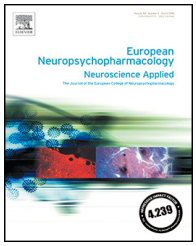
European Neuropsychopharmacology (2019) 29, 691–700

www.elsevier.com/locate/euroneuro



Monotherapy vs. combination therapy for post mania maintenance treatment: A population based cohort study

Louise Wingård[a,*], **Lena Brandt**[a], **Robert Bodén**[a,b], **Helle Kieler**[a], **Morten Andersen**[a,c], **Johan Reutfors**[a]

[a] *Centre for Pharmacoepidemiology, Department of Medicine, Solna, Karolinska Institutet, Karolinska University Hospital, T2, SE-171 76 Stockholm, Sweden*
[b] *Department of Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden*
[c] *Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

Received 31 October 2018; received in revised form 30 March 2019; accepted 23 April 2019

KEYWORDS
Cohort studies;
Bipolar disorder;
Maintenance treatment;
Antipsychotic agents;
Lithium

Abstract
In recent years, the use of atypical antipsychotics and combination therapy for relapse prevention in bipolar disorder has increased substantially. However, real-world data on the comparative effectiveness of these treatment options are largely non-existent. We conducted a population-based cohort study, using data from Swedish national registers. All patients aged 18–75 years who were hospitalized for mania 2006–2014 and filled at least one prescription of lithium, valproate, olanzapine, quetiapine, aripiprazole or any combination of these drugs were included, and followed for up to one year after hospital discharge, generating follow-up data from 5 713 hospitalizations. We used Cox proportional hazard regression models to study time to treatment failure for each individual drug and combination therapy, using lithium as comparator. Treatment failure was defined as treatment discontinuation, switch, or rehospitalization, and the results were adjusted for clinical and sociodemographic factors. We found that treatment failure occurred in 85% of cases and that the majority of combination therapies were associated with lower risks of treatment failure compared to monotherapies. Patients combining lithium + valproate + quetiapine had the lowest risk of treatment failure (adjusted HR [AHR] 0.40, 95% CI 0.30–0.54), followed by patients on lithium + valproate + olanzapine (AHR

* Corresponding author.
E-mail address: louise.wingard@ki.se (L. Wingård).

https://doi.org/10.1016/j.euroneuro.2019.04.003

0.55, 95% CI 0.45–0.68). In contrast, monotherapies with antipsychotics were associated with significantly higher risks of treatment failure compared to single use of lithium. In conclusion, our results support experimental findings, suggesting that combination therapy is more effective than monotherapy after a manic episode.

1. Introduction

In recent decades, the number of drugs approved for relapse prevention in bipolar disorder have multiplied and so have the possibilities for individualized maintenance treatment. Despite these advances, recurrence rates in bipolar disorder remain high, with 50% of patients relapsing in mania or depression within two years (Hong et al., 2010; Perlis et al., 2006). Reports on prescription trends from around the world show that antipsychotics and combination therapies are increasingly used for maintenance treatment (Bjorklund et al., 2016; Chang et al., 2016; Kessing et al., 2016). However, data on the comparative effectiveness of these treatments are limited.

Lithium, valproate, lamotrigine (jointly referred to as mood-stabilizers) and some atypical antipsychotics are currently approved for maintenance treatment in bipolar disorder. The majority of randomized controlled trials (RCTs) on which the regulatory approvals of these drugs are based have evaluated the efficacy of one atypical antipsychotic at a time (in monotherapy or as add-on), compared to one or two mood-stabilizers and/or placebo (Carlson et al., 2012; Nierenberg et al., 2016; Suppes et al., 2013; Tohen et al., 2004, 2005; Weisler et al., 2011; Woo et al., 2011; Yatham et al., 2013). Observational studies of maintenance treatment have generally studied lithium and several anticonvulsants in parallel, but only one atypical antipsychotic, and few, if any, combination therapies (Altamura et al., 2008; Garnham et al., 2007; Gonzalez-Pinto et al., 2011; Hayes et al., 2016; Simhandl et al., 2014; Lahteenvuo et al., 2018). Our group recently found that patients who combine lithium or valproate with olanzapine after a manic episode have the lowest rehospitalization risk (Wingard et al., 2017). However, most other observational studies have found a superior effectiveness of lithium monotherapy compared to other treatment alternatives (Garnham et al., 2007; Hayes et al., 2016; Simhandl et al., 2014; Lahteenvuo et al., 2018). Unlike our study and most RCTs, these studies have not differentiated between patients with bipolar disorder type I and II, nor accounted for whether maintenance treatment was initiated following mania or depression, which is a limitation.

Treatment failure – including medication switch, discontinuation, and psychiatric rehospitalization – is a compound measure, which due to its high clinical relevance has been used in both clinical trials and observational studies of maintenance treatment in severe mental disorders (Hayes et al., 2016; Lieberman et al., 2005; Miura et al., 2014). Our study objective was to compare rates of treatment failure after a manic episode across all drugs approved for post mania relapse prevention in Sweden, including combinations of these. Based on our previous findings, we hypothesized that patients combining lithium or valproate and olanzapine would experience the lowest rates of treatment failure.

2. Experimental procedures

2.1. Study design and data sources

We conducted a nation-wide cohort study using data from national longitudinal population-based registers in Sweden. The unique personal identity number assigned to all Swedish residents at birth or immigration was used to link information across registers. Eligible patients were identified in the National Patient Register (NPR), which covers all psychiatric inpatient care in Sweden since 1987 and includes admission and discharge dates and discharge diagnoses assigned by the treating physician (coded according to the *International Classification of Diseases*, 10th revision, ICD-10, since 1997) (Ludvigsson et al., 2011).

For each patient, information on filled prescription drugs was obtained from The Swedish Prescribed Drug Register (PDR), in which all prescribed drugs purchased in Swedish pharmacies are recorded since July 2005 (Wettermark et al., 2007). Medications were identified based on their World Health Organization's Anatomical Therapeutic Chemical Classification (ATC) code. Through the individual dosage text linked to each prescription and information on the dispensed amount and subsequent refills, we identified time periods during which the patient had access to a specific substance or combination therapy. These periods were defined as active treatment periods.

We further collected data on migration and sociodemographic information from registers maintained by Statistics Sweden and information on deaths from the Cause of Death Register.

