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Reducing the rehospitalization risk after a manic episode: A population based cohort study of lithium, valproate, olanzapine, quetiapine and aripiprazole in monotherapy and combinations

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Abstract

Background

Data on real-world rehospitalization risks in patients using different drugs and combination therapies for relapse prevention after a manic episode is limited.

Methods

We conducted a nationwide population based cohort study using data from Swedish national registers. Swedish residents aged 18-75 years who were hospitalized for a manic episode between July 1, 2006 and December 31, 2014 were included. Prescription fills of lithium, valproate, olanzapine, quetiapine and aripiprazole were recorded throughout the first four weeks after hospital discharge, after which the patients were followed for up to one year. General and treatment specific rehospitalization risks were determined and results were adjusted for clinical and sociodemographic factors.

Results

The study included follow-up data from 6 502 hospitalizations for mania. Pharmacologic relapse prevention was used after 78% of these hospitalizations. Monotherapies and combination therapies were equally common. The average one-year rehospitalization risk for patients who did versus did not initiate prophylactic treatment was 39% and 46%, respectively. The lowest rehospitalization risks were seen in patients on combination therapy with olanzapine and valproate or olanzapine and lithium, experiencing one year rehospitalization risks of 32% and 34% (adjusted hazard ratios 0.76 (95% confidence interval [CI] 0.62-0.93) and 0.83 (95% CI 0.70-0.98), compared to lithium monotherapy).

Limitations

Register data do not provide information on all clinical parameters affecting treatment choices.

Conclusions

One-year rehospitalization rates after a manic episode are considerable also for patients who initiate prophylactic treatment. Combination therapies including olanzapine and a classic mood-stabilizer may be beneficial for reducing rehospitalization risks after a manic episode.

Keywords

Bipolar disorder

Cohort study

Treatment outcome

Lithium

Anticonvulsants

1. Introduction

The growing pharmacopoeia of mood-stabilizing drugs have provided a greater opportunity for individualized maintenance treatment in bipolar disorder. However, preventing relapses and subsequent rehospitalizations remain a significant challenge. Decade-old data show two year relapse rates of 50 % in individuals receiving state-of-the-art treatment (Hong et al., 2010; Perlis et al., 2006), indicating a lower real-world effectiveness of mood-stabilizing drugs than would be expected based on findings from randomized controlled trials (RCTs) (Calabrese and Kemp, 2008). High rates of medication non-adherence and discontinuation is probably one explanation (Baldessarini et al., 2008; Sajatovic et al., 2007). In addition, the generalizability of RCT findings may be limited as RCTs frequently use extensive exclusion criteria and enrichment study designs, allowing only treatment-responders to be studied (Calabrese and Kemp, 2008; Goodwin et al., 2011).

Limited data on the comparative effectiveness of mood-stabilizing pharmacotherapies add to the complexity when choosing between different treatment options. As RCTs so far only have compared a limited number of treatment alternatives neck-to-neck, studies based on observational data provide an important complement through assessing and comparing outcomes of multiple treatment options (Reed et al., 2009). To date, a handful of observational studies have included all drug classes approved for relapse prevention in bipolar disorder, including lithium, anticonvulsants and atypical antipsychotics (Altamura et al., 2008; Garnham et al., 2007; Hayes et al., 2016; Simhandl et al., 2014). In contrast to results of RCTs, a majority of these studies have found a superior effectiveness of lithium over more modern treatment alternatives (Garnham et al., 2007; Hayes et al., 2016; Simhandl et al., 2014). In addition, lithium therapy has

been linked to better psychosocial functioning as compared to atypical antipsychotics (Pompili et al., 2014). However, none of these observational studies have differentiated between patients with a recent manic, depressive or mixed episode, nor between patients with bipolar disorder type 1 and 2, limiting possible comparisons with RCTs. Further, comparisons between different treatment options have been restricted to only including one atypical antipsychotic and few, if any, combination therapies, although prescription trends around the world move towards an increased use of atypical antipsychotics and combination therapies (Bjorklund et al., 2016; Chang et al., 2016).

