between drugs. It is possible that misclassification or nonrecording of suicides occurred. However, similarities with other cohorts suggest that this limitation is not a major problem,[10,11] and there is no evidence to indicate that misclassification of cause of death would be differential by drug. Exposure time was foreshortened because of both left truncation (eg, practices joining THIN later than 1995) and right censoring (eg, switch to or addition of another drug, patients leaving the primary care practice, or dying of nonsuicide causes). This censoring was equally distributed by exposure drug.

Potential biases relating to selection into the study should have been avoided by the use of contemporaneous, representative medical records, as well as information bias minimized by the use of THIN's detailed and well-recorded prescribing data as the exposure. However, exposure to the study drug is approximated through prescriptions issued and may not reflect how the patient used the medication. It is possible that erratic adherence is more likely for drugs other than lithium (because lithium is more closely monitored through regular blood tests) and may have contributed to lithium's perceived superiority. However, these patients had no more physician contacts than those taking other medication, all individuals had to fill more than 1 prescription during their follow-up period (suggesting drug adherence), and other longitudinal cohort studies have not shown differential adherence.[63] Because people taking lithium tended to be older, suicides could have occurred in this group before the start of follow-up, thus reducing the observed rate relative to other treatment groups. However, this occurrence should not be the case in the matched analysis.

Through PS adjustment and PS matching, we attempted to account for potential confounding, including confounding by indication, and it is reassuring that both analyses produce similar results. Despite the numerous variables included in the PS, it is possible that residual confounding remained. It may be that important sociodemographic or clinical factors were not captured by the score, and we cannot confirm balance of unobserved covariates.[64,65] Notably, detailed information on educational level and individual socioeconomic status is lacking from the database. However, although these covariates are likely to be associated with self-harm, unintentional injury, and suicide, they should not be associated with treatment allocation. For these (or any) unmeasured covariates to have an important effect on the results, they would have to be strongly associated with exposure and outcome and be independent of covariates included in the PS.[66,67]

Previously, it has been shown that a combination of lithium and valproate was associated with the lowest rate of suicide attempt.[16] This group (and other combinations) were excluded from our study because we wanted to examine the association with monotherapy; in fact, treatment with this combination was rare despite recommendations for its use.[68]

Conclusions

In this representative UK study, individuals with BPD who were prescribed lithium had lower rates of self-harm and unintentional injury than those with BPD receiving other commonly prescribed maintenance treatments. Contrary to the warning from the US Food and Drug Administration,[18] we did not find higher self-harm rates in those prescribed valproate than those receiving other (nonlithium) maintenance drug treatments. These findings are important because they support and augment the existing evidence from randomized clinical trials and smaller cohort studies. Self-harm, unintentional injury, and suicide are important morbidity and mortality outcomes in BPD that appear to be amenable to modification through appropriate drug treatment.

ARTICLE INFORMATION

Submitted for Publication: December 10, 2015; final revision received January 22, 2016; accepted February 15, 2016.

Published Online: May 11, 2016. doi:10.1001/jamapsychiatry.2016.0432.

Author Contributions: Dr Hayes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Hayes, Pitman, Marston, Walters, King, Osborn.
Drafting of the manuscript: Hayes.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hayes, Marston.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Hayes is supported by Medical Research Council Population Health Scientist Fellowship MR/KO21362/1.

Role of the Funder/Sponsor: The funding organization had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Singhal A, Ross J, Seminog O, Hawton K, Goldacre MJ. 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*. 2014;107(5):194-204.

2. Berghöfer A. Lithium and suicide. *BMJ*. 2013;347:f4449.

3. Owens D, Horrocks J, House A. Fatal and non-fatal repetition of self-harm: systematic review. *Br J Psychiatry*. 2002;181(3):193-199.

4. Baldessarini RJ, Pompili M, Tondo L. Suicide in bipolar disorder: risks and management. *CNS Spectr*. 2006;11(6):465-471.

5. Hayes JF, Miles J, Walters K, King M, Osborn DP. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatr Scand*. 2015;131(6):417-425.

6. Severus E, Taylor MJ, Sauer C, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *Int J Bipolar Disord*. 2014;2(1):15.

7. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2014;1(5):351-359.

8. Perlis RH. Hard outcomes: clinical trials to reduce suicide. *Am J Psychiatry*. 2011;168(10):1009-1011.

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

10. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA*. 2003;290(11):1467-1473.