2.2. Participants

The identification of the study cohort is illustrated in Fig. 1. All residents aged 18–75 years with a main diagnosis of a manic episode (ICD-10 codes F30.1–F30.9 and F31.1–F31.2) registered upon discharge from psychiatric inpatient care in Sweden from July 1, 2006 to December 3, 2014 were identified in the NPR and included in the study on the day they were admitted to the hospital. As it is not uncommon for patients to have recurrent manic episodes, the question of what drug/drugs to choose may for some be a repeated issue. In order to account for this circumstance, patients who were hospitalized for mania multiple times during the study period were included in the study upon each hospitalization. However, hospitalizations for mania with less than seven days apart were linked and counted as one episode, based on our assumption that rehospitalization within seven days is more likely a result of incomplete recovery than of actual manic relapse. To reduce the risk of diagnostic misclassification, we did not include individuals with a previous diagnosis of schizophrenia (ICD-10 code F20), schizoaffective disorder (F25), or dementia (F00—F03). We further excluded patients

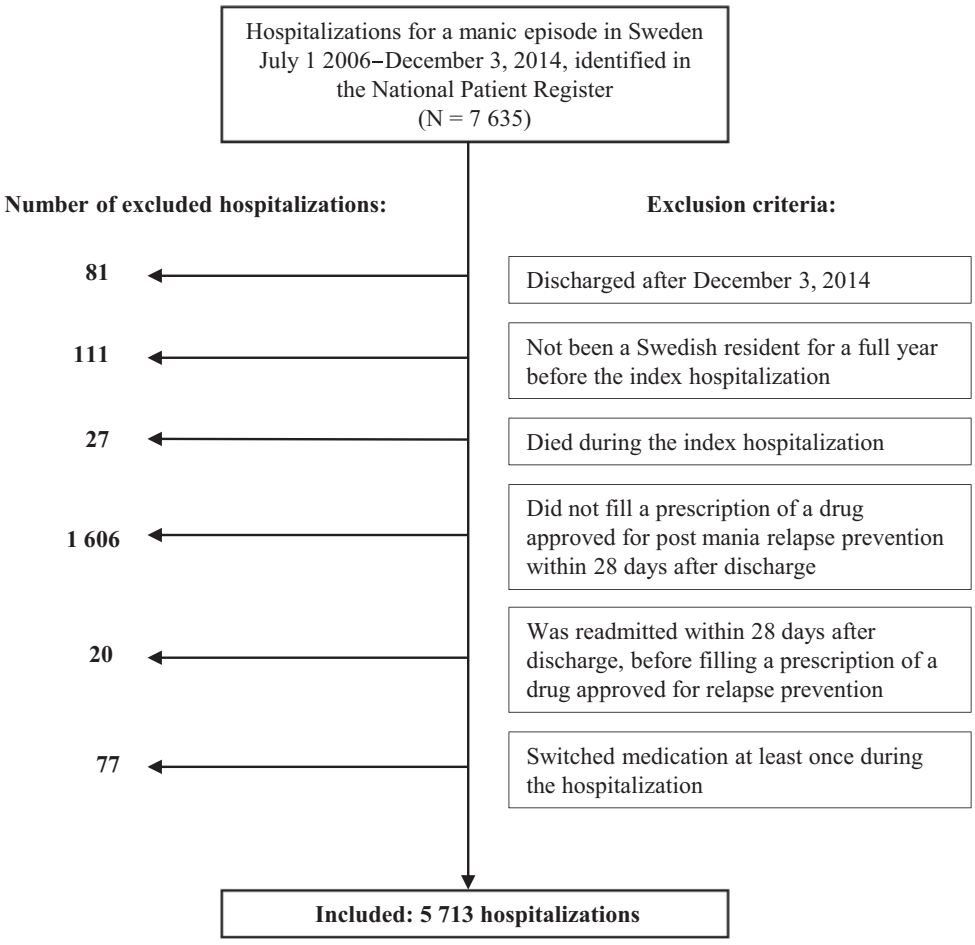


Fig. 1 Identification of the study cohort.

who had not been Swedish residents for a full year prior to study inclusion due to incomplete coverage in the national registers, and patients who died during the index hospitalization.

Individuals with several hospitalizations for mania during the study period were included upon each such hospitalization, if there were more than seven days between discharge and readmission.

2.3. Exposures and outcomes

After each included hospitalization for mania (index hospitalization), active treatment periods of lithium (ATC-code N05AN01), valproate (N03AG01), olanzapine (N05AH03), quetiapine (N05AH04), and aripiprazole (N05AX12), alone or in combinations, were recorded. Each active treatment period was defined as starting on the day of a prescription fill of any of the studied drugs, or on the day of hospital discharge, if the patient filled one or several prescriptions during the index hospitalization. If the index hospitalization was longer than four weeks, only prescription fills during the last four weeks of the hospitalization were considered. Patients who filled prescriptions of more than one drug within a time period of less than two weeks were considered to use combination therapy. Follow-up started on day 14 of the first active treatment period and ended after 365 days or upon the earliest of any of the following events: treatment failure, emigration, death, or the end of the study period, December 31, 2014.

We defined treatment failure as 1) discontinuation of medication, 2) switch of medication, or 3) being readmitted to inpatient psychiatric care during an active treatment period. Patients were censored on the first of either of these events. Medication discontinuation was defined as not having access to medication for a period of 28 days or more and based on our calculations of active treatment periods. Patients who initiated a combination therapy and subsequently stopped one drug while continuing with the other/others were not considered to have discontinued their medication. Medication switch was defined as filling a prescription of another psychotropic drug (mood-stabilizer, antipsychotic, antidepressant, or anxiolytic, ATC-codes N03AX09, N03AG01, N05A, N06A, or N05B) during an active treatment period or within 28 days after an active treatment period. Finally, readmission to psychiatric inpatient care was considered a treatment failure, including admissions to somatic wards due to suicide attempts (ICD-10 codes X60–X84 or Y10–Y34).

2.4. Potential confounders

We considered potential confounders possibly related to the choice of a specific prophylactic drug or combination therapy and treatment failure. The potential confounders were grouped into three categories: 1) sociodemographic factors, 2) factors related to the index hospitalization, and 3) factors related to the psychiatric history of the patient. Sociodemographic factors included age, sex, the patient's marital status, country of birth, level of education, and annual income. We characterized the index hospitalization based on whether the patient had any previously recorded manic

Table 1 Patient characteristics associated with treatment failure. Risks of treatment failure shown as hazard ratios with 95% confidence intervals.