Accordingly, this nationwide register based cohort study was designed to increase knowledge on the real-world effectiveness of prophylactic treatment options used after a manic episode. The study had two major aims: (1) to assess the current rehospitalization risk in patients discharged from a hospitalization for mania; and (2) to compare one-year rehospitalization risks across the entire span of prophylactic treatments approved for relapse prevention after a manic episode. In addition to all single drugs with regulatory approval for prophylactic use after a manic episode in Sweden (lithium, valproate, lamotrigine, olanzapine, quetiapine and aripiprazole), we assessed the 14 most common combinations of mood-stabilizers and/or antipsychotics. Based on previous real-world evidence summarized above (Garnham et al., 2007; Hayes et al., 2016; Simhandl et al., 2014), we hypothesized that patients initiated on lithium monotherapy would have the lowest rehospitalization risk.

2. Methods

2.1. Data sources

Our study was based on data from national longitudinal population-based registers in Sweden. The unique personal identity number assigned to all Swedish residents at birth or immigration enabled linkage of information across registers. Eligible patients were identified in the National Patient Register (NPR) (Ludvigsson et al., 2011), in which psychiatric inpatient care in Sweden has been fully covered since 1987. Available information includes admission and discharge dates and discharge diagnoses assigned by the treating physician (currently coded according to the *International Classification of Diseases*, 10th revision, ICD-10).

Information on filled drug prescriptions was obtained from The Swedish Prescribed Drug Register (PDR), to which all prescribed drugs purchased in Swedish pharmacies have been reported since July 2005 (Wettermark et al., 2007). As all of the studied medications were prescription drugs that could only be obtained in pharmacies unless administered at hospital wards, we expect virtually all medication periods to be covered with regard to the date of dispensing, amount, substance name and World Health Organization's Anatomical Therapeutic Chemical Classification (ATC) code.

We further collected socioeconomic and demographic data from the Total Population Register, maintained by Statistics Sweden, and information on deaths from the Cause of Death Register, maintained by the Swedish National Board of Health and Welfare.

2.2. Study population

All individuals aged 18-75 years who were hospitalized for a manic episode (ICD-10 codes F30.1-F30.9 and F31.1-F31.2) in Sweden any time between July 1, 2006 and December 31, 2014 were included in the study (N = 5 234), generating a cohort of patients with bipolar disorder type I. Patients who were hospitalized for mania multiple times during the study period were included as such (i.e. after each hospitalization), rendering a total of 8 881 index hospitalizations. Hospitalizations within less than a week from each other were counted as one. Follow-up started four weeks after hospital discharge. To reduce the risk of diagnostic misclassification, patients with a previous diagnosis of schizophrenia (ICD-10 code F20), schizoaffective disorder (F25) or dementia (F00-F03) were excluded, as were patients who were not Swedish residents or who emigrated from Sweden, or died before the start of follow-up. Further patients who were rehospitalized before the start of follow-up were excluded. The final study included follow-up data from 6 502 hospitalizations for mania, representing a cohort of 4 250 patients. **Figure 1** shows the flow of patients through the study and the number of hospitalizations excluded from the analysis.

2.3. Exposures

As we were interested in exploring how the initial choice of one pharmacotherapy over another affected the future rehospitalization risk, we used an “intention-to-treat” approach, classifying treatment groups based on prescription fills of drugs during an assessment period starting on the date of admission to the index hospitalization for mania and ending four weeks after hospital discharge. The following drugs were studied, based on their regulatory approval for prophylactic use after a manic episode in Sweden: lithium (ATC-code N05AN01), valproate (N03AG01), olanzapine (N05AH03), quetiapine (N05AH04), and aripiprazole (N05AX12). Patients who filled

one or more prescriptions of the same drug during the assessment period were classified as using monotherapy, whereas patients who filled prescriptions of two or more different drugs were considered to use a combination therapy.

