

1 **Full title**

2 Pharmacological Treatment and Risk of Psychiatric Hospitalization in Bipolar Disorder

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21 Bipolar Disorder/drug therapy, Humans, Psychotropic Drugs/administration & dosage,
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23

1 **Abstract**

2 Background

3 Clinical trials have examined the efficacy of drugs to prevent relapse in patients with bipolar
4 disorder, however their design often limits generalization to routine clinical practice.

5 Aims

6 To estimate the effectiveness of drugs used for maintenance treatment in bipolar disorder.

7 Methods

8 We used national registers to identify 35,022 individuals diagnosed with bipolar disorder and
9 information on lithium, valproate, carbamazepine, lamotrigine, quetiapine, and olanzapine
10 treatment from 2006-2009. The main outcome was psychiatric hospitalizations. We used
11 stratified cox regression to compare periods on and off medication within the same individual.

12 Results

13 Medication with lithium, valproate, lamotrigine, olanzapine, and quetiapine was associated
14 with reduced the rates of hospitalization. Lithium was more effective than quetiapine and
15 olanzapine. The effects of specific drugs depended on the polarity of the mood episode.

16 Conclusions

17 Our findings complement results from RCTs, but suggest that lithium is more effective than
18 both quetiapine and olanzapine in routine clinical practice.

1 INTRODUCTION

2 Bipolar disorder is characterized by recurrent hypomanic/manic and depressive episodes that
3 frequently result in hospitalization. The goal of maintenance treatment is to prevent new
4 mood episodes and relapse from previous acute episodes. Lithium was the first drug to be
5 used for long-term prophylactic treatment. While lithium is still widely used, several other
6 drugs have been introduced to prevent mood episodes, such as anticonvulsants (e.g.,
7 valproate, lamotrigine, and carbamazepine) and second generation antipsychotics (e.g.,
8 olanzapine and quetiapine)¹. Randomized controlled trials (RCTs) have demonstrated the
9 efficacy of several alternatives to lithium², but their results have been criticized and even
10 discounted because of study design and attrition at follow up¹. Moreover, RCTs are often
11 conducted in specialized clinics with more severe and treatment refractory cases, and typically
12 employs strict enrollment criteria that limit the generalizability of the findings³⁻⁵. For
13 example, bipolar disorder treatment trials might exclude patients with comorbid substance
14 abuse⁶, which is common in clinical practice. Generalizability might be improved by
15 simulating routine clinical practice in randomized effectiveness trials^{7,8}, but such studies are
16 expensive and find difficulty attracting funding. Accordingly, definitive large-scale
17 independent RCTs have not been conducted in psychiatry. The dependence on evidence from
18 industry supported RCTs has attracted increasingly nihilistic criticism (e.g., *Psychiatry Under*
19 *the Influence*⁹) that has arguably reduced public confidence in psychiatry.

20
21 For these reasons, convincing naturalistic studies on the real-world effectiveness of
22 psychiatric drugs is important. Observational register studies suggest that lithium is superior
23 to other mood stabilizing medications (e.g., lamotrigine and valproate) in preventing new
24 mood episodes¹⁰⁻¹². Such studies have a strong outcome measure (hospital admissions) and
25 are statistically powerful. However, observational studies are limited by the fact that

1 medications are not prescribed randomly. Drugs are selected by the psychiatrist based on the
2 patient's clinical features, which may be associated with the outcome. This leads to bias
3 called *confounding-by-indication*. For example, if patients with less severe illness were more
4 likely to be prescribed lithium than valproate, this could create the impression that lithium is
5 more effective than valproate.

6
7 The aim of this study was to yield a better estimate of the association between drugs used for
8 maintenance treatment in bipolar disorder with rates of psychiatric hospitalizations. We limit
9 confounding-by-indication by a *within-individual design*, in which all time-stationary
10 covariates, even those that are unobserved, are controlled for by making the individual serve
11 as his or her own control¹³. Thus, we compare periods when patients were medicated with
12 periods when they were not. We study the effect of lithium, valproate, carbamazepine,
13 lamotrigine, quetiapine, and olanzapine on relapse to manic, depressive, and mixed episodes.