		Total	Treatment failure events		Treatment failure, hazard ratio (95% CI)	
		N[a]	N	%	Crude	Adjusted[b]
Sex	Female	3 261	2 810	86.2	*Ref=1*	*Ref=1*
	Male	2 452	2 061	84.1	0.92 (0.87-0.98)	0.95 (0.90-1.01)
First ever manic episode	No	3 122	2 703	86.6	*Ref=1*	*Ref=1*
	Yes	2 591	2 168	83.7	1.20 (1.13-1.27)	1.13 (1.05-1.22)
Length of index hospitalization (days)	<15	1 337	1 182	88.4	1.22 (1.14-1.31)	1.19 (1.11-1.28)
	15–42	3 056	2 615	85.6	*Ref=1*	*Ref=1*
	>42	1 320	1 074	81.4	0.83 (0.77-0.89)	0.81 (0.76-0.88)
Medications after discharge (anti-manic drugs excluded)	Antidepressants	728	639	87.8	1.05 (0.97-1.14)	0.85 (0.77-0.93)
	Lamotrigine	485	427	88.0	1.17 (1.06-1.29)	1.05 (0.95-1.16)
	Other antipsychotics	1 362	1 139	83.6	0.90 (0.84-0.96)	0.90 (0.84-0.96)
	Depot antipsychotics	220	176	80.0	0.76 (0.66-0.89)	0.79 (0.68-0.93)
	Anxiolytics	1 418	1 238	87.3	1.12 (1.05-1.20)	1.06 (0.99-1.13)
	Psychostimulants	91	83	91.2	1.35 (1.09-1.68)	0.82 (0.62-1.08)
Anti-manic treatment before the index hospitalization	Not for one year	1 628	1 361	83.6	*Ref=1*	*Ref=1*
	Not for ≥90 days	693	590	85.1	1.13 (1.03-1.24)	1.00 (0.90-1.10)
	Within <90 days	250	215	86.0	1.20 (1.04-1.39)	1.00 (0.86-1.16)
	Ongoing	3 142	2 705	86.1	1.31 (1.22-1.39)	1.11 (1.03-1.20)
Antidepressant treatment before the index hospitalization	Not for one year	3 523	2 948	83.7	*Ref=1*	*Ref=1*
	In the past year	2 190	1 923	87.8	1.26 (1.19-1.33)	1.24 (1.16-1.33)
History of depression	Not for 5 years	3 058	2 547	83.3	*Ref=1*	*Ref=1*
	In the past 5 years	2 655	2 324	87.5	1.21 (1.15-1.28)	1.07 (1.01-1.14)
Psychiatric hospitalizations, past 10 years	0	1 134	930	82.0	*Ref=1*	*Ref=1*
	<5	2 296	1 926	83.9	1.14 (1.05-1.23)	1.01 (0.92-1.10)
	≥5	2 283	2 015	88.3	1.49 (1.38-1.61)	1.22 (1.09-1.36)
History of self-harm, ever	No	5 062	4 277	84.5	*Ref=1*	*Ref=1*
	Yes	651	594	91.2	1.45 (1.33-1.57)	1.23 (1.12-1.34)
Psychiatric comorbidities	Anxiety disorder/OCD[c]	525	469	89.3	1.29 (1.17-1.41)	1.15 (1.04-1.27)
	Any PD[d]	288	262	91.0	1.41 (1.25-1.60)	0.99 (0.84-1.18)
	Borderline PD[d]	125	121	96.8	2.05 (1.71-2.46)	1.57 (1.22-2.00)
	Alcohol-related disorder	424	374	88.2	1.16 (1.05-1.29)	1.02 (0.91-1.14)
	Substance-related disorder	374	336	89.8	1.20 (1.08-1.34)	1.04 (0.92-1.17)
	ADHD[e]	198	180	90.9	1.42 (1.22-1.64)	1.28 (1.05-1.55)
	Autism spectrum disorder	68	60	88.2	1.45 (1.12-1.87)	1.26 (0.97-1.64)

[a] Number of included index hospitalizations.
[b] Adjusted for all other variables in the model. A sandwich covariance estimate was used to account for intra-cluster dependence as the same patient could be included multiple times.
[c] Obsessive-compulsive disorder.
[d] Personality disorder.
[e] Attention-deficit hyperactivity disorder.

episodes in the NPR or if the index hospitalization represented a first manic episode. Further, a discharge- or secondary diagnosis specifying psychotic symptoms (ICD-10 codes F30.2, F31.2, F21-F24, or F28-F29) and the length of the index hospitalization were used as proxy variables for the severity of the manic index episode. We also considered any use of other psychotropic drugs, including antidepressants (ATC-code N06A), lamotrigine (N03AX09), non-mood-stabilizing antipsychotics (N05A except N05AN01, N05AH03, N05AH04, and N05AX12), anxiolytics (N05B), hypnotics (N05C), psychostimulants (N06B), and anti-addiction drugs (N07BB, N07BC01, N07BC02, and N07BC51) after hospital discharge.

Factors related to the psychiatric history of the patient included use of anti-manic drugs or antidepressants within the past year, psychiatric comorbidities (anxiety disorder/obsessive-compulsive disorder (OCD) (F40-F42), any personality disorder (F60-F61), borderline personality disorder (F60.3), alcohol-related disorder (F10), any other substance-related disorder (F11-F16 or F18-F19), attention-deficit hyperactivity disorder (ADHD) (F90), eating disorder (F50), or autism spectrum disorder (F84.0, F84.1, or F84.5)) recorded within the past year, a registered diagnosis of depression (ICD-10 codes F31.3-F31.5, F32, or F33) within the past five years, the number of psychiatric hospital-