2.4. Outcomes

The main outcome was the one-year rehospitalization risk for patients overall and in each treatment group. After the assessment period, patients were followed for 365 days with regard to psychiatric rehospitalizations, including somatic hospitalizations due to suicide attempts. Patients were censored at psychiatric rehospitalization, a diagnosis of schizophrenia, schizoaffective disorder or dementia, emigration, death, or at the end of follow-up on December 31, 2014.

2.5. Potential confounders

For adjustment purposes, we collected information on potential confounders possibly related to the choice of treatment and the future risk of rehospitalization. The investigated covariates included prescription fills of other psychotropic drugs during the assessment period, including lamotrigine (ATC-code N03AX09), antipsychotics without regulatory approval for prophylactic use in bipolar disorder (N05A except N05AN01, N05AH03, N05AH04 and N05AX12), benzodiazepines (N05B), hypnotics (N05C), antidepressants (N06A), psychostimulants (N06B), and drugs used to treat alcohol or substance use disorder (N07BB and N07BC). We used the length of the index hospitalization and a discharge- or secondary diagnosis indicating psychotic symptoms (ICD-10 codes F21-F24, F28-F29, F30.2 and F31.2) as proxy variables for the severity of the manic index episode. We further considered the number of previous psychiatric admissions, any history of self-inflicted harm, other psychiatric diagnoses registered in the year prior to the index hospitalization and use of lithium, valproate, olanzapine, quetiapine or

aripiprazole in the year prior to the index hospitalization. Whether or not the patient was given a first-time diagnosis of bipolar disorder during the index hospitalization (defined as having no previously recorded diagnoses of bipolar disorder: ICD-code F31, or mania: F30.1-F30.8) was also noted. Finally, sociodemographic data including marital status, country of birth, years of education and income level were collected.

2.6. Statistical analyses

In a first step, we investigated how clinical and sociodemographic characteristics and potential confounders were associated with the rehospitalization risk. The one-year rehospitalization risk associated with each covariate was assessed using Cox proportional hazard regression models and estimated as a hazard ratio [HR] with a 95% confidence interval [CI]. In a second step, the HR of each covariate was adjusted for the effects of all other clinical and sociodemographic characteristics in a multivariable model. A sandwich covariance estimate was used to account for intra-cluster dependence as the same patient could be included multiple times (Lee, 1992).

Next, we estimated the overall one-year rehospitalization risk and absolute and relative treatment specific one-year rehospitalization risks. Lithium monotherapy was used as comparator and results were adjusted for potential confounders with a significant association with the rehospitalization risk, selected through backwards elimination of non-significant covariates from the full model. In a subsequent sensitivity analysis, any previous diagnosis of unipolar or bipolar depression in the past five years (ICD-10 codes F31.3-F31.5, F32 and F33) and use of antidepressant medication in the past year were added as covariates in the model. The proportion of patients within each treatment group with no rehospitalization was plotted in Kaplan Meier

curves. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.7. Ethics

The study was approved by the regional ethical review board in Stockholm (No: 2011/1358-31/3 and 2012/262-32).

3. Results

Of the 4 250 individuals who contributed to the 6 502 included index hospitalizations, the majority of patients (3 061) only contributed with one hospitalization, whereas 943 patients contributed with 2-3 hospitalizations and 246 patients contributed with 4 or more hospitalizations. There were no significant differences in age or sex distribution between patients who contributed with one versus several hospitalizations (median age at first hospitalization 48, interquartile range 34-59, 56% women). Pharmacological relapse prevention was used after 78% of index hospitalizations. Prophylactic monotherapies and combination therapies were equally common. In 29 out of the 6 502 studied index hospitalizations, the patient was censored from the analysis due to death or emigration.

3.1. Rehospitalization risks in relation to clinical and sociodemographic characteristics

Clinical and sociodemographic characteristics of the included patients and their association with the rehospitalization risk are presented in **Table 1**. A majority of patients were born in Sweden, not married, had not attended university, and had a lower-than-average income. Anxiety disorders and alcohol- or substance use disorders were the most prevalently recorded psychiatric comorbidities in the year prior to index hospitalization.