15 **METHODS**

16 *National registries*

17 We used a linkage of several national registries in Sweden: the National Patient Register
18 (NPR), the Swedish Prescribed Drug Register (SPDR), the Swedish national quality assurance
19 register for bipolar disorders (Bipolär), the Total Population Register, Cause of Death
20 Register, and Migration Register. The NPR covers inpatient (since 1973) and outpatient (since
21 2001) psychiatric admissions. The register contains discharge date, main diagnosis, and
22 secondary diagnoses based on the International Classifications of Diseases (ICD). The
23 inpatient part of the register has full coverage since 1973 and $\geq 90\%$ of admissions have a
24 registered main diagnosis. The outpatient part was launched in 2001 and the coverage has

increased gradually: from 18.2% in 2001 to 87.3% in 2012¹⁴. The SPDR contains prescription and dispense dates on all prescribed drugs in Sweden from July 2005. BipoläR, established in Sweden in 2004, contains individualized data on diagnosis, medical interventions, and treatment outcomes¹⁵. The Regional Ethics Committee at Karolinska Institutet, Sweden approved the study. The data was anonymized before analysis.

Patients

We identified persons with bipolar disorder in the NPR according to a modified version of a validated algorithm¹⁶. If the patient had at least two diagnoses of bipolar disorder as either outpatient or inpatient in the NPR (ICD-8 codes 1973–1986: 96.0-296.3, 296.8, 296.9; ICD-9 codes 1987–1996: 296A-296E, 296W, 296X; ICD-10 codes from 1997: F30–31), then he/she was classified as a bipolar disorder case. Cases were excluded if they had more than one diagnosis of schizophrenia or schizoaffective disorder, or if the diagnosis of bipolar disorder was only based on ICD-8 296.20 (manic-depressive psychosis, depressed type) and/or ICD-9 296.B (unipolar affective psychosis, melancholic form)¹⁶. We also included individuals registered in BipoläR if the algorithm in NPR had not captured them since diagnoses in BipoläR are considered highly reliable¹⁶. The follow-up time started January 1st, 2006 or at the date of first registered diagnosis in the NPR if this occurred after January 1st, 2006. For those individuals (n=262) that were identified only in BipoläR, the start of the follow-up was set to January 1st, 2006. Time spent in psychiatric inpatient care was not used as observed time.

Exposure

From the SPDR, we extracted data on lithium (ATC: N05AN01), valproate (ATC: N03AG01), lamotrigine (ATC: N03AX09), carbamazepine (ATC: N03AF01), olanzapine

(ATC: N05AH03), and quetiapine (ATC: N05AH04). Treatment periods were defined using sequences of at least two dispense dates. Treatment periods continued until the time between two consecutive dispense dates became larger than 3 months (92 days), then the treatment period ended at the last dispense date. The rationale for using this cut-off is that a single dispensing in Sweden is generally limited to a maximum of 3 months' supply. However, since the rule of 3 months' supply is possible to circumvent, and previous research has used other cut-off periods^{13,17}, we also tested alternative cut-offs (4 and 6 months) in sensitivity analyses. We used SPDR data from July 1st, 2005 until June 30th, 2010 to determine if the individual was on treatment at the start and end of the study period.

Outcomes

The primary outcome in this study was psychiatric hospitalization for any reason, defined as at least one overnight stay at a psychiatric clinic. We also used the discharge diagnoses for the secondary outcomes analyses, i.e., hospitalization due to i) a manic episode (ICD-10 codes F30-, F310-312), ii) a depressive episode (F313-315, F320-323, and F328-F33), or iii) a mixed episode (F316).

Statistical methods

We defined “on” and “off” periods for all six different medications based on dispense dates, and added psychiatric hospitalization events as outcomes. Our main analysis was the within-individual models where we used stratified Cox regression. Here, each individual entered the model as a separate stratum with an individual baseline hazard function. Different time-periods from the same individual, with differing medication status and adjusting for the other

1 medications, were then compared with respect to the outcome, making the individual his/her
2 own control. This design controls for non-time-varying confounders such as sex and genetic
3 makeup, but can still be influenced by time-varying confounders. Only individuals with
4 changing medication status during follow-up contribute information on medication. Other
5 individuals can, however, contribute information on confounders. Additionally, only strata
6 with events contribute information. This statistical design have been used in several previous
7 studies^{13,17,18} and has been described in detail previously¹³. These models were adjusted for
8 previous time spent in psychiatric inpatient care (four level categorical variable), and age
9 (continuous). The results should be interpreted as the effect of the medication adjusted for
10 both confounders and the five other medications. We also conducted a post-estimation test to
11 compare the effect estimates of the different medications. Since there are 15 pairwise
12 comparisons in each model, we adjusted the p-values using the *False Discovery Rate-*
13 *method*¹⁹.