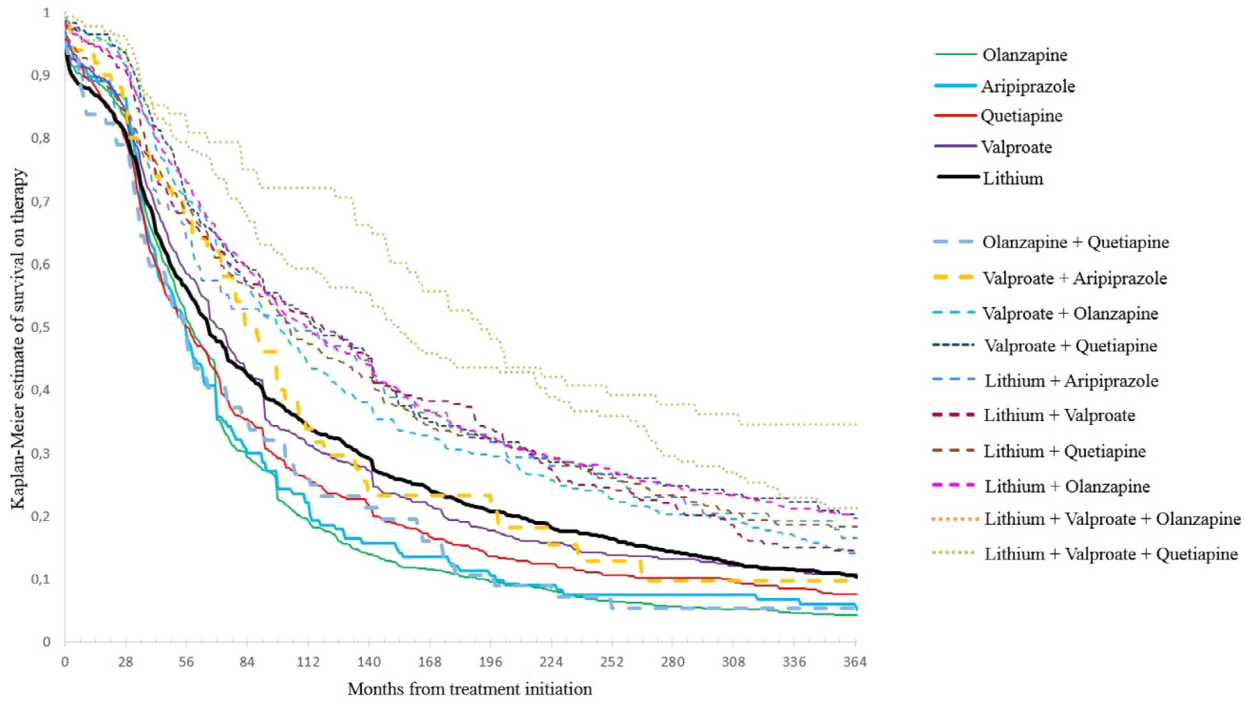


Fig. 2 Kaplan Meier estimates of time without treatment failure for all studied treatment alternatives.

izations within the past ten years, and any history of self-harm (X60–X84 or Y10–Y34).

2.5. Statistical analyses

In a first step, we investigated how potential confounders were related to treatment failure. The association between each variable and treatment failure was assessed using Cox proportional hazard regression models and estimated as a hazard ratio with a 95% confidence interval. We subsequently adjusted each hazard ratio for the effects of all other potential confounders in a multivariable model.

Next, we estimated the absolute risk for treatment failure associated with each of the studied prophylactic drugs and treatment combinations, after which hazard ratios for treatment failure were determined, using lithium monotherapy as comparator. Bias was handled through adjustment for potential confounders with a significant association with treatment failure, selected through backwards elimination of non-significant covariates from the full model. Potential confounders included in the final model are listed in Table 1.

A sandwich covariance estimate was used to account for intracluster dependence as the same patient could be included multiple times. In addition, we performed two analyses in which hazard ratios for treatment failure were assessed in 1) a cohort in which patients were only allowed to participate after the first hospitalization for mania during the study period, and 2) a sub cohort of patients with a first time hospitalization for mania.

Lastly, time to treatment failure in each treatment group was plotted in Kaplan Meier curves. All analyses were conducted using SAS software, version 9·4 (SAS Institute Inc., Cary, NC, USA).

2.6. Ethics

The study was approved by the regional ethical review board in Stockholm (Nos: 2011/1358-31/3, 2012/262-32, and 2013/735-32).

3. Results

The study included follow-up data from 5 713 hospitalizations for mania, representing 3 772 patients. Of these patients, 2 731 contributed with one hospitalization only whereas the other 1 041 contributed with two or more hospitalizations. Total follow-up time amounted to 1 773 patient-years. Treatment failure within one year after a manic episode was seen in 4 871 cases (85.3%). Of these, 2 667 patients switched treatment, 1 108 discontinued treatment and 1 096 were rehospitalized despite ongoing treatment. A slight majority of patients (57.5%) used a prophylactic monotherapy after discharge from the manic index episode.

3.1. Distribution of patient characteristics

Patient characteristics in the complete cohort are displayed in Table 1, while the distribution of those same characteristics across separate treatment groups is shown in Table S1. The majority of patients were women and 45 years or older. Fifty-five percent had been diagnosed with bipolar disorder before their index hospitalization or had a previously recorded manic episode. A similar proportion of all patients had an ongoing treatment with at least one anti-manic agent at the time they were admitted to the index hospitalization. Although most characteristics were equally distributed across patients who used different prophylactic treatments, some differences emerged. Patients on aripiprazole monotherapy were younger compared to other patients, whereas individuals with a first time manic episode or who were naïve to anti-manic drugs were overrepresented in the olanzapine group. The longest index-hospitalizations were seen in patients on triple ther-

Table 2 Comparative risks for treatment failure with each monotherapy and combination, presented as absolute risks and hazard ratios with 95% confidence intervals.