The rehospitalization risk was significantly higher in individuals who were 30 years or older and/or unmarried, divorced or widowed. Further, individuals with a first-time manic episode had a lower rehospitalization risk compared to patients with a history of previous manic episodes. Comorbid anxiety disorder, borderline personality disorder and/or alcohol- or substance use disorder all predicted rehospitalization, borderline personality disorder being associated with a

68% absolute risk of rehospitalization within one year after a manic episode. A history of more than five psychiatric admissions in the past 10 years was associated with a 60% absolute rehospitalization risk and a more than twofold increased relative rehospitalization risk compared to having no previous psychiatric admissions. Further, patients with a history of self-inflicted harm had an increased risk of rehospitalization.

3.2. Rehospitalization risks in relation to prescription fills after hospital discharge

Apart from drugs with regulatory approval for relapse prevention after a manic episode, common psychotropic drugs after hospital discharge included hypnotics (used by 42%), benzodiazepines (27%), other oral antipsychotics (24%), antidepressants (12%), lamotrigine (9%), and depot neuroleptics (6%). With the exception of antidepressants, use of any of these drugs predicted a higher rehospitalization risk, as did use of anti-manic drugs in the year before the index hospitalization.

The overall rehospitalization risk for patients who initiated pharmacologic relapse prevention was 39%, compared to 46% for patients who did not use relapse prevention within the first four weeks after hospital discharge. **Figure 2** illustrates the proportion of patients with no rehospitalization during follow-up. Absolute rehospitalization risks for patients on monotherapy and combination therapies with 2 or 3 or more prophylactic drugs were 40%, 38% and 41% respectively. The difference in rehospitalization risk compared to untreated patients was only significant for patients on combination therapy with 2 prophylactic drugs (adjusted hazard ratio [AHRs] 0.76, 95% confidence interval [CI] 0.77-0.94), whereas the AHR for prophylactic monotherapy was 0.83 (95% CI 0.75-1.02) and for combination therapies with 3 or more prophylactic drugs 0.75 (95% CI 0.74-1.05).

Table 2 displays absolute and relative risks of psychiatric rehospitalization in each treatment group. Overall, absolute one-year rehospitalization risks ranged from 32% to 65% across treatment groups. In the monotherapy group, no drug was associated with a significantly altered risk of rehospitalization compared to lithium monotherapy (**Table 2** and **Figure 3**). Combination therapies with olanzapine and valproate or olanzapine and lithium were associated with the lowest rehospitalization risks of all treatment options, the one-year rehospitalization risk being 32% and 34%, respectively, compared to 42% for patients on lithium monotherapy, AHRs: 0.76 (95% CI 0.62-0.93) and 0.83 (95% CI 0.70-0.98) (**Table 2** and **Figure 4**). The results were unaffected by further adjustments for any previous diagnosis of depression or previous use of antidepressants (results not shown in tables).

4. Discussion

In this extensive neck-to-neck comparative study of rehospitalization risks among bipolar disorder type I patients initiated on prophylactic medication after a manic episode, we found that rehospitalization risk remains high, despite an extensive use of modern treatment alternatives. Nonetheless, the rehospitalization risk differed significantly depending on what prophylactic treatment was used following hospital discharge, with the lowest observed risk in patients initiated on a combination therapy with olanzapine and a classic mood-stabilizer.

The use of a nationwide population based cohort with few exclusion criteria and minimal loss to follow-up minimized the risk for selection bias in this study. Information bias was curtailed through the use of prospectively collected data from Swedish national registers, which are recognized for their high quality (Ludvigsson et al., 2011; Wettermark et al., 2007). To further mirror clinical reality, in which some patients are subject to repeated hospitalizations, we allowed patients to participate in the study after each hospitalization for mania during the study period. Any possible clustering effect due to some patients being included several times were handled statistically (Lee, 1992). The size of the cohort allowed us to specifically study relapse prevention after a manic episode, thus enabling comparisons with pre-existing RCT findings.