14
15 To be able to compare our results with previous studies that did not use the within-individual
16 method, we also analyzed the risk of hospitalization using a *between-individual design*. Here,
17 medications were compared between individuals as time-varying covariates. As each
18 individual could potentially contribute with several time-periods of medication, we used
19 robust standard errors. We also conducted a between-individual analysis restricted to those
20 who had received medication at any time during the study period, because untreated subjects
21 might comprise a subset of less ill individuals. These analyses were adjusted for sex, previous
22 time spent in psychiatric inpatient care (four level categorical variable), and age (continuous)
23 as time-varying covariates. The results should be interpreted as the effect of the medication
24 adjusted for both confounders and the other five medications.

We conducted secondary outcomes analyses (hospitalization due to manic, depressive, or mixed episodes) with the within-individual and the two between-individual models.

SAS 9.3 and R 3.2.2 were used for all analyses. The *texreg* package²⁰ was used for table production.

Sensitivity analyses

We performed seven sensitivity analyses with the primary outcome to test the robustness of our findings. (1) We first conducted six separate within-individual analyses, one for each medication, where we excluded all intervals with other medications and only included individuals who at some point received the medication in question. The interpretation of these analyses is straightforward: the effect of the drug is compared with the effect of not being on the drug. (2) We tested the importance of the sequence of treatments for lithium, which is the first-line treatment for bipolar disorder in Sweden. Here, we only included individuals who had received lithium treatment prior to any of the other study drugs (separate analyses were done for all study drugs except carbamazepine as this drug was rarely used). (3) We did separate within-individual models for patients that had, and patients that had not, started the observation time on medication to test the influence on starting and stopping medication. (4 & 5) We used 4 and 6 months as cut-offs defining treatment discontinuation instead of 3 months. (6) We also tested using 3 months as cut-off but with 30 days added at the end of the medication period. In this analysis, we also included single dispenses of drugs that resulted in 30 day treatment interval from the dispense date and onwards. (7) We also analyzed the

sample using a 3-day cut-off because patients, instead of 1, as those who are admitted to inpatient care during a weekend may not see a specialist in person until the first working day (Monday). But patients who have been admitted for at least 3 days are quite certain to have been examined by a consultant psychiatrist.

RESULTS

We identified 35,022 individuals with bipolar disorder alive and living in Sweden at some interval between January 1st, 2006 and December 31st, 2009. Sample characteristics are displayed in Table 1. Of these, 72.3% had a period with any of the six study drugs, with lithium being the most prevalent and carbamazepine the least common. 67.1% of individuals changed their medication status during the study period and one quarter of the study subjects were hospitalized at least once during follow-up. Table S1 in the online data supplement outlines the main discharge diagnoses.

Insert Table 1 about here

Within-individual analyses

When combining all studied medications into a single variable, medication with any of the study drugs was associated with a reduced rate of psychiatric hospitalization (HR: 0.67, 95% CI: 0.64-0.71).

Table 2 shows the results of our main within-individual analyses, adjusting for age, previous time spent in psychiatric inpatient care, and the five other drugs. Lithium was associated with

a 34% reduction of psychiatric hospitalization rate, valproate with 27%, olanzapine with 23%, lamotrigine with 22%, and quetiapine with 18% compared with when the individuals were off the respective drug. Unadjusted analyses (not adjusting for age and previous time spent in psychiatric inpatient care) showed similar results as the adjusted analysis for all drugs, lithium (HR 0.64, 95% CI 0.61-0.69), valproate (HR 0.72, 95% CI 0.66-0.78), carbamazepine (HR 0.92, 95% CI 0.77-1.10), lamotrigine (HR 0.77, 95% CI 0.71-0.82), quetiapine (HR 0.77, 95% CI 0.71-0.84), and olanzapine (HR 0.76, 95% CI 0.71-0.82).