		All cause treatment failure			Medication switch			Medication discontinuation			Psychiatric rehospitalization		
	N	%	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	%	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	%	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	%	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Monotherapies													
Lithium	1 133	87.0	*Ref=1*	*Ref=1*	46.5	*Ref=1*	*Ref=1*	20.2	*Ref=1*	*Ref=1*	20.4	*Ref=1*	*Ref=1*
Valproate	525	87.4	1.01 (0.90-1.13)	1.10 (0.98-1.23)	44.2	0.94 (0.81-1.10)	1.06 (0.91-1.24)	26.1	1.34 (1.09-1.66)	1.38 (1.11-1.71)	17.1	0.84 (0.66-1.07)	0.94 (0.74-1.21)
Olanzapine	1 013	93.3	1.38 (1.26-1.51)	1.51 (1.37-1.66)	53.5	1.37 (1.22-1.55)	1.59 (1.40-1.80)	26.1	2.13 (1.79-2.55)	1.73 (1.43-2.09)	13.7	0.83 (0.67-1.02)	1.06 (0.85-1.32)
Quetiapine	468	90.2	1.21 (1.08-1.35)	1.20 (1.06-1.34)	56.0	1.36 (1.17-1.58)	1.34 (1.15-1.56)	16.5	1.05 (0.81-1.36)	0.99 (0.76-1.29)	17.7	0.99 (0.77-1.28)	1.02 (0.79-1.32)
Aripiprazole	146	92.5	1.34 (1.12-1.60)	1.28 (1.07-1.54)	60.3	1.53 (1.22-1.92)	1.48 (1.17-1.86)	15.8	1.22 (0.79-1.87)	1.09 (0.71-1.69)	16.4	0.96 (0.63-1.47)	0.95 (0.62-1.45)
Combination therapies													
Lithium + Valproate	217	83.4	0.74 (0.63-0.86)	0.72 (0.62-0.85)	38.2	0.66 (0.52-0.83)	0.62 (0.49-0.79)	17.5	0.60 (0.42-0.84)	0.63 (0.44-0.89)	27.6	1.06 (0.80-1.41)	1.05 (0.78-1.40)
Lithium + Olanzapine	696	76.5	0.67 (0.60-0.74)	0.69 (0.62-0.76)	41.8	0.71 (0.62-0.82)	0.72 (0.63-0.84)	16.9	0.57 (0.46-0.71)	0.50 (0.40-0.62)	17.9	0.68 (0.54-0.84)	0.84 (0.67-1.04)
Lithium + Quetiapine	314	79.6	0.72 (0.62-0.82)	0.66 (0.57-0.76)	40.4	0.71 (0.59-0.86)	0.61 (0.50-0.74)	12.7	0.44 (0.32-0.62)	0.43 (0.30-0.60)	26.4	1.04 (0.81-1.34)	1.08 (0.84-1.39)
Lithium + Aripiprazole	92	79.3	0.75 (0.59-0.95)	0.66 (0.52-0.84)	45.7	0.84 (0.61-1.15)	0.74 (0.54-1.01)	13.0	0.48 (0.27-0.85)	0.46 (0.26-0.83)	20.7	0.84 (0.53-1.35)	0.70 (0.44-1.13)
Valproate + Olanzapine	415	83.6	0.76 (0.67-0.86)	0.82 (0.72-0.93)	45.5	0.80 (0.68-0.94)	0.86 (0.73-1.02)	21.0	0.77 (0.60-0.98)	0.67 (0.52-0.86)	17.1	0.66 (0.51-0.87)	0.85 (0.65-1.11)
Valproate + Quetiapine	171	76.6	0.66 (0.55-0.79)	0.61 (0.51-0.74)	38.6	0.65 (0.50-0.84)	0.59 (0.45-0.76)	14.0	0.47 (0.31-0.71)	0.45 (0.30-0.69)	24.0	0.89 (0.64-1.24)	0.86 (0.61-1.20)
Valproate + Aripiprazole	50	86.0	0.95 (0.70-1.29)	0.93 (0.69-1.27)	40.0	0.81 (0.52-1.26)	0.78 (0.50-1.23)	22.0	1.12 (0.61-2.06)	0.94 (0.51-1.72)	24.0	1.14 (0.64-2.04)	1.13 (0.63-2.03)
Olanzapine + Quetiapine	62	91.9	1.31 (1.00-1.71)	1.20 (0.91-1.57)	64.5	1.64 (1.19-2.26)	1.33 (0.96-1.84)	8.1	0.58 (0.24-1.40)	0.66 (0.27-1.61)	19.4	1.15 (0.65-2.06)	1.13 (0.63-2.04)
Lithium + Valproate + Olanzapine	136	76.5	0.57 (0.47-0.70)	0.55 (0.45-0.68)	32.4	0.48 (0.36-0.66)	0.46 (0.34-0.63)	15.4	0.42 (0.27-0.66)	0.39 (0.25-0.61)	28.7	0.94 (0.67-1.32)	0.99 (0.70-1.39)
Lithium + Valproate + Quetiapine	68	64.7	0.43 (0.32-0.58)	0.40 (0.30-0.54)	38.2	0.52 (0.35-0.78)	0.45 (0.30-0.66)	7.4	0.17 (0.07-0.41)	0.18 (0.07-0.44)	19.1	0.57 (0.32-0.99)	0.57 (0.32-0.99)
Other combinations	207	75.8	0.69 (0.58-0.81)	0.62 (0.52-0.73)	42.0	0.75 (0.60-0.94)	0.64 (0.51-0.81)	7.7	0.27 (0.16-0.44)	0.26 (0.16-0.44)	26.1	1.03 (0.76-1.38)	0.99 (0.73-1.33)

[a] Adjusted for all factors displayed in Table 1. A sandwich covariance estimate was used to account for intra-cluster dependence as the same patient could be included multiple times.

apy with lithium + valproate + quetiapine, among whom almost 43% had been hospitalized for more than 42 days.

3.2. Patient characteristics associated with treatment failure

Patient characteristics that were significantly associated with treatment failure in the crude analysis are presented in Table 1. The factors with the strongest association with overall treatment failure were comorbid borderline personality disorder (adjusted hazard ratio [AHR] 1.57, 95% confidence interval [CI] 1.22–2.00), ADHD (AHR 1.28, 95% CI 1.05–1.55), and autism spectrum disorder (AHR 1.26, 95% CI 0.97–1.64). Use of antidepressants in the past year also predicted treatment failure after a manic episode (AHR 1.24, 95% CI 1.16–1.33). Notably, use of depot antipsychotics in addition to any of the studied prophylactic treatments was associated with a lower risk of treatment failure (AHR 0.79, 95% CI 0.68–0.93), as was a long index hospitalization of more than 42 days (AHR 0.81, 95% CI 0.76–0.88).

3.3. Comparative risks for treatment failure within the different treatment groups

Kaplan–Meier curves of the proportion of patients without treatment failure in each treatment group are shown in Fig. 2, with absolute and relative risks for treatment failure being displayed in Table 2. In the monotherapy group, all atypical antipsychotics were associated with significantly higher risks of overall treatment failure compared to lithium, whereas valproate was associated with a non-significantly higher risk. The risk for medication switch was significantly higher among patients on atypical antipsychotics, whereas medication discontinuation was most common among patients on valproate or olanzapine. No monotherapy was associated with a significantly higher or lower rehospitalization risk compared to lithium.

In general, risks for overall treatment failure were significantly lower among patients on combination therapy compared to monotherapy users, with absolute risks for treatment failure being 1–22.3% percentage points lower compared to lithium monotherapy (Table 2). Combinations of lithium + valproate + quetiapine or lithium + valproate + olanzapine were associated with the lowest overall risks of treatment failure, with AHRs of 0.40 (95% CI 0.30–0.54) and 0.55 (95% CI 0.45–0.68), respectively, compared to lithium monotherapy, followed by a combination of valproate + quetiapine (AHR 0.61, 95% CI 0.51–0.74). The same triple therapies were associated with the lowest rates of medication switch, and discontinuation of all treatment options. Further, lithium + valproate + quetiapine was the only treatment option associated with a significantly lower rehospitalization risk during ongoing treatment than lithium monotherapy (AHR 0.57, 95% CI 0.32–0.99).

Analyses in which patients were only allowed to contribute with one hospitalization showed similar results, with higher risks of treatment failure among patients on monotherapy with valproate, olanzapine, quetiapine or aripiprazole compared to lithium monotherapy. Similarly, a majority of combination therapies were associated with significantly lower risks of treatment failure compared to lithium, with the lowest risk for treatment failure being observed in patients on triple therapy with lithium + valproate + quetiapine (AHR 0.44, 95% CI 0.30–0.64). Yet again, results did not deviate from these trends when only studying patients with a first time manic episode (results not shown).

4. Discussion

In the present study we have compared risks for treatment failure across all anti-manic drugs and treatment combinations used for maintenance treatment after a manic episode in Sweden. We found that combination therapies were associated with significantly lower risks of treatment failure compared to monotherapies, and that monotherapy with lithium or valproate was associated with lower risks of treatment failure than single use of olanzapine, quetiapine, or aripiprazole. Patients combining lithium, valproate, and quetiapine had the lowest risk of treatment failure, experiencing a 60% lower risk compared to patients on lithium monotherapy, with lower rates of medication switch, discontinuation, and rehospitalization compared to patients on any other regimen.