11. Smith EG, Søndergård L, Lopez AG, Andersen PK, Kessing LV. Association between consistent purchase of anticonvulsants or lithium and suicide risk: a longitudinal cohort study from Denmark, 1995-2001. *J Affect Disord*. 2009;117(3):162-167.

12. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review [published correction appears in *Bipolar Disord*. 2007;9(3):314]. *Bipolar Disord*. 2006;8(5, pt 2):625-639.

13. Schou M. The effect of prophylactic lithium treatment on mortality and suicidal behavior: a review for clinicians. *J Affect Disord*. 1998;50(2-3):253-259.

14. Søndergård L, Lopez AG, Andersen PK, Kessing LV. Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. *Bipolar Disord*. 2008;10(1):87-94.

15. Marangell LB, Dennehy EB, Wisniewski SR, et al. Case-control analyses of the impact of pharmacotherapy on prospectively observed suicide attempts and completed suicides in bipolar disorder: findings from STEP-BD. *J Clin Psychiatry*. 2008;69(6):916-922.

16. Ahearn EP, Chen P, Hertzberg M, et al. Suicide attempts in veterans with bipolar disorder during treatment with lithium, divalproex, and atypical antipsychotics. *J Affect Disord*. 2013;145(1):77-82.

17. Bowden CL. Efficacy of lithium in mania and maintenance therapy of bipolar disorder. *J Clin Psychiatry*. 2000;61(suppl 9):35-40.

18. US Food and Drug Administration. Suicidal behavior and ideation and antiepileptic drugs. http://ow.ly/10iLkf. Published May 5, 2009. Accessed April 5, 2016.

19. Redden L, Pritchett Y, Robieson W, et al. Suicidality and divalproex sodium: analysis of controlled studies in multiple indications. *Ann Gen Psychiatry*. 2011;10(1):1.

20. Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicide-related events in patients treated with antiepileptic drugs. *N Engl J Med*. 2010;363(6):542-551.

21. Leon AC, Solomon DA, Li C, et al. Antiepileptic drugs for bipolar disorder and the risk of suicidal behavior: a 30-year observational study. *Am J Psychiatry*. 2012;169(3):285-291.

22. Reid S. Current use of antiepileptic drugs is associated with an increased risk of suicidality in people with depression but not in people with epilepsy or bipolar disorder. *Evid Based Ment Health*. 2011;14(1):3.

23. Koek RJ, Yerevanian BI, Mintz J. Subtypes of antipsychotics and suicidal behavior in bipolar disorder. *J Affect Disord*. 2012;143(1-3):27-33.

24. Yerevanian BI, Koek RJ, Mintz J. Bipolar pharmacotherapy and suicidal behavior, part 3: impact of antipsychotics. *J Affect Disord*. 2007;103(1-3):23-28.

25. Hoang U, Stewart R, Goldacre MJ. Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006. *BMJ*. 2011;343:d5422.

26. Matson JL, González ML, Smith KR, Terlonge C, Thorson RT, Dixon DR. Assessing side effects of pharmacotherapy treatment of bipolar disorder: a 20-year review of the literature. *Res Dev Disabil*. 2006;27(5):467-500.

27. Elvik R. Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies. *Accid Anal Prev*. 2013;60:254-267.

28. Khalsa HM, Salvatore P, Hennen J, Baethge C, Tohen M, Baldessarini RJ. Suicidal events and accidents in 216 first-episode bipolar I disorder patients: predictive factors. *J Affect Disord*. 2008;106(1-2):179-184.

29. Kovacsics CE, Gottesman II, Gould TD. Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. *Annu Rev Pharmacol Toxicol*. 2009;49:175-198.

30. Fawcett J. Treating impulsivity and anxiety in the suicidal patient. *Ann N Y Acad Sci*. 2001;932(1):94-102.

31. Müller-Oerlinghausen B, Lewitzka U. Lithium reduces pathological aggression and suicidality: a mini-review. *Neuropsychobiology*. 2010;62(1):43-49.

32. Tondo L, Baldessarini RJ. Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients. *Epidemiol Psichiatr Soc*. 2009;18(3):179-183.