Insert Table 2 about here

Post-estimation head-to-head comparisons of medication effects revealed that lithium was associated with a significantly lower rate of hospitalizations than lamotrigine, quetiapine, olanzapine, and carbamazepine, while valproate was significantly superior to carbamazepine (table 3).

Insert Table 3 about here

Lithium, carbamazepine, valproate, quetiapine, and olanzapine, but not lamotrigine, were associated with significantly decreased rate of hospital admission due to a manic episode. Lithium, valproate, lamotrigine, quetiapine, and olanzapine, but not carbamazepine, were significantly associated with reduced rate of admissions due to a depressive episode (table 2). Finally, lithium and valproate were significantly associated with a reduced rate of admissions due to a mixed episode. Head-to-head comparisons of treatment effects on secondary outcomes are given in the supplementary Tables S2-S4. These show that lithium, valproate, and olanzapine were more effective than lamotrigine in reducing rates of hospitalizations for mania. No other significant differences were found.

Between-individual analyses

When the six medications were combined into one variable, medication was associated with an increased rate of psychiatric hospitalization in the between-individual model (HR: 1.06, 95% CI: 1.02-1.11). This is likely explained by confounding-by-indication, because when we exclude individuals who never medicated, medication was associated with reduced rates of psychiatric hospitalization (HR: 0.79, 95% CI: 0.76-0.82). All between-individual analyses are presented in supplementary table S5. Note that these analyses are heavily susceptible to confounding-by-indication, even though the counterintuitive positive associations between medication and hospitalizations were attenuated when removing patients that never medicated (tables S6) during the study period.

Sensitivity analyses

Sensitivity analyses are displayed in Tables S7-S13 and generally support the main analysis (Table S7, Table S9, Table S11 and Table S13). However, some differences were notable. If lithium was taken prior to another medication, then the effect of lithium was attenuated (Table S8). When using 4 months between dispenses as a cut-off for treatment discontinuation, carbamazepine was just significantly associated with reduced rate of hospitalizations (HR=0.83, 95% CI: 0.71, 0.99, p=0.033). Finally, when adding 30 days at the end of each treatment interval and including single dispenses as 30 day treatment intervals, olanzapine and quetiapine were no longer significantly associated with reduced rates of hospitalizations in the within-individual model (Table S12).

DISCUSSION

Our results provide strong evidence that lithium, valproate, lamotrigine, olanzapine, and quetiapine lower the risk of psychiatric hospitalization in routine clinical practice. These results are based on the data of 35,022 individuals with bipolar disorder from Swedish national registers, analyzed utilizing a within-individual model to control for time-stationary confounders. The effects of specific drugs were different and depended on the polarity of the mood episode. Thus, lamotrigine was associated only with decreased rate of depressive episodes, while carbamazepine was solely associated with decreased rate of manic episodes. Lithium, valproate, quetiapine, and olanzapine were associated with lower rates of both manic and depressive episodes, supporting their established use as mood stabilizers. Lithium and valproate were the only drugs that were associated with decreased rates of manic, depressive, and mixed episodes. These results provide corroborative evidence for the effectiveness of lithium and valproate in preventing mood episodes of any polarity. However, mixed episode was a relatively rare outcome thus lowering the power of finding an effect for the other medications. Moreover, lithium showed a significantly stronger effect than all other medications, except valproate, when we tested the equality of treatment effects in the within-individual analysis of all psychiatric hospitalizations.

In line with previous pharmacoepidemiological studies, our *between-individual* analyses suggest that lithium is more effective than both valproate¹⁰, lamotrigine¹¹, and atypical antipsychotics²¹. However, these analyses are hampered by confounding-by-indication. For example, our between-individual analysis suggested that quetiapine doubles the rate of manic episodes and that lamotrigine increases the risk of depressive episodes (Table S5). But this is because quetiapine and lamotrigine are more likely to be prescribed to persons prone to mania

1 and depression, respectively. By contrast, our *within-individual* analyses suggest that
2 quetiapine significantly decreases the risk of manic episodes and lamotrigine decreased the
3 risk of depression. The disagreements between these statistical models clearly demonstrate the
4 importance of controlling for confounding-by-indication in observational
5 pharmacoepidemiological studies. It should be noted, however, that the within-individual
6 design does not control for time-varying confounders, e.g., changing disease severity, change
7 of treating physician, or changing social circumstances. This precludes direct causal
8 conclusions from this study.