To our knowledge, this is the first study to compare the effectiveness of a wide range of drugs for prophylactic use after a manic episode, and multiple combinations of these, head-to-head. The inclusion of a nationwide population based cohort with few exclusion criteria and minimal loss to follow-up was a major strength of this study, and should make our findings generalizable to bipolar disorder patients in other countries with the same available treatment options. Information bias was curtailed through the use of prospectively collected data from Swedish national registers, which are recognized for their complete coverage and high validity of recorded diagnoses (Ludvigsson et al., 2011; Wettermark et al., 2007). Further, linkage of information across several population based registers enabled adjustment for important clinical and sociodemographic confounders. The large number of eligible patients allowed us to specifically study maintenance treatment initiated after a manic episode, meaning that straight-off comparisons with RCT data were possible. The robustness of our findings was supported by analyses in which patients were only allowed to participate in the study once, or were included after a first-time hospitalization for mania, respectively, eliminating the possibility that our results were affected by the reinclusion of study subjects.

The current study does however have some important limitations. For one, the register data used in this population-based cohort study do not provide information on some important factors that influence treatment choices, for example patient attitudes towards medication. Neither does it provide answers for *why* patients discontinue or switch medication, such as discontinuation due to side effects. Further, register-data have lower resolution compared to hospital records or clinical interviews, resulting in blunter measurements of clinical factors. For instance, only 0.02% of the included patients in our study had a registered

borderline personality disorder diagnosis, whereas data indicate that as many as 10% of bipolar I patients suffer from comorbid borderline personality disorder (Zimmerman and Morgan, 2013), suggesting that the statistical adjustments made to account for this comorbidity may have been insufficient. There is also a continuous academic debate regarding whether or not borderline personality disorder should in fact be viewed as syndrome on the bipolar spectrum (di Giacomo et al., 2017). Approximately 0.01% of the included patients had a registered autism spectrum disorder, and the inclusion of these patients could also be discussed as data show that bipolar disorder have a somewhat different presentation in patients with autism, with more frequent manic relapses and interepisodic periods commonly being described in the manic symptom profile (Sapmaz et al., 2018). Patients with autism spectrum disorder may also respond differently to drugs used for bipolar disorder maintenance treatment, as they commonly require higher doses of antipsychotic drugs after a psychotic episode (Stralin and Hetta, 2019).

The use of "treatment failure" as outcome measure may to some extent fail to capture what most affects the lives of patients in terms of relapse, recurrence of symptoms, functioning, and life quality. Nonetheless, treatment failure is a reasonable proxy for capturing both the efficacy and tolerability, and hence the real world effectiveness, of treatments. The use of prescription data as a proxy for ongoing treatment also comes with some uncertainty, as patients may not have taken their medication as prescribed. As the aim was to assess treatment failure during the maintenance phase, we chose only to consider active treatment periods that started within four weeks after hospital discharge, based on the rationale that drugs filled after more than four weeks may have been intended as acute treatment of a new manic or depressive episode. In addition, we did not include patients who changed medication before hospital discharge or who were readmitted before initiating maintenance treatment.

Data on the effectiveness of combination therapies for maintenance treatment in bipolar disorder have up until now been limited (Grunze et al., 2013), and a majority of treatment guidelines recommend monotherapy as first-line maintenance treatment (Fountoulakis et al., 2017; Goodwin et al., 2016; Grunze et al., 2013; Kendall et al., 2014). Nonetheless, evidence from RCTs speaks in favour of combination therapies (Suppes et al., 2013; Tohen et al., 2004; Woo et al., 2011; Yatham et al., 2013, 2016). One trial that included 99 patients who had achieved syndromic remission with olanzapine plus lithium or valproate and were randomized to either continuing their regimen or switching to lithium/valproate plus placebo found that patients who continued their combination therapy experienced sustained symptomatic remission for a longer time than patients on lithium or valproate alone (Tohen et al., 2004). In another trial, 159 patients with bipolar I disorder who had recently remitted from a manic episode when treated with risperidone or olanzapine adjunctive to lithium or valproate were randomized to 1) discontinuation of risperidone or olanzapine and substitution with placebo at study entry, 2) substitution with placebo at 24 weeks after entry, or 3) continuation of combination therapy for the full 52 week duration of the study (Yatham et al., 2016). Patients who stayed on combination therapy for 24 weeks had a significantly longer time to any mood episode and a similar trend was observed in the 52-weeks group. RCT data on add-on treatment with aripiprazole to a classic mood-stabilizer further indicate that this combination is more beneficial than mood-stabilizer monotherapy after a manic episode (Yatham et al., 2013).

Altogether, the above mentioned RCT findings are in line with the real-world data presented here, showing that patients on a combination of lithium or valproate plus olanzapine, quetiapine, or aripiprazole experience an absolute risk of treatment failure that is up to 22 percentage points lower compared to patients on lithium monotherapy. They further seem to suggest that combination therapies of mood-stabilizers and antipsychotics are especially beneficial after a manic episode (Yatham et al., 2013, 2016). There are so far no available RCT data on the comparative effectiveness of triple therapies, although our results indicate that patients combining lithium + valproate + olanzapine or quetiapine in fact do better than others. Although practically challenging, our findings highlight the need for more extensive trials in which complex combinations are studied and different antipsychotics are compared head-to-head.

In concordance with previous observational studies (Garnham et al., 2007; Hayes et al., 2016; Simhandl et al., 2014; Lahteenvuo et al., 2018; Pompili et al., 2014), we found that lithium monotherapy was associated with significantly better outcomes compared to single use of any atypical antipsychotic. However, previous observational studies have failed to show an advantage of combination therapies over monotherapies in the maintenance phase of bipolar disorder (Gonzalez-Pinto et al., 2011; Kulkarni et al., 2012). Notably, these studies have only assessed treatment combinations including olanzapine and a classic mood-stabilizer and differ significantly from our study in terms of numbers and study design, as one included 239 patients of whom the majority were depressed or euthymic at study entry (Kulkarni et al., 2012), and the other, which included 1 076 patients, only measured drug exposure for 12 weeks although patients were followed for 24 months, which may have resulted in misclassification (Gonzalez-Pinto et al., 2011).