33. IMS Health. Statistics. http://www.epic-uk.org/our-data/statistics.shtml. Accessed January 14, 2015.

34. Blak B, Thompson M, Bourke A. National representativeness and data quality of The Health Improvement Network (THIN) database of primary care information for epidemiological research. Paper presented at: 9th Annual Conference of the UK Federation of Primary Care Research Organisations; November 27, 2006; Liverpool, England.

35. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*. 2011;19(4):251-255.

36. Lis Y, Mann RD. The VAMP Research multi-purpose database in the U.K. *J Clin Epidemiol*. 1995;48(3):431-443.

37. Chisholm J. The Read clinical classification. *BMJ*. 1990;300(6732):1092.

38. Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiol Drug Saf*. 2009;18(8):704-707.

39. Health and Social Care Information Centre. *Prescriptions Dispensed in the Community, Statistics for England: 2001-2011*. Leeds, England: Health and Social Care Information Centre; July 31, 2012.

40. National Collaborating Centre for Mental Health. *Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents*. Leicester, England: British Psychological Society; 2014. NICE Clinical Guidelines CG185.

41. Nazareth I, King M, Haines A, Rangel L, Myers S. Accuracy of diagnosis of psychosis on general practice computer system. *BMJ*. 1993;307(6895):32-34.

42. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69(1):4-14.

43. Hardoon S, Hayes JF, Blackburn R, et al. Recording of severe mental illness in United Kingdom primary care, 2000-2010. *PLoS One*. 2013;8(12):e82365. doi:10.1371/journal.pone.0082365.

44. Horsfall L, Walters K, Petersen I. Identifying periods of acceptable computer usage in primary care research databases. *Pharmacoepidemiol Drug Saf*. 2013;22(1):64-69.

45. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf*. 2009;18(1):76-83.

46. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. *Am J Psychiatry*. 1994;151(12)(suppl):1-36.

47. Mok YM, Chan HN, Chee KS, et al; Ministry of Health. Ministry of Health clinical practice guidelines: bipolar disorder. *Singapore Med J*. 2011;52(12):914-918.

48. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013;15(1):1-44.

49. Hayes J, Prah P, Nazareth I, et al. Prescribing trends in bipolar disorder: cohort study in the United Kingdom THIN primary care database 1995-2009. *PLoS One*. 2011;6(12):e28725. doi:10.1371/journal.pone.0028725.

50. National Collaborating Centre for Mental Health. *Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents*. Leicester, England: British Psychological Society; 2006. NICE Clinical Guidelines CG38.

51. Lewitzka U, Jabs B, Fülle M, et al. Does lithium reduce acute suicidal ideation and behavior? a protocol for a randomized, placebo-controlled multicenter trial of lithium plus treatment as usual (TAU) in patients with suicidal major depressive episode. *BMC Psychiatry*. 2015;15(1):117.

52. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. *J Clin Psychiatry*. 1999;60(suppl 2):77-84.

53. Haw C, Casey D, Holmes J, Hawton K. Suicidal intent and method of self-harm: a large-scale study of self-harm patients presenting to a general hospital. *Suicide Life Threat Behav*. 2015;45(6):732-746.

54. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc*. 1984;79(387):516-524

55. Holmes WM. *Using Propensity Scores in Quasi-Experimental Designs*. Thousand Oaks, CA: SAGE Publications; 2013.

56. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci*. 2010;25(1):1-21.

57. Seeger JD, Kurth T, Walker AM. Use of propensity score technique to account for exposure-related covariates: an example and lesson. *Med Care*. 2007;45(10)(suppl 2):S143-S148.

58. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):239-241.

59. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.

60. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Stat*. 1985;39(1):33-38.

61. StataCorp LP. *Stata Statistical Software* [computer program]. Release 14. College Station, TX: StataCorp LP; 2015.

62. Gibbons RD, Hur K, Brown CH, Mann JJ. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. *Arch Gen Psychiatry*. 2009;66(12):1354-1360.

63. Sajatovic M, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. *Psychiatr Serv*. 2007;58(6):855-863.

64. Austin PC, Mamdani MM, Stukel TA, Anderson GM, Tu JV. The use of the propensity score for estimating treatment effects: administrative versus clinical data. *Stat Med*. 2005;24(10):1563-1578.

65. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007;297(3):278-285.

66. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006;15(5):291-303.

67. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc*. 1999;47(6):749-754.

68. Geddes JR, Goodwin GM, Rendell J, et al; BALANCE Investigators and Collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet*. 2010;375(9712):385-395.