9 10 Strengths and limitations

11 The strengths of this study include the large sample, the use of within-individual analyses to
12 minimize the effect of confounding-by-indication, and the inclusion of several sensitivity
13 analyses to test the robustness of our results. There are also limitations to consider: First, our
14 data on treatment is derived from drug dispenses. We have no data on adherence, which might
15 differ across the studied drugs. However, being a naturalistic study attempting to measure the
16 effectiveness of the study drugs, such differences are embedded into the estimate of the
17 effectiveness of the respective drug. It could thus be argued that this is not a limitation but
18 rather a more correct estimate of the effect of the drug in a real-world setting. Second, our
19 definition on treatment discontinuation (>3 months between two dispense dates) was based on
20 prescriptive standards in Sweden, but these rules are possible to circumvent. Therefore, we
21 added analyses where we used >4 and >6 months as cut-offs. These sensitivity analyses
22 showed similar results. Third, ascertainment of bipolar disorder cases was based on an
23 algorithm with high positive predictive value but with moderate sensitivity. We might thus
24 have missed patients with bipolar disorder. We attempted to remedy this by including

individual who had not been diagnosed through the algorithm but were identified in the quality register BipoläR. Fourth, although our within-individual model handles time-stationary confounders, time-varying confounders are still a potential source of unmeasured confounding. We included age and time spent hospitalized as a proxy for illness severity and progression in our model, but there might be other unmeasured confounding. Direct causal interpretation is therefore not possible from our results. Fifth, one form of time-varying confounding is the order in which patients try the respective medication. In a sensitivity analysis where we only included patients who had lithium prior to the other medications, we found that the effect of lithium was attenuated while the effect of other medications was slightly enhanced. This suggests that patients who switched from lithium to a second drug were more likely to be non-responders to lithium. Sixth, we were unable to perform separate analyses of treatment effects in bipolar type I and II as there is no information on bipolar subtypes in the NPR. All patients admitted to hospital with mania or mixed episode will, however, necessarily meet criteria for bipolar I disorder. In our sample 39.8% (n=13,920) had received an inpatient diagnosis of either mania or mixed episode. Seventh, we did not test all different combinations of pharmacological treatments separately, but instead adjusted for concomitant treatment with other drugs. This is a simplification as the effect of a medication might differ when given together with another drug. Testing all possible combinations of drug treatments were, however, beyond the scope of this article. Eight, predominant polarity is a conceivable effect modifier for the drugs of study. However, we could not address this issue herein as the registers do not allow for a reliable estimate on the number of distinct episodes.

The relationship with relapse prevention RCTs

1 Our effect estimates of lithium, valproate, and lamotrigine to prevent mood episodes resemble
2 efficacy estimates in meta-analyses of maintenance treatment in bipolar disorder^{2,22,23}. In the
3 most recent, the relative risk point estimates for lithium, valproate, and lamotrigine were
4 remarkably similar to our HRs², which is striking even though these measures are not
5 completely interchangeable. Thus, the effectiveness of these three drugs in routine clinical
6 practice corresponds well to the effect seen in randomized controlled trials.

7
8 By contrast, the effectiveness of the two second generation antipsychotic drugs - quetiapine
9 and olanzapine - ranked behind that of lithium. This conflicts with results from RCTs². A
10 possible explanation is that enrichment of the sample with acute responders and the choice of
11 mania as index episode have inflated effect in RCTs^{2,6}. Indeed, comparisons of lithium
12 studies with and without enrichment show that effect sizes are larger in enriched samples²⁴.
13 Finally, it is notable that the lamotrigine maintenance studies were enriched primarily for
14 tolerability but not efficacy²⁵. Also, the effect of carbamazepine were lower than previously
15 suggested, but previous studies on maintenance treatment with carbamazepine are scarce²⁶.