As for all observational studies, confounding effects need to be thoroughly considered. We handled potential confounding by indication through adjusting for clinical and sociodemographic factors affecting the rehospitalization risk in a multivariable regression model. These adjustments had no significant effect on the point estimates, indicating a low degree of confounding by these covariates. It should, however, be acknowledged that register-data have a lower resolution

compared to, for example, hospital records, resulting in blunter measurements of clinical factors. Further, all variables and clinical parameters that could influence treatment choices and outcomes are not available in register data, meaning that residual confounding cannot be ruled out. The use of an “intention-to-treat” design in which patients were allocated to different treatment groups based on their initial prescription fills after hospital discharge may have resulted in some misclassification, as one third of all patients used anti-manic drugs before their index hospitalization and may have restarted that medication without filling a new prescription after discharge; however, such potential misclassification is likely to be non-differential. Although our aim was to study rehospitalization risks after a manic episode in patients with bipolar disorder type I, a subgroup of the included patients may have suffered from non-bipolar types of mania induced by drugs or illegal substances, as bipolar I disorder is not a separate diagnosis in the ICD-10 classification. Another limitation to this study is that the use of prescription fills as a proxy for ongoing treatment comes with some uncertainty, as we cannot know to what degree the patients actually took their drugs.

Contrary to our hypothesis and to previous observational findings (Garnham et al., 2007; Hayes et al., 2016; Kessing et al., 2012; Kessing et al., 2011; Simhandl et al., 2014; Pompili et al., 2014), our results do not suggest a superior effectiveness of lithium monotherapy over other treatment options. Notably, all previous real-world studies on the comparative effectiveness of relapse prevention in bipolar disorder have included a mix of patients with bipolar disorder type 1 and 2 (Garnham et al., 2007; Hayes et al., 2016; Kessing et al., 2012; Kessing et al., 2011; Simhandl et al., 2014), all but one (Simhandl et al., 2014) including psychiatric outpatients or patients managed in primary care. In contrast, our study focused on patients with bipolar disorder type 1 with a recent manic episode. The discrepancies between our observations and findings from previous real-world

studies highlight the importance of considering the bipolar disorder subtype and current illness burden related to mania or depression when choosing relapse prevention. Our findings provide complementary real-world evidence to RCTs which have suggested that olanzapine is more effective than lithium in preventing affective recurrence after a manic episode (Ketter et al., 2006; Tohen et al., 2005), possibly explaining why observational data show that patients with bipolar disorder type 2 are overrepresented among lithium responders (Garnham et al., 2007).

Further, the present study provides evidence for a superior effectiveness of combination therapies after a manic episode. On average, patients on combination therapy with two prophylactic drugs had a lower rehospitalization risk compared to patients on monotherapy. The lowest rehospitalization risks were seen in patients using combination therapies including olanzapine and valproate or olanzapine and lithium, both groups experiencing a circa 10% lower rehospitalization risk than patients on lithium monotherapy. This observation is in line with RCT findings showing comparative advantages of combination therapies encompassing olanzapine and a classical mood-stabilizer in bipolar disorder type 1 (Tohen et al., 2004; Yatham et al., 2016), especially following a manic episode (Yatham et al., 2016). Other observational studies have failed to show improved outcomes with combination therapies (Gonzalez-Pinto et al., 2011; Kulkarni et al., 2012), but have either included patients of whom the majority were depressed or euthymic at study entry (Kulkarni et al., 2012), or not differentiated between different treatment combinations (Gonzalez-Pinto et al., 2011). As we would expect patients on combination therapy to have a more severe symptomatology at baseline compared to monotherapy users, there is a possibility that such therapies may be even more beneficial than observed.