Despite indications of a relatively lower tolerability of combination therapies vs. monotherapies in the long-term treatment of bipolar disorder (Buoli et al., 2014), our findings suggest lower rates of discontinuation and medication switch among patients on combination therapy, whereas rehospitalization risks did not differ significantly across most groups. One possible explanation could be that combination therapies are generally better tolerated after a manic episode, another that the perceived benefits of the treatment in terms of symptomatic or syndromic remission outweigh any negative effects. The finding that 43% of patients in our study used two or more anti-manic drugs, and the variety of combinations used, reflect a general trend towards an increased use of combination therapies (Bjorklund et al., 2016; Chang et al., 2016; Kessing et al., 2016), and indicate a high ambition among clinicians and patients to individualize treatment, despite the more rigid treatment recommendations (Fountoulakis et al., 2017; Goodwin et al., 2016; Grunze et al., 2013; Kendall et al., 2014).

In summary, this study provides new real-world evidence of a relatively higher effectiveness of combination therapies over monotherapies after a manic episode, echoing the

findings from several RCTs (Suppes et al., 2013; Tohen et al., 2004; Woo et al., 2011; Yatham et al., 2013, 2016). These results indicate that the increasing use of combination therapies may benefit patients with a recent manic episode and serve as a reminder that various treatment regimens may be needed throughout the different phases of bipolar illness, requiring vigilance and flexibility among physicians to improve patient outcomes.

Conflict of interest

The Centre for Pharmacoepidemiology at Karolinska Institutet, where LW, LB, HK, JR are currently employed, has received money from several drug companies for performing post-approval safety studies and comparative effectiveness studies, why these authors report financial relationships with Abbvie, Astellas, Astra-Zeneca, Bayer, Janssen Biotech, Novartis, Pfizer, and Reckitt Benckiser, outside the submitted work. RB reports grants from the Swedish Research Council during the conduct of the study; and has been in research collaboration with Jansen for which grant support has been received by The Centre for Pharmacoepidemiology, Karolinska Institutet. MA reports grants from AstraZeneca, H. Lundbeck & Mertz, Novartis, Pfizer, Janssen, and NovoNordisk Foundation, outside the submitted work, all received by his institutions, and personal fees from Medicademy, the Danish Pharmaceutical Industry Association, for leading and teaching pharmacoepidemiology courses.

Contributors

All authors contributed to the original idea for the study and were responsible for the hypotheses, design, and data specification. LW had the overall responsibility for the conduct of the study and was responsible for the literature search. LB undertook the statistical data analysis, with advice from LW and JR. The results were interpreted by all authors. All authors contributed to and have approved the final manuscript.

Role of the funding source

This study was supported by grants from the Bror Gadelius Memorial Fund (2015, 2016), the Swedish Society of Medicine (SLS-502541, SLS-587661), the Capio Research Foundation (2014-2722), the Söderström-Königska Foundation (SLS-480131), the Fredrik O Ingrid Thurings Foundation (2015-00114), Karolinska Institutet Funds (2013-37903), and the Swedish Research Council (2016-02362). Co-author MA was supported by a grant from the Novo Nordisk Foundation to the University of Copenhagen (NNF15SA0018404). The funding sources had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgment

The authors have no acknowledgments to report.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.04.003.

References

Altamura, A.C., Mundo, E., Dell'Osso, B., Tacchini, G., Buoli, M., Calabrese, J.R., 2008. Quetiapine and classical mood stabilizers in the long-term treatment of Bipolar Disorder: a 4-year follow-up naturalistic study. J. Affect. Disord. 110, 135–141.

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

Buoli, M., Serati, M., Altamura, A.C., 2014. Is the combination of a mood stabilizer plus an antipsychotic more effective than mono-therapies in long-term treatment of bipolar disorder? A systematic review. J. Affect. Disord. 152-154, 12–18.

Carlson, B.X., Ketter, T.A., Sun, W., Timko, K., McQuade, R.D., Sanchez, R., Vester-Blokland, E., Marcus, R., 2012. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). Bipolar Disord 14, 41–53.

Chang, C.M., Wu, C.S., Huang, Y.W., Chau, Y.L., Tsai, H.J., 2016. Utilization of psychopharmacological treatment among patients with newly diagnosed bipolar disorder from 2001 to 2010. J. Clin. Psychopharmacol. 36, 32–44.

di Giacomo, E., Aspesi, F., Fotiadou, M., Arntz, A., Aguglia, E., Barone, L., Bellino, S., Carpiniello, B., Colmegna, F., Lazzari, M., Lorettu, L., Pinna, F., Sicaro, A., Signorelli, M.S., Clerici, M.BRT Group, 2017. Unblending borderline personality and bipolar disorders. J. Psychiatr. Res. 91, 90–97.

Fountoulakis, K.N., Grunze, H., Vieta, E., Young, A., Yatham, L., Blier, P., Kasper, S., Moeller, H.J., 2017. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. Int. J. Neuropsychopharmacol 20, 180–195.

Garnham, J., Munro, A., Slaney, C., Macdougall, M., Passmore, M., Duffy, A., O'Donovan, C., Teehan, A., Alda, M., 2007. Prophylactic treatment response in bipolar disorder: results of a naturalistic observation study. J. Affect. Disord. 104, 185–190.

Gonzalez-Pinto, A., Vieta, E., Reed, C., Novick, D., Barraco, A., Aguado, J., Haro, J.M., 2011. Effectiveness of olanzapine monotherapy and olanzapine combination treatment in the long term following acute mania–results of a two year observational study in bipolar disorder (EMBLEM). J. Affect. Disord. 131, 320–329.

Goodwin, G.M., Haddad, P.M., Ferrier, I.N., Aronson, J.K., Barnes, T., Cipriani, A., Coghill, D.R., Fazel, S., Geddes, J.R., Grunze, H., Holmes, E.A., Howes, O., Hudson, S., Hunt, N., Jones, I., Macmillan, I.C., McAllister-Williams, H., Miklowitz, D.R., Morriss, R., Munafo, M., Paton, C., Saharkian, B.J., Saunders, K., Sinclair, J., Taylor, D., Vieta, E., Young, A.H., 2016. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J. Psychopharmacol. 30, 495–553.

Grunze, H., Vieta, E., Goodwin, G.M., Bowden, C., Licht, R.W., Moller, H.J., Kasper, S.WFSBP Task Force on Treatment Guidelines for Bipolar Disorders, 2013. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J. Biol. Psychiatry 14, 154–219.

Hayes, J.F., Marston, L., Walters, K., Geddes, J.R., King, M., Osborn, D.P., 2016. Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. World Psychiatry 15, 53–58.

Hong, J., Reed, C., Novick, D., Haro, J.M., Windmeijer, F., Knapp, M., 2010. The cost of relapse for patients with a manic/mixed episode of bipolar disorder in the EMBLEM study. PharmacoEconomics 28, 555–566.