16 In conclusion, lithium, valproate, lamotrigine, quetiapine, and olanzapine substantially
17 decrease the risk of hospitalizations in bipolar disorder patients in a real-world clinical setting,
18 thus largely confirming the findings from relapse prevention RCTs. This is a reassuring
19 message for both patients and clinicians. However, the effects of olanzapine and quetiapine
20 were smaller compared with results from RCTs, tentatively due to the use of enriched design
21 RCTs with limited generalizability to the routine clinical setting. High quality
22 pharmacoepidemiological studies - as well as comparable studies of psychosocial
23 interventions - should assume increasing prominence in developing recommendations for
24 practice in psychiatry. The essential conditions are a study design that avoids as much

1 confounding-by-indication as possible, a defined treatment exposure, and meaningful clinical
2 endpoints. The results will be notably free of any question of industry or allegiance bias and
3 could improve confidence globally in the practice of psychiatry.

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Table 1. Characteristics of the study sample

	Men		Women		Total	
	n	%	n	%	n (%)	
Total	13435	38.4	21587	61.6	35022	100
Any of the six medications*	9763	72.7	15567	72.1	25330	72.3
Change in medication status*	9093	67.7	14393	66.7	23486	67.1
Lithium*	6106	45.4	8940	41.4	15046	43
Valproate*	2158	16.1	2967	13.7	5125	14.6
Lamotrigine*	2864	21.3	5722	26.5	8586	24.5
Carbamazepine*	525	3.9	728	3.4	1253	3.6
Quetiapine*	1459	10.9	2732	12.7	4191	12
Olanzapine*	2624	19.5	3842	17.8	6466	18.5
Hospitalization during observation time	3419	25.4	5873	27.2	9292	26.5
	mean	sd	mean	sd	mean	sd
Age on January 1 st , 2006	49.6	17.0	49.2	19.0	49.4	18.2

*At any time 2006-2009

Table 2. Associations between different treatments and psychiatric hospitalization estimated using within-individual models (n=35,022).

	Hazard Ratio (95% CI)			
	All psychiatric hospitalizations	Manic episodes	Depressive episodes	Mixed episodes
Lithium	0.66* (0.62, 0.70)	0.56* (0.48, 0.65)	0.61* (0.53, 0.69)	0.56* (0.39, 0.79)
Valproate	0.73* (0.67, 0.79)	0.64* (0.53, 0.78)	0.73* (0.59, 0.89)	0.66* (0.44, 0.99)
Carbamazepine	0.92 (0.77, 1.10)	0.50* (0.29, 0.86)	0.98 (0.64, 1.48)	1.65 (0.59, 4.62)
Lamotrigine	0.78* (0.73, 0.84)	1.00 (0.78, 1.28)	0.73* (0.63, 0.84)	0.82 (0.53, 1.27)
Quetiapine	0.82* (0.76, 0.89)	0.73* (0.58, 0.93)	0.66* (0.54, 0.81)	0.92 (0.62, 1.39)
Olanzapine	0.77* (0.72, 0.83)	0.56* (0.46, 0.67)	0.80* (0.68, 0.93)	0.78 (0.52, 1.17)
Num. events	23383	4363	6637	973

* 1 outside the confidence interval

All models adjusted for previous time spent in psychiatric inpatient care and age.

Table 3. Post-estimation comparisons of associations between treatment and psychiatric hospitalizations (within-individual analysis). The table displays hazard ratios and 95% CI. A value below 1.0 indicates that the column treatment is superior to the row treatment.

Medication	Lithium	Valproate	Carbamazepine	Lamotrigine	Quetiapine	Olanzapine
Lithium						
Valproate	0.9 (0.82, 1)					
Carbamazepine	0.71 (0.59, 0.86)	0.79 (0.65, 0.95)				
Lamotrigine	0.84 (0.76, 0.92)	0.93 (0.84, 1.04)	1.19 (0.98, 1.43)			
Quetiapine	0.8 (0.72, 0.89)	0.89 (0.79, 1)	1.13 (0.92, 1.36)	0.95 (0.85, 1.06)		
Olanzapine	0.85 (0.77, 0.94)	0.94 (0.84, 1.05)	1.2 (0.99, 1.45)	1.01 (0.91, 1.13)	1.06 (0.95, 1.19)	

Results marked in bold are significant after False Discovery Rate p-value adjustment for multiple testing.

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