One in five patients did not use any relapse prevention in the first four weeks after hospital discharge. Notably, these patients only had a modestly increased rehospitalization risk compared to patients on prophylactic pharmacotherapy. It is however important to consider that these patients may have initiated relapse prevention later on, improving the outcomes in this group. Further, it cannot be ruled out that patients with a low relapse risk could be overrepresented in this group as they may not have been prescribed relapse prevention, although recommended by treatment guidelines (The Swedish National Board of Health and Welfare, 2010; Goodwin et al., 2016; Grunze et al., 2013; Yatham et al., 2013).

In conclusion, our results support recent RCT findings indicating that a combination therapy including olanzapine and a classic mood-stabilizer may be the most effective treatment option for preventing severe affective relapses after a manic episode. The present study indicates that clinicians may be right in joining the global trend of prescribing more combination therapies (Bjorklund et al., 2016; Chang et al., 2016), in particular when treating patients with a recent manic episode.

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Table 1. Clinical and sociodemographic characteristics of the patients at study entry and associated rehospitalization risks

		Total (N = 6 502)		Rehosp	Rehospitalization, Hazard Ratio (95% CI)		
		N	%	%	Unadjusted	Model 1	Model 2
Sex	Female	3 729	57.4	41.4	Ref=1	Ref=1	
	Male	2 773	42.6	39.0	0.95 (0.88-1.03)	0.98 (0.90-1.06)	
Age (years)	<30	1 088	16.7	33.2	Ref=1	Ref=1	Ref=1
	30-44	1 561	24.0	42.6	1.35 (1.19-1.54)	1.24 (1.08-1.41)	1.26 (1.10-1.43)
	≥45	3 853	59.3	41.5	1.34 (1.20-1.50)	1.27 (1.12-1.44)	1.29 (1.14-1.46)
Marital status	Married	1 474	22.7	26.8	Ref=1	Ref=1	Ref=1
	Unmarried/Divorced/Widowed	5 028	77.3	37.2	1.55 (1.40-1.72)	1.29 (1.16-1.44)	1.32 (1.19-1.46)
Years of education	≤9	1 428	22.0	45.1	1.13 (1.03-1.24)	1.13 (1.02-1.24)	1.14 (1.04-1.25)
	10-12	3 072	47.2	41.2	Ref=1	Ref=1	Ref=1
	≥13	2 002	30.8	35.8	0.83 (0.75-0.91)	0.94 (0.86-1.03)	0.93 (0.85-1.02)
Country of birth	Sweden	5 382	82.8	41.3	Ref=1	Ref=1	Ref=1
	Other European country	664	10.2	35.4	0.81 (0.71-0.93)	0.81 (0.71-0.93)	0.82 (0.72-0.94)
	Country outside Europe	456	7.0	36.6	0.83 (0.71-0.97)	0.88 (0.75-1.04)	0.89 (0.76-1.05)
Income level^a	Low income	3 811	58.6	44.5	1.37 (1.26-1.48)	1.10 (1.01-1.20)	
	Middle income	2 525	38.8	34.6	Ref=1	Ref=1	
	High income	166	2.6	34.3	1.00 (0.76-1.30)	1.09 (0.83-1.42)	
First manic episode	No	1 712	26.3	48.4	Ref=1	Ref=1	Ref=1
	Yes	914	14.1	30.9	0.56 (0.52-0.61)	0.83 (0.76-0.91)	0.83 (0.76-0.91)
Psychotic symptoms during index episode	No	2 854	43.9	42.4	Ref=1	Ref=1	
	Yes	3 648	56.1	38.8	0.89 (0.82-0.96)	0.96 (0.89-1.04)	
Length of index hospitalization (days)	<14	1 616	24.9	42.3	Ref=1	Ref=1	Ref=1
	15-42	3 414	52.5	38.9	0.85 (0.78-0.94)	0.87 (0.79-0.95)	0.86 (0.79-0.95)
	>42	1 472	22.6	41.8	0.94 (0.84-1.05)	0.86 (0.77-0.96)	0.86 (0.77-0.96)
Psychiatric comorbidities^b	Anxiety disorder	660	10.2	45.8	1.27 (1.13-1.44)	1.15 (1.02-1.31)	1.17 (1.03-1.32)
	Any personality disorder	351	5.4	57.5	1.86 (1.61-2.14)	1.14 (0.94-1.38)	
	Borderline personality disorder	131	2.0	67.9	2.59 (2.10-3.20)	1.51 (1.13-2.01)	1.76 (1.41-2.19)