Kendall, T., Morriss, R., Mayo-Wilson, E., Marcus, E.Guideline Development Group of the National Institute for Health and Care Excellence, 2014. Assessment and management of bipolar disorder: summary of updated NICE guidance. BMJ 349, g5673.

Kessing, L.V., Vradi, E., Andersen, P.K., 2016. Nationwide and population-based prescription patterns in bipolar disorder. Bipolar Disord 18, 174–182.

Kulkarni, J., Filia, S., Berk, L., Filia, K., Dodd, S., de Castella, A., Brnabic, A.J., Lowry, A.J., Kelin, K., Montgomery, W., Fitzgerald, P.B., Berk, M., 2012. Treatment and outcomes of an Australian cohort of outpatients with bipolar I or schizoaffective disorder over twenty-four months: implications for clinical practice. BMC Psychiatry 12, 228.

Lahteenvuo, M., Tanskanen, A., Taipale, H., Hoti, F., Vattulainen, P., Vieta, E., Tiihonen, J., 2018. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry 75, 347–355.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K.Clinical Antipsychotic Trials of Intervention Effectiveness Investigators, 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209–1223.

Ludvigsson, J.F., Andersson, E., Ekbom, A., Feychting, M., Kim, J.L., Reuterwall, C., Heurgren, M., Olausson, P.O., 2011. External review and validation of the Swedish national inpatient register. BMC Public Health 11, 450.

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

Nierenberg, A.A., McElroy, S.L., Friedman, E.S., Ketter, T.A., Shelton, R.C., Deckersbach, T., McInnis, M.G., Bowden, C.L., Tohen, M., Kocsis, J.H., Calabrese, J.R., Kinrys, G., Bobo, W.V., Singh, V., Kamali, M., Kemp, D., Brody, B., Reilly-Harrington, N.A., Sylvia, L.G., Shesler, L.W., Bernstein, E.E., Schoenfeld, D., Rabideau, D.J., Leon, A.C., Faraone, S., Thase, M.E., 2016. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. J. Clin. Psychiatry 77, 90–99.

Perlis, R.H., Ostacher, M.J., Patel, J.K., Marangell, L.B., Zhang, H., Wisniewski, S.R., Ketter, T.A., Miklowitz, D.J., Otto, M.W., Gyulai, L., Reilly-Harrington, N.A., Nierenberg, A.A., Sachs, G.S., Thase, M.E., 2006. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am. J. Psychiatry 163, 217–224.

Pompili, M., Innamorati, M., Gonda, X., Serafini, G., Erbuto, D., Ricci, F., Fountoulakis, K.N., Lester, D., Vazquez, G., Rihmer, Z., Amore, M., Girardi, P., 2014. Pharmacotherapy in bipolar disorders during hospitalization and at discharge predicts clinical and psychosocial functioning at follow-up. Hum. Psychopharmacol. 29, 578–588.

Sapmaz, D., Baykal, S., Akbas, S., 2018. The clinical features of comorbid pediatric bipolar disorder in children with autism spectrum disorder. J. Autism Dev. Disord. 48, 2800–2808.

Simhandl, C., Konig, B., Amann, B.L., 2014. A prospective 4-year naturalistic follow-up of treatment and outcome of 300 bipolar I and II patients. J. Clin. Psychiatry 75, 254–262.

Stralin, P., Hetta, J., 2019. First episode psychosis and comorbid ADHD, autism and intellectual disability. Eur. Psychiatry. 55, 18–22.

Suppes, T., Vieta, E., Gustafsson, U., Ekholm, B., 2013. Maintenance treatment with quetiapine when combined with either lithium or divalproex in bipolar I disorder: analysis of two large randomized, placebo-controlled trials. Depress. Anxiety 30, 1089–1098.

Tohen, M., Chengappa, K.N., Suppes, T., Baker, R.W., Zarate, C.A., Bowden, C.L., Sachs, G.S., Kupfer, D.J., Ghaemi, S.N., Feldman, P.D., Risser, R.C., Evans, A.R., Calabrese, J.R., 2004. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br. J. Psychiatry 184, 337–345.

Tohen, M., Greil, W., Calabrese, J.R., Sachs, G.S., Yatham, L.N., Oerlinghausen, B.M., Koukopoulos, A., Cassano, G.B., Grunze, H., Licht, R.W., Dell'Osso, L., Evans, A.R., Risser, R., Baker, R.W., Crane, H., Dossenbach, M.R., Bowden, C.L., 2005. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am. J. Psychiatry 162, 1281–1290.

Weisler, R.H., Nolen, W.A., Neijber, A., Hellqvist, A., Paulsson, B.Trial 144 Study Investigators, 2011. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). J. Clin. Psychiatry 72, 1452–1464.

Wettermark, B., Hammar, N., Fored, C.M., Leimanis, A., Otterblad Olausson, P., Bergman, U., Persson, I., Sundstrom, A., Westerholm, B., Rosen, M., 2007. The new Swedish prescribed drug register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol. Drug. Saf. 16, 726–735.

Wingard, L., Boden, R., Brandt, L., Tiihonen, J., Tanskanen, A., Kieler, H., Andersen, M., Reutfors, J., 2017. Reducing the rehospitalization risk after a manic episode: a population based cohort study of lithium, valproate, olanzapine, quetiapine and aripiprazole in monotherapy and combinations. J. Affect. Disord. 217, 16–23.

Woo, Y.S., Bahk, W.M., Chung, M.Y., Kim, D.H., Yoon, B.H., Lee, J.H., Ahn, Y.M., Chung, S.K., Kim, J.G., Lee, K.H., Paik, K.C., 2011. Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. Hum. Psychopharmacol. 26, 543–553.

Yatham, L.N., Fountoulakis, K.N., Rahman, Z., Ammerman, D., Fyans, P., Marler, S.V., Baker, R.A., Carlson, B.X., 2013. Efficacy of aripiprazole versus placebo as adjuncts to lithium or valproate in relapse prevention of manic or mixed episodes in bipolar I patients stratified by index manic or mixed episode. J. Affect. Disord. 147, 365–372.

Yatham, L.N., Beaulieu, S., Schaffer, A., Kauer-Sant'Anna, M., Kapczinski, F., Lafer, B., Sharma, V., Parikh, S.V., Daigneault, A., Qian, H., Bond, D.J., Silverstone, P.H., Walji, N., Milev, R., Baruch, P., da Cunha, A., Quevedo, J., Dias, R., Kunz, M., Young, L.T., Lam, R.W., Wong, H., 2016. Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: a CANMAT randomized double-blind trial. Mol. Psychiatry 21, 1050–1056.

Zimmerman, M., Morgan, T.A., 2013. The relationship between borderline personality disorder and bipolar disorder. Dialogues Clin. Neurosci. 15, 155–169.