Filled prescriptions after discharge	Alcohol use disorder	601	9.2	51.1	1.49 (1.32-1.67)	1.16 (1.02-1.33)	1.16 (1.02-1.32)
	Substance use disorder	532	8.2	53.4	1.62 (1.43-1.83)	1.26 (1.10-1.43)	1.27 (1.11-1.44)
	Hyperactivity disorder	265	4.1	47.2	1.30 (1.09-1.55)	0.92 (0.73-1.16)	
	Eating disorder	28	0.4	57.1	1.75 (1.07-2.86)	1.15 (0.70-1.91)	
	Autism spectrum disorder	68	1.0	41.2	1.15 (0.79-1.67)	0.92 (0.63-1.35)	
	Antidepressants	812	12.5	43.3	1.14 (1.02-1.28)	1.06 (0.94-1.19)	
	Lamotrigine	560	8.6	46.1	1.24 (1.09-1.41)	1.14 (1.00-1.30)	1.15 (1.01-1.31)
	Other antipsychotics	1 573	24.2	46.0	1.24 (1.14-1.35)	1.18 (1.08-1.28)	1.18 (1.08-1.29)
	Depot neuroleptics	414	6.4	52.2	1.46 (1.27-1.67)	1.19 (1.03-1.38)	1.19 (1.03-1.38)
	Anti-addiction drugs	156	2.4	49.4	1.32 (1.05-1.65)	0.95 (0.75-1.20)	
	Benzodiazepines	1 788	27.5	47.0	1.34 (1.24-1.46)	1.19 (1.10-1.30)	1.20 (1.10-1.30)
	Hypnotics	2 747	42.2	43.1	1.17 (1.08-1.26)	1.09 (1.01-1.18)	1.09 (1.01-1.18)
	Psychostimulants	100	1.5	58.0	1.86 (1.43-2.41)	1.34 (0.97-1.86)	
	Psychiatric admissions, past 10 years (N)						
	0	1 635	25.1	24.6	Ref=1	Ref=1	Ref=1
History of self-inflicted harm^c	1-4	2 485	38.2	32.4	1.36 (1.20-1.53)	1.22 (1.08-1.38)	1.22 (1.08-1.38)
	≥5	2 382	36.6	59.5	3.16 (2.83-3.53)	2.25 (1.99-2.55)	2.29 (2.03-2.59)
	No	5 777	88.8	26.8	Ref=1	Ref=1	Ref=1
Treatment with anti-manic drugs before index hospitalization	Yes	725	11.2	37.2	1.92 (1.73-2.13)	1.32 (1.18-1.48)	1.34 (1.20-1.50)
	Not in the past year	2 653	40.8	31.9	Ref=1	Ref=1	Ref=1
	Discontinued > 90 days before	1 302	20.0	46.3	1.67 (1.50-1.85)	1.17 (1.05-1.30)	1.17 (1.05-1.30)
	Discontinued < 90 days before	365	5.6	45.5	1.59 (1.34-1.87)	1.07 (0.90-1.27)	1.08 (0.91-1.28)
	Ongoing	2 182	33.6	46.3	1.65 (1.51-1.81)	1.17 (1.06-1.29)	1.17 (1.06-1.30)

Note that the same patient could enter the study multiple times, and that 4 250 individuals contributed to the 6 502 included index hospitalizations for mania.

Model 1: adjusted for all displayed clinical and sociodemographic characteristics

Model 2: adjusted for clinical and sociodemographic characteristics with a significant association to the rehospitalization risk, including age; marital status; years of education; country of birth; first manic episode; length of index hospitalization; psychiatric comorbidities: anxiety disorder, borderline personality disorder, alcohol use disorder and substance use disorder; concurrent use of: lamotrigine, other antipsychotics, depot neuroleptics, benzodiazepines and hypnotics; number of previous psychiatric admissions; history of self-inflicted harm; and treatment with anti-manic drugs before the index hospitalization

^a Annual income in relation to the annual income distribution in Sweden: low income representing the bottom 20% of the income distribution, and high income representing the top 20% of the income distribution.

^b ICD-10 codes registered in the NPR in the year prior to the index hospitalization: anxiety disorder: F40-F42; any personality disorder: F60-F61; borderline personality disorder: F60.3; alcohol use disorder: F10; substance use disorder: F11-F16 and F18-F19; hyperactivity disorder: F90; eating disorder: F50; and autism spectrum disorder: F84.0, F84.1 and F84.5

^c Any of the following ICD-10 codes registered in the NPR, ever: X60-X84 and Y10-Y34

Table 2. Risks of psychiatric rehospitalization in relation to prescription fills after hospital discharge

	Total	Rehospitalizations		Rehospitalization, Hazard Ratio (95% CI)	
	N	N	%	Unadjusted	Model 2
Monotherapies					
lithium	859	362	42.1	Ref=1	Ref=1
valproate	404	155	38.4	0.86 (0.71-1.04)	0.89 (0.74-1.07)
olanzapine	775	278	35.9	0.81 (0.69-0.95)	0.90 (0.77-1.06)
quetiapine	344	139	40.4	0.93 (0.77-1.13)	0.91 (0.75-1.11)
aripiprazole	114	55	48.2	1.26 (0.95-1.68)	1.13 (0.85-1.51)
Combination therapies					
lithium + valproate	202	92	45.5	1.06 (0.84-1.33)	0.96 (0.76-1.21)
lithium + olanzapine	729	246	33.7	0.74 (0.63-0.87)	0.83 (0.70-0.98)
lithium + quetiapine	316	137	43.4	0.99 (0.82-1.21)	0.95 (0.78-1.15)
lithium + aripiprazole	98	43	43.9	1.08 (0.79-1.48)	0.87 (0.63-1.20)
valproate + olanzapine	402	130	32.3	0.69 (0.57-0.84)	0.76 (0.62-0.93)
valproate + quetiapine	167	70	41.9	1.00 (0.77-1.29)	0.87 (0.68-1.13)
valproate + aripiprazole	51	19	37.3	0.92 (0.58-1.45)	1.01 (0.64-1.61)
olanzapine + quetiapine	68	27	39.7	0.92 (0.62-1.36)	0.86 (0.58-1.28)
olanzapine + aripiprazole	44	15	34.1	0.82 (0.49-1.38)	0.84 (0.50-1.40)
quetiapine + aripiprazole	17	11	64.7	1.74 (0.95-3.16)	1.42 (0.78-2.59)
lithium + valproate + olanzapine	157	62	39.5	0.87 (0.67-1.14)	0.89 (0.68-1.17)
lithium + valproate + quetiapine	84	34	40.5	0.95 (0.67-1.34)	0.86 (0.61-1.23)
lithium + olanzapine + quetiapine	53	20	37.7	0.91 (0.58-1.42)	0.81 (0.51-1.27)
Other combinations of ≥ 3 drugs	172	73	42.4	1.06 (0.83-1.36)	0.97 (0.75-1.25)
No prescription fills	1 446	658	45.5	1.12 (0.99-1.27)	1.03 (0.90-1.17)

Model 2: adjusted for clinical and sociodemographic characteristics with a significant association to the rehospitalization risk, including age; marital status; years of education; country of birth; first manic episode; length of index hospitalization; psychiatric comorbidities: anxiety disorder, borderline personality disorder, alcohol use disorder and substance use disorder; concurrent use of: lamotrigine, other antipsychotics, depot neuroleptics, benzodiazepines and hypnotics; number

of previous psychiatric admissions; history of self-inflicted harm; and treatment with anti-manic drugs before the index hospitalization